



Bladder Management Following Spinal Cord Injury

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Key Points

Anticholinergic Therapy for SCI-Related Detrusor Overactivity

Propiverine, oxybutynin, tolterodine, solifenacin, and trospium chloride are efficacious for the treatment of neurogenic detrusor overactivity following SCI.

Combinatorial treatment with 2 of oxybutynin, tolterodine or trospium may be effective for the treatment of neurogenic detrusor overactivity in individuals with SCI who have not responded to one medication.

Tolterodine, propiverine (particularly the extended-release formula), or transdermal oxybutynin likely result in less dry mouth but have similarly efficacy to oral oxybutynin in terms of improving neurogenic detrusor overactivity.

Toxin Therapy for SCI-Related Detrusor Overactivity

Onabotulinum toxin type A injections into the detrusor muscle improve neurogenic detrusor overactivity, intradetrusor pressures, bladder capacity and urge incontinence; it may also reduce detrusor contractility.

Vanilloid compounds such as capsaicin or resiniferatoxin increase maximum bladder capacity, and decrease urinary frequency, incontinence, and intradetrusor pressure in neurogenic detrusor overactivity.

Intravesical capsaicin instillation in bladders of individuals with SCI does not increase the rate of common bladder cancers after 5 years of use.

There is evidence that nociceptin/orphanin phenylalanine glutamine, a nociceptin orphan peptide receptor agonist, may be considered for the treatment of neurogenic detrusor overactivity following SCI.

Intravesical Instillations for SCI-Related Detrusor Overactivity

intravesical instillation of both propantheline and oxybutynin improve cystometric parameters in individuals with SCI and neurogenic bladder, but propantheline provides superior improvement in more parameters.

Catheterization combined with intravesical instillation of oxybutynin alone or in addition to oral oxybutynin is effective in improving the symptoms of neurogenic bladder in individuals with SCI.

For individuals with SCI and neurogenic bladder, capsaicin can decrease leak volume and frequency but can also increase residual volume and cystometric capacity as well as induce hyperreflexia.

Intravesical instillation of oxybutynin is ineffective for male individuals with SCI who have an implanted Brindley anterior nerve root stimulator.

Other Pharmaceutical Treatments for SCI-Related Detrusor Overactivity

Tadalafil, vardenafil, intrathecal baclofen, clonidine and mirabegron may improve bladder function following SCI but further confirmatory evidence is needed.

Surgical Augmentation of the Bladder to Enhance Volume

Surgical augmentation of the bladder may enhance bladder capacity, lower filling pressure, and improve continence in persons with SCI.

Extraperitoneal compared to intraperitoneal augmentation enterocystoplasty may result in a quicker postoperative recovery.

Alpha-Adrenergic Blockers for Bladder Emptying

Tamsulosin may improve urine flow in SCI individuals with bladder neck dysfunction.

Mosixylyte is likely able to decrease maximum urethral closure pressure at a dose of 0.75mg/kg in individuals with SCI.

Terazosin may be an alternative treatment for bladder neck dysfunction in individuals with SCI; however, side effects and drug tolerance should be monitored.

Phenoxybenzamine may be useful as an adjunct therapy to reduce residual urine volumes in individuals with SCI who manage their neurogenic bladder dysfunction by performing crede or tapping maneuvers.

Six months of alpha 1-blocker therapy in men with SCI may improve upper tract stasis.

Botulinum Toxin for Bladder Emptying

Botulinum toxin injected into the sphincter can improve bladder emptying for persons with neurogenic detrusor sphincter dyssynergy (DSD) following SCI.

The presence of detrusor contractions and normal bladder neck activity may be strong predictors of good outcomes for DSD treated with BTX.

Other Pharmaceutical Treatments for Bladder Emptying

Isosorbide dinitrate may improve bladder control post SCI; although, more evidence is needed to support this as a treatment option.

4-Aminopyridine at sufficient dosage may return sensation and control of the bladder sphincter following SCI; more evidence is needed to support this as a treatment option.

Comparing Methods of Conservative Bladder Emptying

Electroacupuncture in combination with CIC results in reduced residual volume and CIC frequency while increasing voided volume.

Supervised sequential conservative bladder management is may result in favourable urological complication rates.

Severity of injury and urinary sensation could be predictive parameters for future voiding function.

Comparing Methods of Conservative Bladder Emptying

Intermittent catheterization, whether performed acutely or chronically, may have the lowest complication rate.

Indwelling catheterization, whether suprapubic or urethral or whether conducted acutely or chronically, may result in a higher long-term rate of urological and renal complications than other management methods.

Persons with tetraplegia and complete injuries, and to a lesser degree in females, may have difficulty in maintaining compliance with intermittent catheterization procedures following discharge from rehabilitation.

Bladder management via suprapubic catheterization may be the better option for individuals that are high tetraplegics and respirator-dependent.

Suprapubic catheter use may be more associated with bladder stone occurrence while transurethral catheters may be more associated with bladder stone recurrence.

It is possible that males using IC are more likely to develop urethral strictures of which some might need surgical intervention.

There may be an association with males needing catheterization having a higher mortality rate.

Specific Aspects of using Intermittent Catheterization

Portable ultrasound device can improve the scheduling of intermittent catheterizations.

Lower cervical lesion levels are likely predictive of more IC independence.

Urethral complications and epididymo-orchitis occur more frequently in those using intermittent catheterization programs.

IC self-management educational programs may be modestly helpful.

Comparison of Intermittent Catheterization Catheter Types

Although both pre-lubricated and hydrophilic catheters have been associated with reduced incidence of UTIs as compared to conventional PVC catheters, less urethral microtrauma with their use may only be seen with pre-lubricated catheters.

Compact catheters are more discrete than standard catheters for carrying and disposal but offer comparable performance in bladder emptying and residual urine volumes.

Triggering-Type or Expression Voiding Methods of Bladder Management

TENS biofeedback and electroacupuncture assisted bladder training improve bladder function.

Valsalva or Crede maneuver may assist some individuals to void spontaneously but produce high intra-vesical pressure, increasing the risk for long-term complications.

Indwelling Catheterization (Urethral or Suprapubic)

With diligent care and ongoing medical follow-up, indwelling urethral and suprapubic catheterization may be an effective and satisfactory bladder management choice for some people, though there is insufficient evidence to report lifelong safety of such a regime.

Compared to non-indwelling methods, indwelling catheter users are at higher risk of bladder cancer, especially in the second decade of use, though risk also increases during the first decade of use.

Condom Catheterization

Individuals using condom drainage should be monitored for complete emptying and for low pressure drainage to reduce UTI and upper tract deterioration; sphincterotomy may eventually be required.

Penile implants may allow easier use of condom catheters and reduce incontinence.

Continent Catheterizable Stoma and Incontinent Urinary Diversion

Catheterizable abdominal stomas may increase the likelihood of achieving continence and independence in self-catheterization and may result in a bladder management program that offers more optimal upper tract protection.

Cutaneous ileal conduit diversion may increase the likelihood of achieving continence but may also be associated with a high incidence of various long-term complications.

Continent cutaneous urinary diversion (CCUD) with augmentation enterocystoplasty may improve urethral continence and QoL.

Electrical Stimulation for Bladder Emptying and Enhancing Volumes

Sacral anterior root stimulation (accompanied in most cases by posterior sacral rhizotomy) enhances bladder function and is an effective bladder management technique through the program (surgery and follow-up) requires significant expertise.

Direct bladder stimulation may be effective in reducing incontinence and increasing bladder capacity but requires further study.

Pulsed electromagnetic stimulation may be more effective than transcutaneous electrical nerve stimulation when stimulating the sacral roots for improving bladder capacity and urinary flow.

Posterior sacral, thoracolumbar, pudental, dorsal penile or clitoral nerve stimulation may be effective to increase ladder capacity but requires further study.

Posterior sacral, pudental, dorsal penile or clitoral nerve stimulation may be effective to increase ladder capacity but requires further study.

Early sacral neural modulation may improve management of lower urinary tract dysfunction but requires further study.

Epidural dorsal spinal cord stimulation (T1 or T11) and functional electrical stimulation of the lower limbs are not effective in enhancing bladder function.

Sphincterotomy, Artificial Sphincters, Stents and Related Approaches for Bladder Emptying

Surgical and prosthetic approaches (with a sphincterotomy and stent respectively) to allow bladder emptying through a previously dysfunctional external sphincter both seem equally effective resulting in enhanced drainage although both may result in long-term upper and lower urinary tract complications.

Artificial urinary sphincter implantation and transurethral balloon dilation of the external sphincter may be associated with improved bladder outcomes but require further study.

Transobturator tape implantation is not effective for SCI-related neurogenic stress incontinence and results in high complication rates.

Other Miscellaneous Treatments to Enhance Bladder Emptying

Electroacupuncture therapy as adjunctive therapy may improve bladder function. Intranasal DDVAP may reduce nocturnal urine emissions and decrease the frequency of voids (or catheterizations).

Anastomosis of the T11 or S1 (but not L5) to the S2-S3 spinal nerve roots may result in improved bladder function in chronic SCI.

People with SCI seem to have a lower rate of bladder and prostate cancer than people without SCI.

Individuals with severe SCI may have higher bladder cancer related mortality.

Bladder cancer screening may be an option for people with more severe SCI.

Combined techniques for bladder stone removal likely result in higher complication rates than when stone punch is used alone.

Bladder stone occurrence may occur more frequently with catheter use than with reflex micturition.

Endoscopic application of bulking agents to treat VUR may be more successful if NDO is eradicated first.

Detecting and Investigating UTIs

Both limited and full microbial investigation may result in adequate clinical response to UTI treatment with antibiotics.

Indwelling or suprapubic catheters should be changed just prior to urine collection so as to limit the amount of false positive urine tests.

Urinalysis and urine culture results of SCI individuals are not likely to be affected by sample refrigeration (up to 24 hours).

It is uncertain if dipstick testing for nitrates or leukocyte esterase is useful in screening for bacteriuria to assist treatment decision-making.

Intermittent Catheterization and Prevention of UTIs

Sterile and clean approaches to intermittent catheterization seem equally effective in minimizing UTIs in individual rehabilitation.

Similar rates of UTI may be seen with intermittent catheterization as conducted by the individuals themselves or by a specialized team during individual rehabilitation.

Similar rates of UTI may be seen with intermittent catheterization, whether conducted in the short-term during individual rehabilitation or in the long-term while living in the community.

UTIs were not associated with differences in residual urine volumes after intermittent catheterization.

Catheter reuse may be linked to increased frequency of UTIs.

More severely injured males who use CIC may have higher rates of febrile UTIs.

Transurethral indwelling catheter use may be associated with the highest rate of symptomatic UTIs when compared to rates.

Specially Covered Intermittent Catheters for Preventing UTI

A reduced incidence of UTIs or reduced antibiotic treatment of symptomatic UTIs have been associated with pre-lubricated or hydrophilic catheters as compared to standard non-hydrophilic catheters.

Other Issues Associated with Bladder Management and UTI Prevention

Intermittent catheterization is associated with a lower rate of UTI as compared to use of indwelling or suprapubic catheter.

The Statlock device to secure indwelling and suprapubic catheters may lead to a lower rate of UTI.

Removal of external condom drainage collection systems at night or for 24 hours/day may reduce perineal, urethral or rectal bacterial levels but has no effect on bacteriuria.

The presence of vesicoureteral reflux likely has a greater impact on development of significant infections than the choice of bladder management.

Bacterial Interference for Prevention of UTIs

E. coli 83972 & HU2117 bladder inoculation & may prevent UTIs.

Antibiotic Prophylaxis of UTIs

Ciprofloxacin may be indicated for UTI prophylaxis in SCI but further research is needed to support its use.

Long-term use of TMP-SMX is not recommended for sustained use as a suppressive therapy for UTI prevention.

A weekly oral cyclic antibiotic, customized to the individual, may be beneficial in preventing UTI in SCI.

Antiseptic and Related Approaches for Preventing UTIs

Daily body washing with chlorhexidine and application of chlorhexidine cream to the penis after every catheterization instead of using standard soap may reduce bacteriuria and perineal colonization.

The antiseptic agents delivered via bladder irrigation (5% hemiacidrin solution combined with oral methenamine mandelate; trisdine, kanamycin colistin) may be effective for UTI prevention, whereas others are not (i.e., neomycin/polymyxin, acetic acid, ascorbic acid and phosphate supplementation).

Oral methenamine hippurate, either alone or in combination with cranberry, is not effective for UTI prevention.

Botulinum toxin type A (300 U) injected into the detrusor may prevent UTIs in individuals with neurodetrusor overactivity.

Strict surveillance methods may be helpful to reduce the development of MDRP cases.

Alternative Approaches for UTI Prevention

It is uncertain if cranberry is effective in preventing UTIs in persons with SCI.

Adjunctive homeopathic care may reduce standard antibiotic prophylaxis and UTI frequency.

Educational Interventions for Maintaining a Healthy Bladder and Preventing UTIs

A variety of bladder management education programs are effective in reducing UTI risk in community- dwelling persons with SCI, although limited information exists as to which is the most effective approach.

Pharmacological Treatment of UTIs

Antibiotics administered over longer durations (10-14 days versus 3 days) is likely to result in improved clinical and microbiological SCI UTI treatment outcome including recurrence prevention.

Ofloxacin treatment is likely to result in significant SCI UTI cure rate, more so than trimethoprim-sulfamethoxazole.

Norfloxacin may be a reasonable treatment choice for UTI in SCI but subsequent resistance must be monitored.

Aminoglycosides have a low success rate in the treatment of SCI UTI.

Intermittent neomycin/polymyxin bladder irrigation may be effective in altering the resistance of the offending bladder organism(s) to allow for appropriate antibiotic treatment.

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Bladder Management Following Spinal Cord Injury

1.0 Executive Summary

Neurogenic lower urinary tract dysfunction (NLUTD) is prevalent following the spinal cord injuries (SCI), and contributes to complications such as chronic renal insufficiency, incontinence, and urinary tract infections. Understanding the evidence when choosing treatments for NLUTD is therefore important to clinicians caring for individuals with SCI. Given the many ways in which NLUTD impacts bladder function following a SCI, we begin the chapter by describing the underlying pathophysiology. This is followed by a discussion of therapies for specific dysfunctions. NLUTD increases the risk of urinary tract infections (UTIs), therefore an in-depth exploration of options for preventing and treating UTI treatment is also covered. The systematic organization and presentation of treatment options along with the accompanying evidence, based on underlying pathophysiology, is intended to assist clinicians addressing SCI related bladder management and facilitate an interconnected approach to the genitourinary system as a whole.

Types of NLUTD

NLUTD in spinal cord injury can be classified as suprasacral, sacral, or infrasacral. Suprasacral NLUTD occurs with spinal cord injuries below the brainstem (pons) and above the sacral micturition (voiding) centre. Suprasacral NLUTD is also referred to as upper motor neuron (UMN) bladder dysfunction and is characterized by disinhibited sacral reflexes, overactivity of the detrusor (body of the bladder), overactivity of the external and/or internal sphincters (bladder neck), and impaired coordination between the body of the bladder and the bladder neck. The result is concurrent contraction of the bladder body and neck, as opposed to relaxation of the bladder neck with detrusor (bladder body) contractions. This combination of overactivity of detrusor and bladder neck (sphincters) is referred to as detrusor sphincter dyssynergia, and can lead to incomplete voiding, urgency, frequency, incontinence, and high pressures in the bladder, leading to reflux, hydronephrosis, and kidney failure. Sacral NLUTD is seen with injuries impacting the sacral voiding centre in the conus medullaris (sacral spinal cord). This leads to a mixed picture and is part of the conus medullaris syndrome. Infrasacral NLUTD is seen with injuries to the cauda equina (sacral nerve roots). Sacral and infrasacral NLUTD are also referred to as lower motor neuron (LMN) bladder dysfunction. LMN bladder dysfunction is characterized the absent or impaired efferent input to the bladder and bladder neck. The end result are decreased contractions or areflexia of the detrusor and sphincters, and is part of the cauda equina syndrome. In this scenario there is usually difficulty emptying the bladder and lack of awareness of the need to do so, which leads to overflow and stress incontinence, urinary tract infection, bladder distension, and possible hydronephrosis and renal failure.

Targeted treatment options

The primary therapeutic goals for NLUTD are ensuring adequate storage for individuals with impaired storage, achieving adequate elimination in those with impaired elimination, and maintaining low pressures in the bladder. For individuals

with impaired or high pressure storage, current treatments focus predominantly on the administration of oral medications (e.g., anticholinergics) or intradetrusor botulinum toxin to inhibit detrusor contractions and enhance relaxation, while more invasive procedures (e.g., bladder augmentation surgery) are reserved for treatment failures with more conservative measures. For individuals with impaired emptying, medications or surgery (e.g., sphincterotomy) can be employed to improve emptying by decreasing outlet resistance at the bladder neck. If the above measures are ineffective, the bladder can be mechanically drained with either intermittent or indwelling catheterization.

Gaps in the Evidence

- Comparator studies to identify efficacious first line anticholinergic medicines with the best side effect profiles.
- Larger and longer duration studies to establish the efficacy of beta-3 agonists in the SCI NLUTD population.
- Studies to clarify which individuals with NLUTD require single use and/or hydrophilic catheters for intermittent catheterization, as opposed to cleaning and reusing catheters.
- Methods to decrease the severity and incidence of urinary tract infections in those using intermittent and indwelling catheters.
- Identifying sensitive serum markers for diagnosing early renal insufficiency.
- Identifying the optimal surveillance schedule for those with NLUTD, including when repeat urodynamic studies are indicated.
- Studies on methods for enhancing outlet resistance to prevent stress incontinence in those with infrasacral lesions who are willing to perform intermittent catheterization.

2.0 Introduction

Bladder dysfunction in persons with spinal cord injury (SCI) has medical, physical, and social consequences. Most people with SCI have some degree of bladder dysfunction. Normally, the bladder stores urine at low pressures within a relaxed detrusor (bladder wall smooth muscle), until it is socially appropriate to void. As the relaxed bladder fills to a threshold of approximately 300-400 mL, progressive distention leads to increasing afferent input to the sacral and pontine micturition centers until detrusor contraction and sphincter relaxation are initiated. The timing and coordination of detrusor contraction and sphincter relaxation is mediated by the pontine micturition centre, and leads to voiding in a low pressure environment. The frontal cortex can initiate or suppress voiding volitionally and subsequently contribute to continence by limiting voiding to desired times. The ability to fill and empty the bladder under low pressure is of utmost importance in maintaining the health of the kidneys, ensuring continence and preventing urinary tract infections (UTI).

A SCI disrupts communication between the sacral micturition centre in the spinal cord and the pons and cortex in the brain; resulting in the loss of coordinated bladder filling and emptying. The involuntary functions of the kidney, such as its general metabolism, osmotic regulation, and the filtration and production urine are unaffected by a SCI. In contrast, a SCI can affect bladder function in different ways depending on the level of the injury. This includes an inability to sense a full bladder, overactivity or underactivity of the detrusor muscle and/or internal and external sphincters, and dys-coordination between the detrusor and sphincters during voiding. The latter process is referred to as detrusor sphincter dyssynergy (DSD). A spastic (reflex) bladder usually occurs with a SCI above the conus medullaris (spinal level of T12) while an areflexic (flaccid) bladder usually occurs in injuries at and below T12-L1, including conus medullaris and cauda equina injuries. The spastic bladder is often referred to as an upper motor neuron (UMN) bladder while the flaccid bladder is referred to as a lower motor neuron (LMN) bladder. The functional goal of bladder management following SCI is to tailor a bladder emptying program that is specific to the individual and compatible with his/her lifestyle and activities of daily living. Medical goals include achieving regular bladder emptying and avoiding stasis; avoiding high filling and voiding pressures; maintaining continence while avoiding abnormal frequency and urgency; and preventing and treating complications such as UTI, autonomic dysreflexia (usually only in those with injuries at or above T6), reflux, stones, and strictures.

There is a growing body of research evidence to aid in clinical decision making when managing bladder function following a SCI. While the amount of level 1 and 2 evidence has increased substantially in recent years, it is important to recognize that level 1 and 2 evidence is not available for all aspects of bladder complications, and that level 3, 4 and 5 evidence continues to provide important contributions to this field. The expanding scientific literature, however, presents a challenge when synthesizing and summarizing findings into a chapter of reasonable length. As a result, for sections where several levels of evidence exist and the level 5 evidence studies do not add novel or compelling evidence, level 5 evidence is summarized under the subheading *Summarized Level 5 Evidence Studies*. The contributions from these studies were not included in the related discussion or conclusions.

The present chapter is organized into sections addressing the type of bladder dysfunction (UMN vs. LMN), therapeutic strategies including the prevention and management of complications, and a final section focused on UTI prevention and treatment.

3.0 Types of Bladder Dysfunction in Spinal Cord Injury

There are two main types of neurogenic bladder dysfunction in SCI: 1) neurogenic detrusor overactivity, represented by overactive, reflexic or spastic detrusor muscle activity, usually associated with sphincter dysynergia (Detrusor Sphincter Dyssynergia, DSD); and 2) detrusor underactivity or acontractile detrusor, represented by reduced or absent detrusor activity. The former is also referred to as UMN bladder dysfunction while the latter is referred to as LMN bladder dysfunction. Occasionally, neurogenic detrusor overactivity secondary to SCI is seen without

associated sphincter dyssynergia. This can also result in difficulty maintaining continence. Methods to improve continence in those with or without DSD are often similar and are addressed in the sections on enhancing bladder volumes in DSD.

3.1 Detrusor Overactivity with DSD

Detrusor overactivity associated with DSD (UMN) is a type of dysfunction seen with injuries of the spinal cord that compromise communication between the upper motor neurons in the pontine micturition centre (brain) and the sacral micturition centre (i.e. infrapontine, suprasacral lesions). The detrusor becomes overactive due to loss of descending inhibition and reflexively contracts even with small volumes in the bladder. In these cases, disconnection from the pontine micturition centre also disrupts coordination between the detrusor muscle and the sphincters of the detrusor. During normal voiding, the internal and external sphincters relax while the detrusor simultaneously contracts in a carefully coordinated sequence of events. With DSD, the detrusor and sphincters simultaneously contract. The relative obstruction to urine outflow during voiding leads to elevated bladder pressures. Physiological abnormalities of detrusor overactivity with DSD include incontinence due to detrusor disinhibition, incomplete emptying (due to sphincter co-contraction), and ureteral reflux (due to high bladder pressures); which in turn increase risk of recurrent bladder infections, genitourinary stones, hydronephrosis, pyelonephritis, and renal failure.

3.2 Detrusor Underactivity

In the case of a flaccid (areflexic) bladder, loss of detrusor muscle tone (contractility) compromises bladder emptying and urinary retention and increases infection risk due to urine stasis. This is referred to as LMN bladder dysfunction and is typical of lesions to the conus medullaris and/or cauda equina (sacral nerve roots). External sphincter tone also tends to be flaccid, which can cause incontinence with maneuvers that increase intraabdominal pressure such as a Valsalva maneuver, application of external pressure to the bladder (Crede maneuver), straining during transfers, coughing, and sneezing. Internal sphincter tone may, however, be intact due to the higher origin of sympathetic innervation to the bladder. This may contribute to incomplete emptying, even with externally applied suprapubic pressure.

Compared to overactivity with DSD, individuals with detrusor underactivity comprise a much smaller proportion of the SCI population. It is predominantly seen in conus medullaris and/or cauda equina syndromes, and there is very little literature examining the effectiveness of interventions for this specific subpopulation. In addition, the existing evidence includes studies that address both bladder underactivity and overactivity. Conversely, the current literature more commonly addresses detrusor overactivity with DSD.

4.0 Therapeutic Interventions for Detrusor Overactivity with Detrusor External Sphincter Dyssynergia in Spinal Cord Injury

As reviewed above, SCI commonly results in the loss of the coordinated relationship between the detrusor muscle of the bladder and the urethral sphincters. If this dyssynergia is not managed, increased intravesical pressures can lead to vesicoureteric or vesicorenal reflux, and ultimately lead to hydronephrosis and renal failure. In addition, persistent detrusor overactivity with or without DSD can contribute to maladaptive trabeculation and hypertrophy of the bladder wall, as well as reduced bladder volumes (capacity). The goals of managing detrusor overactivity with or without DSD are twofold: 1) to enhance bladder volume while lowering bladder filling pressures, and 2) to empty the bladder regularly in a low pressure manner. The latter is usually accomplished with intermittent catheterization (IC) in people with an anatomically intact external sphincter, or external drainage in people that have had a procedure to physically or chemically obliterate the external sphincter (sphincterotomy). Methods to enhance bladder volumes will be discussed first; which is most applicable to individuals performing IC.

4.1 Enhancing Bladder Volumes Pharmacologically

4.1.1 Anticholinergic Therapy for SCI-Related Detrusor Overactivity

The body of the detrusor is comprised of smooth muscle that contains muscarinic receptors which bind acetylcholine and initiate muscle contractions. Therefore, muscarinic anticholinergics can therefore inhibit detrusor contractions and increase detrusor relaxation (compliance), thereby facilitating higher volumes during filling under lower pressure. Available medications for overactive bladder in this class include oxybutynin (available as Ditropan, Ditropal XL, Oxytrol, Uromax, etc), tolterodine (available as Detrol, Detrol LA), fesoterodine (marketed as Toviaz), trospium chloride (TCL, Trosec), propiverine hydrochloride (Mictonorm) and M3-receptor specific medications darifenacin (Enablex) and solifenacin (Vesicare).

Table 1 Summary Table of Oral Anticholinergics

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
Propiverine		
Stohrer et al. 2013 Germany RCT PEDro=7 N=66	<p>Population: Mean age: 41.2 yr; Gender: males=41, females=25; Injury etiology: traumatic (n=35, 57%), stroke (n=15, 23%), inflammable (n=12, 18%), degenerative (n=1, 2%); All individuals had urodynamically-confirmed neurogenic detrusor overactivity.</p> <p>Intervention: Individuals were randomly allocated to either extended-release (ER, n=33) or immediate-release (IR, n=33) treatment groups: administration of</p>	<ol style="list-style-type: none"> 1. Reflex volumes improved significantly in both the ER and IR groups, but intergroup differences were non-significant ($p<0.0001$). 2. Leak point volume increased and maximum detrusor pressure decreased significantly in both treatment groups, without significant intergroup differences ($p<0.0001$; $p<0.0043$). 3. Incontinence was significantly reduced in the ER group

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
	<p>propiverine either in ER capsules (45 mg BID) or coated IR tablets (15 mg TID).</p> <p>Outcome Measures: Reflex volumes, Maximum detrusor pressure, Leak point volume, incontinence, all were measured at baseline and 21 d after treatment. Adverse events were assessed as tolerability outcomes.</p>	<p>($p < 0.0005$), and there was a significant intergroup difference.</p> <ol style="list-style-type: none"> 16 individuals (48%) in the IR group and 12 individuals (36%) in the ER group experienced at least one adverse event. Treatment related adverse events occurred in 14 individuals (42%) in the IR group and 12 individuals (36%) in the ER group. Individuals related tolerability of both treatment groups worse in comparison to the investigators. Post void residual volume increased in both treatment groups.
<p>Stohrer et al. 1999 Germany RCT PEDro=9 Initial N=124; Final N=113</p>	<p>Population: Age range=29-30 yr; Gender: males=69, females=44; All individuals had NDO, suprasacral SCI and used IC for bladder management.</p> <p>Intervention: 15 mg of propiverine or placebo were given 3x/d for 14 d.</p> <p>Outcome Measures: Urodynamic parameters, individuals' clinical symptoms, physician's assessment of efficacy, adverse events and laboratory parameters (haematology, bleeding times, clinical chemistry etc.)</p>	<ol style="list-style-type: none"> Significant treatment increases: <ul style="list-style-type: none"> Bladder capacity ($p=0.006$). Maximal cystometric bladder capacity ($p < 0.0001$). Residual urine volume ($p=0.01$). Significant treatment decreases: <ul style="list-style-type: none"> Maximal detrusor contractions ($p < 0.001$). Detrusor contraction duration ($p < 0.03$). Improved clinical symptoms: Treatment=63.3%; placebo=22.6%.
Solifenacin		
<p>Chen et al. 2015 China RCT PEDro=6 Ninitial=100; Nfinal=98</p>	<p>Population: Neurogenic detrusor overactivity; Mean age: 33.2 yr; Gender: males=91, females=6; Level of injury: cervical=28, thoracic=47, lumbar=23; Severity of injury: complete=75, incomplete=23; Mean time post-injury: 3.4 yr.</p> <p>Intervention: Individuals were randomized to receive 1) percutaneous tibial nerve stimulation (PTNS group), consisting of surface electrodes placed at the ankle over the course of the tibia nerve for 30 min, 2 times per week, for 4 weeks or 2) solifenacin succinate (SS group), with 5 mg once a day for 4 weeks.</p> <p>Outcome Measures: Clean intermittent catheterization (CIC) frequency, fluid intake, volume per catheterization, total leakage volume</p>	<ol style="list-style-type: none"> No significant differences were observed post-treatment and between groups in terms of CIC frequency and fluid intake. Compared to baseline, the volume per catheterization significantly increased ($p < 0.05$), the total leakage volume per day decreased ($p < 0.05$), and the I-QOL significantly improved ($p < 0.05$) for both groups at 2 wk and 4 wk follow-up. However, no significant differences were observed between 2 wk and 4 wk follow-up within groups, or between groups. No adverse events were reported in PTNS group, compared to 5 participants in SS group reporting dry mouth (2

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	per day, Incontinence Quality of Life (I-QOL), adverse events.	resulting in study discontinuation).
Krebs et al. 2013 Switzerland Case Series N=35	<p>Population: Median age at treatment initiation: 44.9 yr (IQR 34.4 – 56.3 yr); Gender: 25 male, 7 female Injury Etiology: traumatic (n=30, 85.7%), non-traumatic (n=5, 14.3%); Level of injury: complete SCI (ASIA A (N=15)), incomplete (N=20); Level of injury: 4 tetraplegic, 31 paraplegic (91.4% - suprasacral lesions); All individuals had urodynamically confirmed neurogenic detrusor overactivity (NDO).</p> <p>Intervention: Solifenacin treatment initiated 7.3 yr after SCI (median, IQR 2.7 – 22.0 yr), 33 (94.3%) at 10 mg/d, 2 (5.7%) at 5 mg/d; All procedures were completed between Jan 2008 and Mar 2012</p> <p>Outcome Measures: Bladder capacity, Detrusor compliance, Maximum detrusor pressure, Reflex volume, Risk of renal damage</p>	<ol style="list-style-type: none"> At 13.1 mo (median, IQR 6.1–19.5 mo) after treatment, solifenacin treatment significantly improved all urodynamic parameters. Bladder capacity increased by 6% (+30.0 mL (median, IQR 0.0 to 69.0 mL)), detrusor compliance increased by 66% (+25.0 mLcm⁻¹ H₂O (median, IQR -1.0 to 50.0 mLcm⁻¹ H₂O)), maximum detrusor pressure decreased by 39% (-7.0cm H₂O (median, IQR -17.0 to -1.0cm H₂O)) and reflex volume increased by 39% (+62.5 mL (median, IQR 12.5 to 101.0 mL)). Though not statistically significant (p>0.1), fewer individuals presented with a risk of renal damage based on maximum detrusor pressure (6 vs. 13) and detrusor compliance (8 vs. 11), and the majority of individuals (69%) continued solifenacin treatment.
Oxybutynin		
Stöhrer et al. 2007 Europe RCT PEDro=9 N=131	<p>Population: Mean age: 38.3yr; Gender: males=99, females=32; Injury etiology: Traumatic SCI=122, Myelitis=1, MS=2, Myelodysplasia=4, Spinal tumours=2; All individuals had NDO.</p> <p>Intervention: To compare the efficacy and tolerability of propiverine and Oxybutynin for individuals with NDO. Individuals were randomized (1:1) to receive 15 mg TID propiverine or 5 mg tid Oxybutynin for 21 d.</p> <p>Outcome Measures: Maximum cystometric bladder capacity and bladder pressure.</p>	<ol style="list-style-type: none"> A significant increase was shown in the Max cystometric capacity (mL) for both the propiverine and Oxybutynin treatment groups (198±110 to 309±166 and 164±64 to 298±125, respectively). A significant decrease was shown in the Max detrusor pressure during the filling phase (cm H₂O) for both the propiverine and Oxybutynin groups (56.8±36.2 to 37.8±31.6 and 68.6±34.5 to 43.1±29.2, respectively). During filling cystometry, detrusor compliance showed significant improvements in both groups but no significant inter-group differences resulted. Residual urine for both groups was increased but the inter-group difference was not significant (p=0.13) (propiverine

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		<p>72.6 mL±115 to 140.9 mL±167 versus Oxybutynin 65.3 mL±78 to 149 mL±133).</p> <p>5. The propiverine group reported less frequent adverse events compared to Oxybutynin (63.0% vs. 77.8%) – Dryness of mouth was most frequently reported (47.1% vs. 67.2% respectively (p=0.02).</p>
Ersoz et al. 2016 Turkey Pre-Post N=27	<p>Population: Lower urinary tract dysfunction; Mean age: 35 yr; Gender: males=22, females=5; Level of injury: cervical= 3, thoracic=19, lumbosacral=5; ASIA classification: A=19, B=1, C=6, D=1; Mean time post-injury: 110 d; Injury etiology: traumatic spinal cord injury.</p> <p>Intervention: Oxybutynin HCl (10 mg/d in 15 cases and 15 mg/d in 12 cases).</p> <p>Outcome Measures: Meeting criteria for changing intermittent catheterization (IC) from 6/d to 4/d, maximum cystometric capacity.</p>	<p>1. At a mean follow-up of 30 d, there were 25 participants that had a maximum cystometric capacity of 400 ml or more, meeting the criteria for changing IC from 6/d to 4/d. Among the 2 cases that did not meet the criteria, one had not taken the medication after meals and one had only increased to 350 ml.</p> <p>2. There was a significant increase in maximum cystometric capacity after treatment (p<0.001).</p>
Kennelly et al. 2009 USA Pre-Post N=24	<p>Population: SCI individuals with neurogenic detrusor overactivity and incontinence. Mean age: 41.9 yr; Gender: males=21, females=3; Severity of injury: AIS A=17, B=2, C=5.</p> <p>Intervention: To evaluate the efficacy and safety of Oxybutynin transdermal system (Oxybutynin-TDS) in people with SCI with neurogenic detrusor overactivity and incontinence 8-wk dose titration period, Oxybutynin-TDS doses adjusted every 2 wk.</p> <p>Outcome Measures: Change in daily number of clean Intermittent catheterization (IC) periods without leakage, from baseline - 8 wk or last observation using 3-d voiding diary, clean intermittent catheterization (IC) volume and urodynamic parameters</p>	<p>1. Baseline mean daily total clean IC frequency=5.3±1.4</p> <p>2. Mean daily number of clean IC periods without leakage=2.4±1.8 (all other were associated with leakage)</p> <p>3. During the study, overall mean daily clean IC frequency (observed cases) remained constant</p> <p>4. Significant improvements were seen in:</p> <ul style="list-style-type: none"> • Reflex volume (p=0.0466) • Maximal cystometric bladder capacity (p=0.0009) • Residual urine volume (p=0.0023). • Detrusor pressure (p=0.0457).
O'Leary et al. 2003 USA Pre-Post N=10	<p>Population: SCI: Age range 35-77 yr; Gender: males=2, females=8; Severity of injury: AIS: A-D.</p> <p>Intervention: Initial 10 mg of Oxybutynin (extended release) daily; increased by 5 mg daily until</p>	<p>1. Mean cystometric bladder capacity volume significantly increased (p=0.008).</p> <p>2. Mean number of voids in a 24 hr period decreased (p=0.003).</p>

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	<p>symptoms were controlled or until a max dosage of 30 mg per d.</p> <p>Outcome Measures: Micturition frequency diaries and urodynamics were completed at baseline and repeated at wk 12. Tolerability info was also collected.</p>	<ol style="list-style-type: none"> Residual urine increased (p=0.02). Nocturia decreased but not by a significant amount. Incontinence episodes per wk significantly decreased (p=0.03)
Tolterodine		
<p>Ethans et al. 2004 Canada RCT (Tolterodine vs. placebo) Prospective controlled trial (Oxybutynin vs. tolterodine) PEDro=6 N=14</p>	<p>Population: Mean age: 40.5 yr; Gender: males=9, females=1; Mean time post-injury=13.7 yr. Injury etiology: SCI, MS.</p> <p>Intervention: Neurogenic detrusor overactivity tx. Double-blind design with tolterodine (T) 2 mg twice daily vs. placebo (P). Open label: tolterodine self-selected dose (TSSD) vs. Oxybutynin SSD (OSSD).</p> <p>Outcome Measures: Cystometric capacity, catheterization volumes, number of episodes of urinary incontinence/d, degree of mouth dryness per d using visual analog scale (VAS).</p>	<ol style="list-style-type: none"> No significant difference between T vs. P groups in: <ul style="list-style-type: none"> mean cystometric capacity degree of mouth dryness T vs. P significantly improved: <ul style="list-style-type: none"> mean catheterization volume (263 mL vs. 188 mL, p<0.001) Number of incontinence episodes/d (1 vs. 2.8, p<0.005) No significant difference between TSSD vs. OSSD in: <ul style="list-style-type: none"> mean cystometric capacity catheterization volume number of incontinence episodes/d. TSSD<OSSD for: dry mouth (VAS 2.6 vs. 4.4, p<0.05).
<p>Amend et al. 2008 Germany Prospective Controlled Trial N=27</p>	<p>Population: SCI individuals with hyperreflexia, Mean age: 35.7yr; Gender: males=21, females=6 Level of injury tetraplegia=15, paraplegia=6.</p> <p>Intervention: Individuals from a previous study continued treatment in 3 groups: Group A (n=8) received 8 mg of tolterodine and Oxybutynin (15-30 mg); Group B (n=11) received 90 mg of trospium (TCL) and tolterodine (4-8 mg); Group C (n=8) received 30 mg of Oxybutynin and TCL (45-90 mg) for 4 weeks.</p> <p>Outcome Measures: Incontinence events, bladder capacity, reflex volume, detrusor compliance were all measured at baseline, 4 wk and 6 mo post treatment</p>	<ol style="list-style-type: none"> No significant difference in outcomes was seen between 4 wk and 6 mo follow up. Number of incontinence events decreased significantly in all three groups at 4 wk follow up (Group A p<0.001; Group B p<0.0005; Group C p<0.001). Bladder capacity significantly increased at 4 wk follow up in Groups A (p<0.005), B (p<0.0005), C (p<0.001). Reflex volume increased in all three groups post 4 wk follow up (Group A p<0.005, Group B p<0.0001, Group C p<0.001). Detrusor compliance increased after 4 weeks of treatment in Groups A (p<0.005), B (p<0.0001), C (p<0.001) No significant difference was found among the treatments in detrusor compliance (p=0.97) or incontinence events (p=0.11).

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		7. Group A had significantly lower improvement in bladder capacity compared to the other groups ($p<0.002$). Group C had significantly higher reflex volume than group B.
Horstmann et al. 2006 Germany Prospective controlled trial N=21	<p>Population: Mean age:34 yr; Gender: males=15, females=6; Level of injury: paraplegia=7, tetraplegia=10.</p> <p>Intervention: Individuals were placed into one of two groups: 1) 4 mg of tolterodine once a d; 2) 15 mg of trospium (TCL) 3 times/d. After 4 wk, the dosage was doubled to either 4 mg of tolterodine ER twice/d or 30 mg of TCL three times/d. Follow-up was monitored by a bladder diary and urodynamic evaluation.</p> <p>Outcome Measures: Average reflex volume, detrusor pressure, cystometric capacity,</p>	<ol style="list-style-type: none"> 1. The average reflex volume and cystometric capacity increased significantly ($p<0.001$). 2. The maximum detrusor pressure dropped from 60 to 47cm H₂O ($p<0.05$). 3. Individuals treated with TCL: <ul style="list-style-type: none"> • Average reflex volume increase from 177 to 314 mL ($p<0.05$) • An average cystometric capacity enlargement from 271 to 430 mL ($p=0.0005$) • Maximum detrusor pressure decreased from 66 to 51cm H₂O ($p<0.05$). 4. Individuals treated with tolterodine: <ul style="list-style-type: none"> • Significant increase was seen in average reflex volume ($p<0.05$) and bladder capacity ($p<0.001$). • Average maximum detrusor pressure dropped from 54 to 43 cm H₂O ($p<0.05$). 5. One individual had to stop the medication because of intolerable side effects and five individuals did not experience satisfactory benefits.
Trospium Chloride		
Madersbacher et al. 1995 Germany RCT PEDro=8 N=95	<p>Population: <u>Trospium chloride (TCL; n=52)</u>: Mean age: 32.8 yr (range 16-56); Gender: male=28, females=24; Maximum cystometric bladder capacity: 215.5 mL; Maximum voiding detrusor pressure: 82.1 cmH₂O; Compliance: 74.6 mL/cmH₂O; Residual urine: 49.2 mL.</p> <p><u>Oxybutynine (Oxy; n=43)</u>: Mean age: 31.3 yr (range 18-54); Gender: male=19, females=24; Maximum cystometric bladder capacity: 185.mL; Maximum voiding detrusor pressure: 82.1 cmH₂O; Compliance: 59.5 mL/cmH₂O; Residual urine: 48.1 mL; All individuals had NDO.</p>	<ol style="list-style-type: none"> 1. Maximum bladder capacity increased significantly in both TCL (215.5 mL to 311.9 mL) and Oxybutynin(187.8 mL to 350.9 mL) treatment groups ($p<0.001$), the difference between the two treatment groups was not statistically significant ($p=0.057$). 2. Maximum detrusor pressure decreased significantly in both treatment groups ($p<0.001$), difference between the two was not statistically significant ($p=0.63$). 3. Bladder compliance significantly increased in the TCL group (74.62

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	<p>Intervention: Over a two wk period individuals in the TCL group took TCL (20 mg) twice daily with additional placebo midday. The oxybutynin group took three doses of oxybutynin(5 mg) daily.</p> <p>Outcome Measures: Maximum bladder capacity, maximum voiding detrusor pressure, bladder compliance, residual urine, hyper-reflexive waves, tolerance variables (dryness of mouth). Urodynamic evaluation taken at baseline and follow-up.</p>	<p>ml/cmH₂O to 92.75 ml/cmH₂O; p<0.001).</p> <ol style="list-style-type: none"> Residual Urine increased significantly in both groups (TCL: 49.2 ml to 128.33 ml; Oxy: 48.14 ml to 154.36 ml) with no significant intergroup differences (p=0.19). Frequency of hyper-reflexive waves decreased in both groups, with no significant intergroup differences (p=0.16). Reported severe dryness of mouth was considerably lower in TCL group (4%) compared to the Oxybutynin group (23%). Withdrawal from treatment occurred less in those receiving TCL (6%) compared to those receiving Oxybutynin(16%).
Stohrer et al. 1991 Australia RCT PEDro=6 N=61	<p>Population: SCI with detrusor hyperreflexia.</p> <p>Intervention: Trosipium chloride (20 mg bid, 3weeks) vs. placebo.</p> <p>Outcome Measures: Pre-/post-treatment max cystometric capacity (MCC); max detrusor pressure (MDP), urinary flow rate and residual urine volumes, adverse events.</p>	<ol style="list-style-type: none"> Statistical improvements (p<0.001) in the treatment group vs. placebo: <ul style="list-style-type: none"> increased MCC decreased MDP No effect in either group on: <ul style="list-style-type: none"> max flow rate residual urine volume Side effects low and no difference between groups.
Hadji et al. 2014 France Pre-Post N=231	<p>Population: Neurogenic detrusor overactivity; Mean age=38.4 yr; Gender: males=195, females=36; Level of injury: paraplegia=169, tetraplegia=62; ASIA classification: A=172, B-D=59.</p> <p>Intervention: Either oxybutynin (15 mg/d) or trosipium chloride (40 mg/d) was prescribed as a monotherapy. For those already on an anticholinergic agent, the other drug was added as bitherapy.</p> <p>Outcomes: Maximum bladder capacity (BCmax), involuntary detrusor contraction (IDC), complete continence.</p>	<ol style="list-style-type: none"> At a mean follow-up of 1 mo, the mean BCmax significantly increased by 216 mL (p<0.01) and the mean amplitude of IDC significantly decreased by 26 cm H₂O (p<0.01). No significant associations were found between the type of anticholinergic therapy (mono- or bi-therapy) and urodynamic balance. Only 75 (32%) of participants were fully continent at a mean follow-up of 1 mo.
Cisapride (FDA removal from market on July 14, 2000).		
Wyndaele & Kerrebroeck 1995 Belgium RCT PEDro=5 N=21	<p>Population: Mean age: 32 yr (range 17 -59); Gender: males=17, females=4; Etiology of SCI: traumatic (n=18, 86%), medical cause (n=3, 14%). All individuals had complete SCI and were out of spinal shock for 1.5 mo before entering the study.</p>	<ol style="list-style-type: none"> There were no significant differences in urodynamic parameters between baseline and the end of the study in either group, nor were there any differences found in any of the parameters between groups.

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	<p>Intervention: Individuals were randomly allocated to receive cisapride or a placebo for 4 wk. Cystometry was performed at baseline and during the testing period.</p> <p>Outcome Measures: Maximum cystometric capacity, Volume at the first sensation of filling, Volume at the sensation to void, Maximum detrusor pressure, Compliance, Bladder Capacity at the first involuntary detrusor contraction, and Residual volume.</p>	
Imidafenacin		
Sugiyama et al. 2017 Japan Case Series N=34	<p>Population: Mean age=60±15yr; Gender: males=29; females=5; Etiology: SCI=34; Time since injury=102±45d; Inclusion criteria: SCI with low cystometric volume and/or detrusor compliance.</p> <p>Intervention: Individuals were administered 0.2mg imidafenacin/d. If cystometric capacity and/or detrusor compliance remained low at first follow-up (4 wk), dosage was escalated to 0.4mg imidafenacin/d. Individuals managed their bladders with transurethral catheters during the treatment period. Outcome measures were assessed at baseline, 4 wk, and 8 wk.</p> <p>Outcome Measures: Bladder capacity; detrusor compliance; maximum detrusor pressure.</p>	<ol style="list-style-type: none"> 1. There was a significant increase in bladder capacity and compliance post-imidafenacin (p=0.002; p=0.012) 2. Imidafenacin had no effect on maximum detrusor pressure (p>0.05).

Note: AIS=ASIA Impairment Scale

Discussion

While there are numerous anticholinergics available for use in overactive bladder, few have been tested in clinical trials for people with SCI and neurogenic detrusor overactivity (NDO). Only those that have been trialed for SCI-related neurogenic bladder are presented here.

Propiverine

Propiverine has both anticholinergic and calcium channel blocking properties, thus decreasing involuntary smooth muscle contractions. In the SCI population, a double-blind, placebo-controlled, randomized, multicentre (n=124 with 113 completers)

study, utilizing 15 mg three times daily administration of propiverine over two weeks yielded significant improvement in SCI detrusor hyperreflexia represented by increased maximal cystometric bladder capacity (Stohrer et al. 1999). A subsequent increase in residual urine volume was found (a goal in those on intermittent catheterizations) and side effects (primarily dry mouth) were considered tolerable.

Two propiverine hydrochloride formulations, extended-release versus immediate-release (ER: 45 mg daily versus IR 15 mg thrice daily), proved to be equally effective in 65 people with SCI with proven NDO. This double-blind, randomized, multicenter study (Stohrer et al. 2013) also presented data to demonstrate higher continence and tolerance rates for the ER formulation.

Solifenacin

Another long-acting option is daily oral solifenacin. Solifenacin is an oral antimuscarinic drug that is thought to selectively bind to the bladder's muscarinic (M)₃ receptors responsible for contraction of the detrusor. Krebs et al. (2013) conducted a retrospective analysis of case histories and urodynamic data of 35 SCI individuals over a four year span. Data supporting significantly improved bladder capacity, detrusor compliance, reflex volume and maximum detrusor pressure were reported after an average of 13.1 months of solifenacin treatment.

Oxybutynin

Oxybutynin is an anticholinergic agent used extensively and clinically to treat overactive bladder, yet relatively few studies have been performed in the neurogenic bladder population with this medication. Longer acting versions of oxybutynin in forms have sparked renewed research interest with the hopes of reducing side effects observed with the short acting oxybutynin. In a small (n=10) pre-post trial, O'Leary et al. (2003) showed that controlled-release oxybutynin was efficacious for individuals with SCI and detrusor hyperreflexia as reflected by significantly increased bladder volumes with a decrease in mean number of voids per 24 hours. However, post-void residual volumes, nocturia, and weekly incontinence episodes did not change significantly. In a larger 2016 pre-post trial (Ersoz et al 2016, n=27), sub-acute individuals were able to reduce ICs from 6 to 4 per day, by achieving a maximum cystometric capacity of 400 ml or more with compliant oxybutynin administration. However, Hadiji et al (2014, pre-post study, n=231) caution that oxybutynin (no difference between use as mono- or bi-therapy) only allows full continence in about 32% of individuals despite being effective in raising maximum bladder capacity and decreasing involuntary detrusor contractions.

Oxybutynin use is unfortunately accompanied by many dose limiting side effects (e.g. dry mouth) (del Popolo G et al 2012) and therefore non-pharmacological treatments for NDO are an area of active interest. Surface percutaneous tibial nerve stimulation of L4-S3 fibres (originating from the same spinal segments as bladder and pelvic floor innervations) has been shown to be as effective as oxybutynin for the treatment of NDO but without the aforementioned side effects. (Chen G et al 2015; RCT, N=100). For individuals who are refractory to oxybutynin or opposed to

pharmacological treatments, twice weekly neuromodulatory sessions (30 minutes each) managed at home may be a feasible alternative to pharmacological treatment of NDO.

Tolterodine

Tolterodine, a newer anticholinergic that causes less dry mouth compared to oxybutynin, has also been shown to be efficacious for the treatment of neurogenic bladder dysfunction. In a randomized controlled trial (RCT), use of tolterodine was shown to result in significantly increased IC volumes ($p < 0.0005$) and reduced incontinence ($p < 0.001$) but was similar in its effects on cystometric bladder capacity compared to placebo (Ethans et al. 2004). This trial was small, and thus at risk for type 2 error. As part of the eligibility criteria for this study, subjects were using oxybutynin and IC prior to a 4-day washout in advance of randomization to the tolterodine versus placebo study. This design allowed for a comparison between oxybutynin and tolterodine. The two drugs were found to be equivalent with respect to effectiveness as reflected in IC volumes, degree of incontinence and bladder capacity. Horstmann (2006) found that compared to baseline, tolterodine improved reflex volumes, cystometric capacity, and maximum detrusor pressures. Although this study also evaluated trospium chloride, the two medications were only evaluated in a pre-post manner rather than a head to head comparison.

Trospium Chloride

Trospium chloride (TCL; an anticholinergic medication that is reported not to cross the blood-brain barrier) has only recently been approved in North America for use in overactive bladder, where as it has been available in Europe for many years. The efficacy of TCL (20mg bid) for individuals with SCI and detrusor hyperreflexia was confirmed by Stohrer et al. (1991) in a RCT. Highly significant ($p < 0.001$) responses were found in favour of TCL versus placebo for increased bladder capacity and compliance, and decreased bladder pressure with few side effects. No effect was reported for flow rate and residual urine volumes. Horstmann et al. (2006) found that TCL improved reflex volume, cystometric capacity, and maximum detrusor pressure. Presumably the psychometrically measured cognitive changes seen with medications such as oxybutynin are not seen with TCL as it does not cross the blood brain barrier. However, psychometric testing has not been examined specifically in persons with SCI taking TCL.

In a randomized, double-blind, multicenter trial directly comparing TCL (20 mg bid) versus oxybutynin (5 mg tid) for 2 weeks in the treatment of detrusor hyperreflexia in 95 individuals with SCI, objective urodynamic parameters (maximum bladder capacity and maximum voiding detrusor pressure during micturition) showed that the two medications were equally efficacious (Madersbacher et al. 1995). However, TCL emerged superior with respect to fewer reports of severe dry mouth (4% versus 23%) and subsequently fewer individuals treated with TCL withdrew from the study (6% versus 16%).

Comparisons

Additional investigations have compared the relative efficacy and presence of side effects associated with various anticholinergic drugs (Amend et al. 2008; Stohrer et al. 2007). Stohrer et al. (2007) showed similar efficacy in a comparative study of propiverine versus oxybutynin that employed a double-blind, RCT design. Both treatments significantly improved bladder capacity and reduced maximum detrusor pressure although fewer side effects (most notably dry mouth) were evident in subjects in the propiverine group. Of note, Amend et al. (2008) examined 3 combinations of anti-cholinergics in 27 subjects whose symptoms of incontinence did not completely resolve with an initial treatment option – even with dosages doubled from manufacturer recommendations (i.e., Horstmann et al. 2006). These authors added a second anti-cholinergic medication such that participants took either: 1) tolterodine / oxybutynin, 2) TCL/tolterodine or 3) oxybutynin /TCL and demonstrated that 85% of individuals were treated successfully with a combination treatment option, despite having mostly unsatisfactory outcomes with a single medication. Each initial medication was maintained at the high dose (i.e., double dose) and there were no clear combinations that were superior to the other in terms of either effectiveness or side effect profile. It should be noted that there is a concern for potential effects on cardiac rhythm when administering doses of combinatorial anti-cholinergics. However, neither study reported conducting an electrocardiogram; therefore concerns for potential cardiac abnormalities in those on combination treatment may need further consideration and investigation.

In addition, Kennelly et al. (2009; n=24) reported that transdermal oxybutynin was effective in increasing the proportion of individuals performing clean IC without leaking, as well as improving various urodynamic measures (e.g., reflex volume, amplitude of detrusor contraction, maximum bladder capacity, residual urine volume) in a pre-post investigation. Along with these positive effects there were, more importantly, fewer side effects than typically reported with oral delivery, even at up to three times the standard dose.

Imidafenacin

Imidafenacin is an anticholinergic that does not target the salivary glands (Sugiyama et al., 2017). Imidafenacin is selective for the bladder and has been reported to a lower incidence of constipation compared to other new anticholinergics (Sugiyama et al., 2017). In a retrospective chart review authors investigated 34 SCI individuals prescribed imidafenacin due to low cystometric volume and/or detrusor compliance. The authors found a significant increase in bladder capacity and compliance, but no effect on maximum detrusor pressure post-treatment (Sugiyama et al., 2017).

Conclusion

There is level 1a evidence (from three RCTs; Stohrer et al. 1999; Stohrer et al. 2007; Stohrer et al. 2013) that supports the use of propiverine in the treatment of detrusor hyperreflexia resulting in significantly improved bladder capacity, with one of these trials showing equivalent results to oxybutynin but fewer side effects, notably dry mouth.

There is level 1b evidence (from a single RCT; Stohrer et al. 2013) that demonstrated superiority for continence and tolerability when propiverine extended-release is compared to immediate release formulations.

There is level 4 evidence (from a single case series; Krebs et al. 2013) suggesting that solifenancin id (10 or 5 mg) is effective in improving bladder capacity, detrusor compliance, reflex volume and maximum detrusor pressure in individuals with neurogenic detrusor overactivity secondary to SCI.

There is level 1b evidence (from a single RCT, Ethans et al. 2004) that supports the use of tolterodine versus placebo to significantly increase intermittent catheterization volumes and decrease incontinence in neurogenic detrusor overactivity.

There is level 2 evidence (from a prospective controlled trial; Ethans et al. 2004) that tolterodine and oxybutynin are equally efficacious in SCI individuals with neurogenic detrusor overactivity except that tolterodine results in less dry mouth.

There is level 1b evidence (from an RCT; Chen et al. 2015) that CIC frequency and total leakage volume per day decreased while catheterization volume increased equivocally with oxybutynin administration or percutaneous tibial nerve stimulation (PTNS) where problematic side effects of oxybutynin were not reported in the PTNS group.

There is level 4 evidence (from pre-post studies; O'Leary et al. 2003; Kennelly et al. 2009; Hadiji et al 2014; Ersoz et al 2016) that supports the potential benefits of oxybutinin administration (oral, controlled-release or transdermal), with transdermal administration resulting in a reduced side effect profile.

There is level 4 evidence (from a prospective controlled trial; Amend et al. 2008) that suggests additional benefits, such as reduced incontinence and increased bladder capacity, from combination treatments of two of oxybutinin, trospium chloride or tolterodine, even in individuals with unsatisfactory outcomes following a trial of one medication.

There is level 1a evidence (from two RCTs; Stohrer et al. 1991; Madersbacher et al. 1995) that supports the use of trospium chloride to increase bladder capacity and compliance, and decrease bladder pressure with very few side effects in individuals with SCI and neurogenic bladder.

Propiverine, oxybutynin, tolterodine, solifenacin, and trospium chloride are efficacious anticholinergic agents for the treatment of neurogenic bladder following SCI.

Combinatorial treatment with 2 of oxybutynin, tolterodine or trospium may be effective for the treatment of neurogenic bladder in individuals with SCI who have not previously responded to one medication.

Tolterodine, propiverine (particularly the extended-release formula), or transdermal oxybutynin likely result in less dry mouth but have similar efficacy to oral oxybutynin in terms of improving neurogenic detrusor overactivity.

4.1.2 Toxin Therapy for SCI-Related Detrusor Overactivity

4.1.2.1 Botulinum Toxin

Botulinum toxin A (BTX-A) has been used for many disorders including strabismus, focal spasticity, hyperhidrosis, cosmetic disorders (wrinkles) and others. BTX-A inhibits muscle contractions by preventing the release of the neurotransmitter acetylcholine from axon endings at the neuromuscular junction. A more recent indication in the USA and Canada is for NDO treatment in individuals with SCI and multiple sclerosis. Although anti-cholinergic medications remain first line therapy for this dysfunction, an advantage of botulinum toxin versus systemic oral medications is that botulinum toxin is injected directly into the detruser, thereby minimizing systemic side effects. There are various types of botulinum toxin available, including several variations of BTX-A. While abobotulinumtoxin (AboBTx) and onabotulinumtoxin (OnaBTx) are both derived from BTX-A, they are important differences and unit values cannot be compared or interchanged. Only OnaBTx is approved for NDO. There are also interesting clinical differences when using botulinum toxin for NDO as opposed to spasticity and other neurological indications. As an example, the effect of injecting into the detruser lasts for 6-12 months, 2-3 times that expected for spasticity. Possible reasons include 1) there is less or no peripheral nerve re-sprouting to reform the neuromuscular junctions in smooth muscle, and 2) there is a secondary mechanism of action comprised of blocking afferent C-fibre activity in the membrane bound vesicles of the afferent pathways and the urothelium in addition to the primary mechanism of blocking synaptic transmission at the neuromuscular junction in the efferent pathway. Blocking afferent C-fibre activity is especially important in NDO where afferent C-fibre overactivity after a spinal cord lesion is thought to be a significant contributor to the overactive reflex pathway.

Table 2 Botulinum Toxin Therapy for SCI-Related Detrusor Overactivity

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
Mehta et al. 2013 Canada Meta-analysis & Systematic Review	Methods: A meta-analysis was conducted to examine the effectiveness of BTX-A on neurogenic detrusor overactivity (NDO) in people	1. Fourteen studies met the inclusion criteria. 2. The average ages of the participants range from 32.5 yr

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
AMSTAR=9 N=14 studies	<p>with SCI. The following databases were searched: MEDLINE, CINAHL, EMBASE and PsycINFO for all relevant articles from 1980 to June 2012. Keywords included: spinal cord injury, paraplegia, quadriplegia, tetraplegia, bladder, detrusor, botulinum toxin, Botox, onabotulinumtoxin, abobotulinumtoxin, and BTX-A. The following inclusion criteria were used:</p> <ol style="list-style-type: none"> 1. BTX-A was injected into the detrusor wall with the aim of improving NDO. Studies with single and multiple injections were included. 2. BTX-A was compared with a placebo or active treatment, or in the absence of a control condition, subjects received BTX-A and were assessed before and after treatment. 3. At least 50% of participants in the study had an SCI, and a minimum of 3 participants had an SCI. 4. Participants were 18 yr or older. <p>Data was analyzed in each of the studies by calculating a standardized mean difference, and a 95% confidence interval for the following outcomes: reflex detrusor volume, bladder capacity, bladder compliance, catheterization frequency, max flow rate, and post-residual volume when applicable; where effect sizes were small (>0.2), moderate (>0.5) or large (>0.8).</p>	<p>to 49.9 yr. Of the 10 studies that did report the number and women in the study, there were a total of 324 men and 196 women. The time since injury ranged from 4.5 to 13.3 yr.</p> <ol style="list-style-type: none"> 3. Ten studies used injections of OnaBTx at 200-300 U in 15-40 sites in the bladder. While four studies used aboBTx injections of 750 or 1000 units into the detrusor wall at 30 to 40 sites. 4. Large effect sizes and significant increases in the outcomes of interest were apparent in reflex volume, bladder capacity, bladder compliance, post residual volume, and a mean decrease in catheterization frequency ($p<0.01$). 5. Rate of incontinence episodes decreased from 23.1% to 1.31% after BTX-A treatment. 6. No significant decreases in max flow rate was observed for those that could void ($p=0.403$).
Karsenty et al. 2008 France Systematic Review AMSTAR=9 N=18 studies	<p>Methods: A MEDLINE and EMBASE search for clinical studies with BTX-A injected into the detrusor of adults with neurogenic detrusor overactivity was performed. Databases were searched from 1993 to March 2007 with the following medical subject heading (MeSH) terms: "Urinary bladder, Neurogenic" and "Botulinum Toxin Type A"; with the following filters: "human", "clinical trial", and "adult, 19+yr".</p>	<ol style="list-style-type: none"> 1. 18 articles were selected. The amount of BTX-A was mostly 300U usually as 30 injections. 2. The majority of studies reported significant clinical improvements (40-80% of individuals became completely dry between clean IC). 3. Improvements in urodynamic parameters were also noted: maximum detrusor pressure was reduced to <40 cmH₂O in the majority of studies. 4. Quality of life increased.

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
		5. There were no major adverse events in the majority of studies.
De Laet and Wyndaele 2005 Belgium Systematic Review AMSTAR=2 N=4 studies	Methods: Authors searched pubmed for adverse events after BTX-A injections for lower urinary tract dysfunction. The following keywords were used: "botulinum toxin", "bladder", "external", "urethral sphincter", "lower urinary tract", "adverse events", "complications" and "general muscle weakness".	Four publications were found reporting adverse events following local injection of BTX-A in the lower urinary tract: 1. Dykstra and Sidi after injecting 5 SCI individuals with detrusor-sphincter dyssynergia; 3/5 experienced generalized upper extremity weakness after initial injections. 2. Del Popolo reported hypostenia in 5/61 individuals that were treated with 300 U of onaBTx or 1000 U of aboBTx at 20-30 different sites in the detrusor muscle. 3. Kuo injected 50-100 U of BTX-A in the external urethral sphincter of 20 individuals, one individual had high fever lasting 2 wk after the injection. 4. In a study conducted by the authors, two cases of general muscle weakness after BTX-A injection were reported.
Denys et al. 2017 France RCT PEDro=6 N=47	Population: Dysport 15: Mean age=41.1±12.1yr; Gender: males=7; females=7; Etiology: SCI=9; Multiple Sclerosis=5. Placebo 15: Mean age=46.5±10.7yr; Gender: males=4; females=2; Etiology: SCI=4; Multiple Sclerosis=2. Dysport 30: Mean age=50.5±11.1yr; Gender: males=4; females=12; Etiology: SCI=7; Multiple Sclerosis=9. Placebo 30: Mean age=40.8±10.6yr; Gender: males=4; females=2; Etiology: SCI=2; Multiple Sclerosis=4. Intervention: Individuals were randomized into one of four groups: Dysport 15 injection sites; Placebo 15 injection sites; Dysport 30 injection sites; Placebo 30 injection sites. Subjects were injected with 750 U of BoNT-A-hemagglutinin complex in either 15 or 30 intradetrusor sites (sparing the trigone). Outcome Measures: Incontinence episode frequency (IEF); Maximum cytometric capacity; maximum	1. Dysport 15 was equally effective as Placebo 15 at altering IEF, reflex volume at first detrusor contraction, and compliance at all time points ($p>0.05$). 2. Dysport 15 was more effective than Placebo 15 at decreasing maximum detrusor pressure, but only at the 42 and 84d follow-ups ($p<0.05$). At the 14d follow-up, both groups were equally effective ($p>0.05$). 3. Dysport 15 was also more effective than Placebo 15 at increasing cystometric capacity, but only at 14 and 84d follow-ups ($p<0.05$). 4. There was no improvement in altering compliance in the Dysport 30 group compared to placebo. 5. Dysport 30 was more effective compared to Placebo 30 at decreasing maximum detrusor pressure and increasing

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
	detrusor pressure; reflex volume at first detrusor contraction; compliance. Outcome measures were assessed at baseline, 14, 42, and 84d follow-ups.	maximum cystometric capacity at 14, 42, and 84d follow-ups ($p<0.05$). 6. Dysport 30 was more effective compared to placebo at increasing reflex volume at first detrusor contraction, but only at 14 and 42d follow-up time points ($p<0.05$).
Huang et al. 2016b China RCT PEDro=8 N=80	Population: UI; Experimental; Mean age: 31.85 yr; Gender: males=24, females=17; ASIA classification: A=29, B=11, C=1; Mean time post-injury: 16.81 mo; Control: Mean age: 33.43 yr; Gender: males=26, females=13; ASIA classification: A=28, B=8, C=3; Mean time post-injury: 17.29 mo. Treatment: Experimental individuals received two injections of Botox (OnaBTX) simultaneously, one into the bladder wall (24 mL, 160U) and one into the bladder trigone (6 mL, 40 U). Control individuals only received the bladder wall injection (24 mL, 160 U). Follow-up took place at 4 wk and 12 wk post-injection. Outcome Measures: Treatment success, Incontinence-Specific-Quality-of-Life Instrument (I-QoL), vesicoureteral reflux (VUR), bladder compliance (BC), detrusor leak point pressure (DLPP), UI episodes per 24 h period, complete dryness, voiding volume with combination of catheterization volume and voided volume.	1. 7 subjects experienced mild hematuria and 5 experienced bladder discomfort; none required medication or surgical intervention. 2. No individuals developed VUR after injection. Experimental group had a increase in bladder compliance at 12 wk ($p=0.04$) and a greater improvement in DLPP from baseline to 12 wk ($p=0.01$). 3. Between-subjects measures showed that the experimental group had significantly higher I-QoL scores at both 4 wk ($p=0.04$) and 12 wk ($p=0.02$). Similarly, experimental individuals saw a significant increase in complete dryness (4 wk { $p=0.03$ }, 12 wk { $p=0.01$ }), and voiding volume (4 wk { $p=0.04$ }, 12 wk { $p=0.01$ }) post-injection. UI episodes significantly increased for those in the experimental group at both 4 wk ($p=0.03$), and at 12 wk ($p=0.01$), but decreased overall compared to baselines.
Hui et al. 2016 China RCT PEDro=7 N _{initial} =96; N _{final} =91	Population: SCI NDO, UI; Experimental group: Mean age: 29.83 yr; Gender: males=28, females=19; ASIA classification, A=27, B=12, C=8; Mean time post-injury: 20.04 mo. Control group: Mean age: 28.46 yr; Gender: males=23, females 21; ASIA classification: A=29, B=10, C=5; Mean time post-injury: 19.43 mo. Treatment: Experimental individuals (n=47) received botulinum toxin A (BTX-A) injections, 160 U into the detrusor and a second intratrighonal one of 40 U. Control individuals (n=44) only received a 200 U injection of BTX-	1. No individuals had an occurrence of VUR post-injection. Individuals in the control group demonstrated a significantly stronger decrease for $P_{detmaxIDC}$ ($p=0.04$), V_{FIDC} ($p=0.02$), duration of first detrusor contraction ($p=0.03$), and number of individuals with involuntary detrusor contraction ($p=0.02$). 2. The experimental group did not show as dramatic a decrease in secondary urodynamic parameters as the

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
	<p>A into the detrusor. Follow-up data was collected at 4 wk and 12 wk.</p> <p>Outcome Measures: Incidence of vesicoureteral reflux (VUR), maximum detrusor pressure during first involuntary detrusor contraction ($P_{\text{detmaxIDC}}$), volume at first involuntary detrusor contraction (V_{FIDC}), duration of first DO, incidence of DO, Incontinence-Specific-Quality-of-Life Instrument (I-QoL), UI episodes in 24 hrs, complete dryness.</p>	<p>control group on measures of UI episodes per day (4 wk {$p=0.03$}, 12 wk {$p=0.01$}), voiding volume (4 wk {$p=0.04$}, 12 wk {$p=0.02$}), and I-QoL score (4 wk {$p=0.02$}, 12 wk {$p=0.01$}).</p> <p>Individuals in the experimental group reported higher rates of complete dryness compared to those in the control group both at 4 wk ($p=0.03$) and 12 wk ($p=0.01$).</p>
<p>Chen et al. 2014 Taiwan RCT PEDro=5 N=72</p>	<p>Population: Urinary incontinence; Mean age: 41.5 yr; Gender: males=43, females=29; Level of injury: cervical=31, thoracic=39, lumbar=2; ASIA classification: A=56, B=4, C=6, D=5, E=1; Mean time post-injury: 8.7 yr.</p> <p>Treatment: Individuals were randomly assigned to receive two injections of either 200U or 300U Onabotulinumtoxin-A (OnaBTX) into the detrusor 6 mo apart.</p> <p>Outcome Measures: Quality of life (Urogenital Distress Inventory (UDI-6), Incontinence Impact Questionnaire (IIQ-7), International Prostatic Symptom Score questionnaire); cystometric bladder capacity (CBC), maximum flow rate (Q_{max}), post-void residual (PVR) volume, voided volume, detrusor pressure at maximum flow rate ($P_{\text{det.Qmax}}$)</p>	<ol style="list-style-type: none"> 1. Incontinence severity did not significantly decrease within or between groups over time or as a result of treatment. There were no significant changes on the quality of life score on individual questionnaires or the overall quality of life score within or between groups. 2. Compared to the 300-U group, the 200-U group saw a significant decrease in Q_{max} ($p=0.02$) and Volume ($p=0.028$) from baseline to 12 mo. Both groups showed similar significant increases in CBC ($p<0.05$) and PVR volume ($p<0.05$) when comparing baseline to 12 mo. Both groups showed a similar significant decrease in $P_{\text{det.Qmax}}$ ($p<0.05$) from baseline to 12 mo. There were no significant changes in compliance within or between groups.
<p>Krhut et al. 2012 Czech Republic RCT PEDro=5 N=32</p>	<p>Population: SCI with NDO. Mean age: 32.1 yr (20-55); Gender: males=26, females=6; Level of injury: Cervical=16, Thoracic=14, Lumbar=2; Neurological level: ASIA A=24, B=6, C=2; Time post-injury: Group A=16 to 154 mo (average=58.8), Group B=11 to 276 mo (average=60.7).</p> <p>Intervention: Individuals received either 300U onabTX (30 injections =1 mL each) into the intradetrusor (Group A) or suburothelial (Group B).</p> <p>Outcome Measures: Frequency of urinary catheterization, incontinence episodes, Catheterized volume (Void Volume (VV)), Cystometric capacity</p>	<ol style="list-style-type: none"> 1. The number of individuals requesting repeat treatment greater in Group A (64%) than Group B (89%). 2. The following parameters decreased post-intervention in both groups, although there was no significant different between groups: bladder catheterizations ($p=0.331$), incontinence episodes ($p=0.492$), and P_{detF} ($p=0.568$). 3. The following parameters increased post-intervention in both groups, although there was no significant different

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
	(CBC), Volume at first involuntary detrusor contraction (Vol at FC), Maximal detrusor pressure during filling (p_{detF}), Detrusor compliance. Urodynamics measured at baseline and 3 mo post-treatment.	<p>between groups: VV ($p=0.254$), CBC ($p=0.314$), and Vo at FC ($p=0.482$).</p> <ol style="list-style-type: none"> Detrusor compliance increased in both groups but significantly greater in group A compared to group B ($p=0.021$). One individual from Group A had a treatment-related adverse effect (loss of muscle strength for 7 d) which resolved completely.
Herschorn et al. 2011 Canada RCT PEDro=10 N=57	<p>Population: Mean age: 42.8 yr (range 32-50); Gender: males=34, females=23. All individuals had NDO secondary to SCI (N=38) or MS (N=19).</p> <p>Intervention: Individuals received 1 intradetrusor injection cycle (30 injection sites sparing trigone) of 300U (N=28) of onaBTX (diluted in 30ml of saline), or saline placebo (N=29). Baseline - 3-d voiding diary and multichannel urodynamics. Wk 1, 3 and 4 – telephone followups. wk 6, 24 and 36.</p> <p>Outcome Measures: Urinary incontinence (UI), detrusor volume at filling, maximum cystometric capacity (CBC), complete continence, maximum detrusor pressure during filling; (P_{detF}), adverse events.</p>	<ol style="list-style-type: none"> Of the 52 subjects who completed to wk 36, 24 individuals per group (N=48) received open label onaBTx and completed the study. The following parameters significantly decreased more in the treatment group than the control group: incontinence episodes ($p<0.001$ at 6, 24, 36 wk), and P_{detF} (6, 24 wk $p<0.001$; 36 wk $p=0.001$). The following parameters significantly decreased more in the treatment group than the control group: detrusor volume at filling (6 wk $p=0.002$, 24 wk $p=0.023$), CBC (6wk $p=0.002$, 24 wk $p=0.031$). Compared to the control group at wk 6, the treatment group had significantly less incontinence episodes when asleep ($p<0.05$) or when physically active or exercising ($p<0.01$). Complete continence was achieved by wk 24 for 10.7% in the treatment group and 0% in the control group. At week 6, 14/21 (67%) of individuals in the onaBTx group resumed antimuscarinics, versus 17/18 (94%) in the placebo group resp. ($p=0.0489$) Adverse events included urinary tract infection, muscle weakness, mild arm weakness, difficult transfers; one individual had an increase in detrusor pressure of >102 cmH₂O.

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
Abdel-Meguid 2010 Saudia Arabia RCT PEDro=10 N=36	<p>Population: SCI individuals: Mean age: 25 yr (range 20-37); Gender: males=34, females=2; Time post-injury: 31 mo (range 10 mo-11 yr).</p> <p>Intervention: Individuals were randomized to receive either 300 U onaBTX injections into the detrusor (detrusor arm, n=18) or 200 U onaBTX injections into the detrusor plus 100 U onaBTX into the trigone (combined arm, n=18).</p> <p>Outcome Measures: Incontinence episodes, complete dryness, maximum detrusor pressure, maximum cystometric capacity, reflex volume, vesicoureteral reflux, and adverse events.</p>	<ol style="list-style-type: none"> 1. All parameters within both treatment groups improved significantly compared to baseline. 2. Between group analysis showed greater improvements for the combined group than detrusor only group for the following parameters: incontinence reduction, complete dryness, and reflex volume ($p<0.001$ for all). 3. There were no significant differences between groups in cystometric capacity ($p<0.22$) or maximum detrusor pressure ($p<0.21$). 4. No individuals showed new or upgraded vesicoureteral reflux or reported significant adverse events.
Ehren et al. 2007 Sweden RCT PEDro=6 N=31	<p>Population: Mean age: 36 yr; Gender: males=17, females=14.</p> <p>Treatment: Participants were randomly selected to receive intravesical injections of either 500 U of aboBTX or placebo. Participants not experiencing any therapeutic effects of the injection were allowed to use a maximum of 2 tablets of tolterodine daily.</p> <p>Outcome Measures: Intake of tolterodine, bladder capacity, maximum detrusor pressure, leakage d. Individuals were followed for 26 wk.</p>	<ol style="list-style-type: none"> 1. Individuals in the placebo group had a significantly higher intake of tolterodine tablets than the aboBTX group ($p=0.003$). 2. Cystometric bladder capacity was significantly higher in the aboBTX group than the placebo group at 6 ($p<0.001$) and 12 wk ($p=0.026$); but not at 26 wk. 3. Maximum bladder pressure was significantly lower in the aboBTX group compared to the placebo group ($p<0.01$). 4. aboBTX group had significantly less leakage than the placebo group ($p<0.01$). 5. No muscular weakness was reported.
Schurch et al. 2007 Switzerland RCT PEDro=5 N=59	<p>Population: Individuals with urinary incontinence caused by neurogenic detrusor overactivity >6 weeks with SCI (n=53) or multiple sclerosis (n=6); individuals were aged >18 yr.</p> <p>Intervention: Individuals were randomized to receive single dose intradetrusor injections of onaBTX at 1) 200U, or 2) 300U, or 3) a placebo.</p> <p>Outcome Measures: Incontinence Quality of Life questionnaire (I-QoL).</p>	<ol style="list-style-type: none"> 1. I-QoL scores were similar for all three treatment groups at baseline; post-treatment, median total I-QoL scores improved in both onaBTX groups but not in the placebo group ($p<0.05$ for both) 2. Twice as many onaBTX recipients compared to placebo recipients achieved a minimally important difference

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
		in total I-QoL score at 2,6,12 and 24 wk.
Schurch et al. 2005 USA RCT PEDro=8 N=59	<p>Population: Mean age: 41 yr; Gender: males=36, females=23; Severity of injury: AIS: A=33, B=10, C=5, D=4, E=1.</p> <p>Intervention: Participants were randomized in a 1:1:1 ratio into one of three groups: 300 U onaBTX, 200 U onaBTX, and placebo. Participants received a single dose into the detrusor.</p> <p>Outcome Measures: Incontinence episodes, maximum cystometric capacity, reflex detrusor volume and maximum detrusor pressure. Subjects were followed up at 2, 6, 12, 18, and 24 wk.</p>	<ol style="list-style-type: none"> Significant decrease was seen in: <ul style="list-style-type: none"> Incontinence episodes for each onaBTX group ($p<0.05$). Maximum detrusor pressure for each onaBTX group ($p<0.023$). Significant increase was seen in: <ul style="list-style-type: none"> Mean maximum cystometric capacity in each onaBTX group ($p<0.020$). Mean reflex detrusor volume at 6 wk in the 300 U onaBTX group and at 24 wk in the 200 U onaBTX group ($p<0.021$).
Chen et al. 2018 Taiwan Prospective Controlled Trial N=36	<p>Population: Experimental group: SCI with urinary incontinence +/-difficulty emptying bladder, +/- intermittent catheterization Mean age=42.7±13.1yr; males=17; females=9; Etiology: complete SCI=20; incomplete SCI=6; Control group: Non-SCI with stress urinary incontinence without urgency frequency Mean age=52.4±10.5 yr; Males=0; females=10; Etiology: Stress urinary incontinence=10);</p> <p>Intervention: Individuals in both groups received 200 U onabotulinumtoxinA injections diluted in 20mL of saline, injected into 40 sites in the detrusor. A urethral catheter was inserted and removed the next morning. Individuals also received broad-spectrum antibiotics for 3d post-intervention.</p> <p>Outcome Measures: Urodynamic parameters including: first sensation of filling (FSF); full sensation (FS); urge sensation (US); compliance; cystometric capacity (CBC), detrusor pressure at Qmax (Pdet); Qmax; post-void residual volume (PVR); voided volume (VV). Urothelial dysfunction parameters and sensory protein expression including: E-cadherin; zonula occludens (ZO-1); Mast cells; terminal deoxynucleotidyl transferase time-point within spinal</p>	<ol style="list-style-type: none"> There were no significant differences in FSF, US, compliance, Qmax, and VV when comparing the experimental group with the control at all time points ($p>0.05$). Pdet decreased and CBC and PVR increased significantly 3mo post- onabotulinumtoxinA injection, but these effects faded at 6mo ($p<0.05$). TUNEL increased significantly in SCI individuals when comparing 3mo to 6mo follow-up post- onabotulinumtoxinA injection ($p=0.047$). E-cadherin and ZO-1 decreased significantly at 3mo compared to baseline in the SCI individuals ($p=0.001$; $p=0.027$). The remaining urothelial dysfunction parameters and sensory protein expression did not change significantly in individuals with SCI ($p>0.05$).

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
	cord injured individuals (TUNEL); muscarinic receptor 2 (M2); muscarinic receptor 3 (M3); β 3-adrenoreceptor (β 3-AR); purinergic receptor (P2X3); inducible nitric oxide (iNOS); epithelial nitric oxide (eNOS). Outcome measures were assessed at baseline, 3mo follow-up, and 6mo follow-up.	
Chen et al. 2016a Taiwan Prospective Controlled Trial N=20	<p>Population: SCI with NDO; Mean age: 48.2 yr; Gender: males=11, females=9; Level of injury: cervical=7, thoracic=11, lumbar=2. Control: Mean age; 54.4 yr; Gender: female=10.</p> <p>Treatment: Individuals with NDO and that were refractory to anti-muscarinic treatment received 4 injections every 6 mo of 10 mL OnabotulinumtoxinA (OnaBTX) into the detrusor. Controls received no intervention.</p> <p>Outcome Measures: Treatment outcome, cystometric capacity (CBC), post-void residual (PVR) volume, maximum flow rate (Q_{max}), detrusor pressure (P_{det.} Q_{max}), volume voided, compliance. Histological measures include E-cadherin and ZO-1 expression, mast cell activation, urothelial cell apoptosis (TUNEL).</p>	<ol style="list-style-type: none"> 1. Satisfactory dryness was reported by 60% of individuals, no severe adverse events occurred after OnaBTX injection, and five individuals had slight hematuria which spontaneously resolved without intervention. 2. CBC and PVR significantly increased six mo after each injection. Q_{max}, P_{det.} Q_{max}, and volume all significantly decreased with treatment. Compliance was non-significant. 3. At baseline, expression of E-cadherin and ZO-1 was significantly lower in SCI individuals compared to controls (p<0.01). SCI individuals showed a significant increase in urothelial cell apoptosis compared to controls at baseline (p<0.047). 4. Six mo after each injection E-cadherin and ZO-1 expression significantly improved compared to baseline, E-cadherin expression was significantly higher at the third injection (p=0.004) compared to baseline. There were no significant differences in mast cell activity or TUNEL expression with treatment compared to baseline.

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
Chen et al. 2016b Taiwan Prospective Controlled N=26	<p>Population: Experimental, NDO; Mean age: 42.7 yr; Gender: males=17, females=9; Level of injury: cervical=12, thoracic=14; Control, urinary stress incontinence; Mean age: 51.4 yr; Gender: females=10.</p> <p>Treatment: Participants with NDO received a 10mL injection of Onabotulinumtoxin-A (OnaBTX) into the detrusor muscle. Participants were evaluated at 3 mo and 6 mo after treatment. Controls received no intervention.</p> <p>Outcome Measures: Treatment success, cystometric bladder capacity (CBC), detrusor pressure, maximum flow (Qmax), post-void residual (PVR), compliance, detrusor overactivity, glomerular filtration rate, and serum creatinine. Histological measures include E-cadherin and ZO-1 expression, mast cell activation, and urothelial cell apoptosis (TUNEL).</p>	<ol style="list-style-type: none"> 1. No severe side effects were reported as a result of OnaBTX injection, 5 participants had slight hematuria which spontaneously resolved without intervention, 6 participants developed UTIs and 7 developed urinary retention. 2. CBC, Qmax, and glomerular filtrate did not significantly change with treatment. Detrusor pressure significantly increased with treatment at 3 mo only ($p<0.001$). PVR significantly increased at both 3 mo ($p<0.001$) and 6 mo ($p=0.033$), compliance demonstrated the same trend at both 3 mo ($p=0.017$), and 6 mo ($p=0.003$), and serum creatinine significantly increased after 6 mo only ($p=0.007$). 3. E-cadherin was significantly lower in participants at baseline compared to controls, post treatment, there was a significant increase both compared to baseline and controls at 3 mo ($p=0.07$) and 6 mo ($p=0.07$). ZO-1 expression was significantly lower in participants compared to controls at baseline and significantly increased compared to baseline at 3 mo ($p=0.05$), but remained significantly lower than controls over time. Mast cell count was significantly higher in individuals compared to controls at all times and there were no significant changes in mast cell activation as a result of treatment. TUNEL expression was significantly higher in participants compared to controls at all times and did not significantly change post-treatment.

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
Anquetil et al. 2016 France Cohort N=30	<p>Population: Detrusor overactivity; Mean age: 41.9 yr; Gender: males=16, females=14; Level of injury: paraplegia=12, tetraplegia=18; Severity of injury: complete=23, incomplete=7; Mean time post-injury: 16.57 yr.</p> <p>Treatment: Participants had received either at least two successive intra detrusor botulinum therapy injections (BTX) or augmentation enterocystoplasty (AC).</p> <p>Outcome Measures: Method of bladder drainage, urinary incontinence, complications, maximum detrusor pressure, low compliance, maximum cystometric bladder capacity, Qualiveen-30.</p>	<ol style="list-style-type: none"> 1. In the BTX group, 12 used clean intermittent self-catheterization, two used clean intermittent catheterization, and zero used indwelling catheterization, while in the AC group, 14 used clean intermittent self-catheterization, one used clean intermittent catheterization, and one used indwelling catheterization. 2. Urinary incontinence occurred more frequently in BTX than AC ($p=0.0187$). 3. Four AC participants had postoperative complications while there were no complications for BTX participants. No significant differences between groups were observed in terms of urinary lower tract infections. 4. Two participants had a high maximum detrusor pressure and one participant had low compliance in the BTX group compared to none in the AC group. 5. Maximum cystometric bladder capacity in BTX group was 418 mL compared to 550 mL in AC group. 6. The mean Qualiveen-30 score was significantly higher in BTX group than in AC group ($p=0.037$).
Chartier-Kastler et al. 2016 USA Case Control N=435	<p>Population: SCI (n=190), MS (n=245).NDO; Mean age: 40.7 yr; Gender: males=67, females=30; MS (n=245).</p> <p>Treatment: Participants received either a 200 U onabotulinumtoxin (BTX) injection into the detrusor, or a placebo injection. Six wk after injection follow-up data was collected.</p> <p>Outcome Measures: Treatment goals (self-identified) such as 'be dry', reduce incontinence' and 'improve bladder control', proportion of participants who achieved their goals, and goal achievement by etiology and use of catheterization.</p>	<ol style="list-style-type: none"> 1. Overall, 62% of participants in the OnaBTX group achieved their goals compared to only 17% in the placebo group. 2. Based on etiology, participants with SCI and MS both reported significantly greater goal achievement with BTX treatment compared to placebo ($p<0.001$). 3. Regardless of catheterization use at baseline, goal achievement was still significantly higher in participants in the BTX group

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
		compared to those in the placebo group ($p<0.001$).
Grosse et al. 2009 Germany Case Control N=56 N _{aboBTx} =28 N _{onaBTx} =28	<p>Population: <i>aboBTx group (n=28):</i> Mean age: 36.8yr; Gender: males=19, females=9; Type of injury: SCI=23, myelomeningocele=3, MS=2; Level of injury: paraplegia=24, tetraplegia=4; Severity of injury: incomplete=13, complete=15; Bladder management type: intermittent catheter=25, reflex voiding=3; <i>OnaBTx group (n=28):</i> Mean age: 37.4yr; Gender: males=22, females=6; Type of injury: SCI=24, myelomeningocele=1, MS=1, central trauma=2; Level of injury: paraplegia=24, tetraplegia=4; Severity of injury: incomplete=12, complete=16; Bladder management type: intermittent catheter=26, reflex voiding=1, indwelling catheter=1.</p> <p>Intervention: Participants were retrospectively divided into two groups: aboBTx group included those who had been previously been treated with aboBTx (500 IU, 750 IU, or 1000 IU); onaBTx group consisted of participants previously treated with onaBTx (300 IU, 200 IU or 400 IU). Both types of injections were into the detrusor. The efficacy of both treatments was assessed.</p> <p>Outcome Measures: Continence volume, medication use, dosage change, repeat injections</p>	<ol style="list-style-type: none"> 1. The aboBTx (469mL) and onaBTx (396mL) groups only differed significantly at 3 mo for the continence volume, $p=0.015$. 2. No significant difference was seen in individuals' medication use or dosage between the two groups. 3. 21 individuals in the aboBTx group had repeat injects when their condition relapsed at about 13 months, while 26 onaBTx group individuals required a repeat injection at an average of 10 months. 4. Treatment failure (reinjection in less than 3 mo) was seen in 5 aboBTx group individuals.
Huang et al. 2016a China Pre-Post N=59	<p>Population: DO and DESD; Mean age: 39.1 yr; Level of injury: cervical=28, thoracic=25, lumbar=6; ASIA classification: A=42, B=14, C=3; Mean time post-injury: 11.74 mo.</p> <p>Treatment: Participants received 200 U Botox (OnaBTX) injections in two areas, 30 mL into the detrusor muscle, and 4 mL into the external urethral</p>	<ol style="list-style-type: none"> 1. Compared to baseline I-QoL scores significantly increased from 32.06 to 62.45 at 12 wk follow-up ($p<0.05$). Overall participants reported satisfaction with the treatment, reporting less autonomic dysreflexia, decreased UI, less

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
	<p>sphincter with a follow-up of 12 wk post-injection.</p> <p>Outcome Measures: Treatment success, Incontinence-Specific Quality-of-Life Instrument (I-QoL), maximum detrusor pressure at first DO and DESD ($P_{\text{detmaxDO-DESD}}$), volume at first DO and DESD ($V_{\text{DO-DESD}}$), maximum urethral closure pressure (MUCP), duration of first DO and DESD, voiding volume, urinary incontinence, and complete dryness.</p>	<p>symptomatic UTI and more complete dryness.</p> <ol style="list-style-type: none"> Significant decreases were seen in $P_{\text{detmaxDO-DESD}}$ ($p<0.05$), MUCP ($p<0.05$), and duration of first DO and DESD ($p<0.05$) post-injection at 12 wk. Voiding volume consistently increased from 2 wk to 12 wk post-injection ($p<0.05$), as did the occurrence of complete dryness ($p<0.05$). Urinary infections significantly decreased with injection from 2 wk to 12 wk ($p<0.05$).
Fougere et al. 2016 Canada Pre-Post N=17	<p>Population: NDO; Mean age: 44 yr; Gender: males=12, females=5; Level of injury: cervical=11, thoracic=6; ASIA classification: A=9, B=5, C=3; Mean time post-injury: 21 yr.</p> <p>Treatment: All participants had confirmed anticholinergic drug resistance and received one cycle of 200 U Onabotulinumtoxin-A (OnaBTX) injections into the detrusor. Baseline, post-injection, and one month post-injection data was examined.</p> <p>Outcome Measures: Quality of life (Health-Related Quality of Life Questionnaire, Incontinence Quality of Life Questionnaire), hemodynamic measures (systolic blood pressure (SBP) and heart rate (HR)) during urodynamic studies (first urge to perform clean intermittent catheterization and maximum volume infused).</p>	<ol style="list-style-type: none"> All subsections of the HR-QoL ($p<0.001$) and the I-QoL ($p=0.001$) questionnaire showed significant improvement post-treatment, overall bladder function was improved post-injection. SBP at first urge to perform CIC ($p<0.001$) and at maximum volume infusion ($p<0.001$) and overall SBP ($p=0.001$) all significantly decreased with botox treatment. Treatment resulted in a 59% decrease in the incidence of autonomic dysreflexia (AD), as well as a 35% decrease in associated symptoms such as goosebumps, chills/tingles, flushing or headache. Following injection both maximum SBP and ΔSBP significantly decreased during bladder related events. No significant changes in HR were seen when examining the effects of treatment on urodynamic parameters.
	<p>Population: Experimental; NDO; Mean age: 46 yr; Gender: males=7, females=5. ASIA classification: A=6, C=2, D=1; Injury etiology: SCI=9, MS=2, Meningomyelocele=1. Control; Mean age: 46 yr; Gender: males=7, females=5.</p> <p>Treatment: NDO individuals (n=12) were given a 300 U intradetrusor injection of onabotulinumtoxinA,</p>	<ol style="list-style-type: none"> At baseline and 1st visit there were no significant differences between the experimental group and control group. On the 3rd visit, the experimental group had significantly higher power ($p=0.046$) as well as a higher resting heart rate ($p=0.004$) than controls at the 4th visit. These were the only

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
	(OnaBTX) and compared to age-matched healthy controls (n=12) Outcome Measures: ECG measures: r-waves, RR intervals and discrete event series (DES), power spectra from DES integral very low frequency (VLF), low frequency (LF), high frequency (HF) ranges, and power. Measures were calculated at baseline, and 3 subsequent visits post-injection.	statistically significant outcomes.
Peyronnet et al. 2016a France Pre-Post N=26	Population: NDO, failed first abobotulinum toxin injection; Mean age: 40.8 yr; Gender: males=11, females=15; ASIA classification: A=9, B=2, C=1, D=1, E=1; Injury etiology: SCI=14, MS=9, SB=2, Myelitis=1; Mean time from onset: 9.4 yr. Treatment: All participants received 2 series of injections, one dose of 300 U of Botox (OnaBTX), and one dose of 750 U of Dysport (abobotulinum toxin) into the detrusor muscle. Participants were evaluated at baseline and 6 wk after injection. Outcome Measures: Mean number of micturition per day, mean number of UI episodes per day, UI between catheterizations, voided volume, volume at first involuntary detrusor contraction, maximum detrusor pressure, maximum cystometric capacity, detrusor over activity.	<ol style="list-style-type: none"> 1. There was a significant reduction in mean number of micturition per day ($p<0.001$), as well as mean UI episodes per day ($p<0.001$) from baseline to 6 wk post-injection. 2. The number of participants experiencing incontinence between catheterizations also significantly decreased with treatment ($p<0.001$). 3. Urodynamic parameters of voided volume ($p<0.001$) as well as maximum cystometric capacity ($p=0.048$) significantly increased with treatment, while max detrusor pressure ($p=0.048$) significantly decreased with treatment from baseline to 6 wk post-injection. 4. Detrusor overactivity was seen to be eliminated in approximately half of the participant population ($p<0.001$) as a result of treatment.
Chen & Kuo 2015 Taiwan Pre-Post N=59	Population: NDO, refractory to anticholinergics; Mean age: 42.1 yr; Gender: males=38, females=21; Level of injury: cervical=26, thoracic=28, lumbar=5; ASIA classification: A=39, B=9, C=5, D=5, E=1; Mean time post-injury: 8.7 yr. Treatment: 4 injection cycle every 6 mo of 20 mL of OnabotulinumtoxinA (OnaBTX) into the bladder wall, with follow-up every 3 mo (Phase I), with the option of progressing to two more injection cycles 6 months apart (Phase II). Outcome Measures: Treatment success, cystometric bladder capacity (CBC), maximum flow rate (Q _{max}),	<ol style="list-style-type: none"> 1. After the first OnaBTX injection 17 of 52 participants did not continue treatment. Twenty participants reported failure to one or repeated injections, 10 had improvement fluctuate after one or repeated injections, and 10 reported no significant improvement. 2. CBC and PVR volumes significantly increased with treatment, P_{det.} Q_{max} had a significant decrease. IDC decreased at 3mo and increased slightly at 6 mo. Q_{max} and voided volume,

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	post-voiding residual volume (PVR), voided volume, involuntary detrusor contractions (IDC), voiding detrusor pressure at Q _{max} (P _{det.} Q _{max}), lower urinary tract symptoms (using Urogenital Distress Inventory short form).	decreased with treatment both at 3 mo and 6 mo. 3. Lower urinary tract symptoms decreased with treatment overall. Moderate and severe incontinence was noted in 74.6% of participants at baseline, which decreased to 25.9% and 44.4% at 3 mo and 6 mo respectively after the fourth injection. However, the overall therapeutic effect of the treatment was seen to decrease after the fourth injection.
Sengoku et al. 2015 Japan Pre-Post N=19	Population: SCI with NDO; Gender: males=13, females=6. Treatment: All participants received 200 U of onabotulinumtoxinA (OnaBTX) injected in to the sub-epithelial bladder. Evaluation took place at baseline and one month post-injection. Outcome Measures: UI frequency, proportion of continence cases, frequency of clean intermittent catheterization, catheterized volume, International Consultation on Incontinence Questionnaire (ICIQ), maximum cystometric capacity, bladder compliance, maximum pressure of DO.	1. UI frequency (p=0.004), and frequency of CIC (p=0.014) significantly decreased with treatment, while proportion of continence cases (p<0.001) and catheterized volume (p=0.003) increased with treatment. 2. ICIQ scores significantly decreased on both parameters of overall score (p<0.001) and interference with everyday life (p<0.001). 3. All cystometric variables significantly changed as a result of treatment. MCC (p<0.001) and bladder compliance (p=0.031) significantly increased, while incidence of DO cases (p=0.016) and max pressure of DO (p=0.002) significantly decreased.
Ge et al. 2015 China Pre-Post N=24	Population: SCI with NDO Mean age: 42.6 yr; Gender: males=19, females=5; Level of injury: cervical=14, thoracic=4, lumbar=6; ASIA classification: A=13, B=3, C=5, D=3. Treatment: All participants received an injection of 300 IU Botulinum toxin type A (BXT-A) into the detrusor muscle and were followed-up at 2, 6, 12, 18 and 24 weeks. Outcome Measures: Urodynamic parameters included maximum cystometric capacity (MCC), reflex detrusor volume (RDV), and maximum detrusor pressure during bladder contraction (MDP) (measures taken at	1. MCC significantly increased with injection at 2 wk (p=0.001), 6 wk (p=0.001), and 24 w (p=0.002) compared to baseline. Both RDV and MDP significantly increased with treatment over 2 wk (p=0.001, p=0.034), 6 wk (p<0.001, p=0.029), and 24 wk (p<0.001, p=0.036) compared to baseline. 2. I-QOL scores increased from 19.7 to 80.3 two wk after injection (p=0.001), indicating that individuals were satisfied/very satisfied with the treatment results. Satisfaction

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	2, 6, and 24 weeks). The Incontinence Quality of Life Questionnaire (I-QOL) was also used to assess quality of life along with self-reported measures of involuntary urine loss frequency, catheterization frequency, and % of individuals completely dry over 24 h.	level was correlated to fewer leakages per day. Involuntary urine loss frequency significantly decreased at 2 wk ($p=0.017$) and was still significantly lower at 24 wk ($p=0.02$) compared to baseline. Catheterization frequency also decreased at 2 wk ($p=0.001$) and remained significantly lower than baseline at 24 wk ($p=0.006$). Percentage of participants completely dry increased from 0% at baseline to 82% at 2 wk and 68% at 24 wk.
Al Taweel et al. 2015 Saudi Arabia Pre-Post N=103	<p>Population: Drug-resistant NDO; Mean age: 29 yr; Gender: males=71, females=32; Level of injury: cervical=10, thoracic=42, lumbar=51.</p> <p>Treatment: Participants received one series of OnabotulinumtoxinA (OnaBTX) injections, totalling 30ml into detrusor muscle.</p> <p>Outcome Measures: Frequency of urge urinary incontinence, maximum cystometric bladder capacity (MCBS), reflex volume (RV), maximum detrusor pressure (MDP), side-effects, antimuscarinic drug consumption, quality of life measured as a visual analogue scale (VAS).</p>	<ol style="list-style-type: none"> 1. Compared to baseline, there was a significant reduction in the number of incontinence episodes after treatment (diary recordings). 2. All urodynamic bladder parameters significantly increased post treatment, MCBS ($p<0.001$), RV ($p<0.001$), and MDP ($p<0.001$). 3. Of the 103 participants, 14 showed poor clinical improvement (nonresponders), 20 participants experienced mild hematuria, and 15 participants experienced urinary tract infections. 4. Before treatment, 89 of 103 participants used anticholinergic drugs. After treatment, 55 remained without anticholinergics. Twenty more were able to reduce their daily requirements. 5. A significant improvement in participant satisfaction was found after treatment, with a mean improvement of three points (VAS). Mean duration of symptomatic improvement was 8 mo, with earliest recurrence of clinical symptoms at 10 wk.
Alvares et al. 2014 Brazil Pre-Post	Population: SCI with incontinence due to NDO refractory to intravesical oxybutynin doses greater or equal	<ol style="list-style-type: none"> 1. After treatment, 24 participants remained continent for more

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
N=34	<p>than 40mg Mean age: 31.2 yr; Gender: males=23, females=11; Level of injury: paraplegia=28, tetraplegia=6; Injury etiology: traumatic=25, non-traumatic=9; Mean time post-injury: 5.9 yr.</p> <p>Treatment: Received one series of Botulinum toxin A injections totalling 30ml into the detrusor muscle.</p> <p>Outcome Measures: Treatment success, reflex volume (RV), maximum detrusor pressure (MDP), bladder compliance, maximum cystometric capacity (MCC), presence of diverticula, anticholinergic drug use.</p>	<p>than 4 mo and were considered successful.</p> <ol style="list-style-type: none"> At 4 mo post-treatment, RV was significantly increased ($p<0.001$), MCC was significantly increased ($p<0.001$), and MDP was significantly decreased ($p<0.001$). Bladder compliance did not significantly change with treatment. Pre-treatment, 24 participants had no diverticula, eight had between 1 and 10, and two had greater than 10. No correlation was found between the presence of diverticula and response to treatment. After four mo follow-up, 20 participants had reduced their dose of anticholinergics, 5 had discontinued use, and 9 had not changed dose.
Chen & Kuo 2013 Taiwan Pre-Post N=59	<p>Population: SCI participants with neurogenic detrusor overactivity and urinary incontinence: Mean age: 42.1 yr (range 22-74); Gender: males=38, females=21; Mean injury duration: 8.7 yr; Level of injury: cervical (n=26), thoracic (n=28), lumbar (n=5); Severity of injury: AIS A=39, B=9, C=5, D=5, E=1.</p> <p>Intervention: Four repeated injections of 200-U of onabTx injected at 20 different sites in the bladder wall every 6 mo.</p> <p>Outcome Measures: Urogenital Distress Inventory 6-item short form (UDI-6).</p>	<ol style="list-style-type: none"> The overall treatment satisfaction rate was 59.3% (35/59 participants), the failure rate was 33.9% (20/59 participants), and the discontinuation rate was 6.8% (4/59 participants). The rate of dryness and mild incontinence as measured by UDI-6 scores improved from 25.4% at baseline to 74% at 3 mo after the fourth injection.
Kuo 2013 Taiwan Pre-Post N=55	<p>Population: Injury etiology: SCI=47, MS=6, myelitis=2; All participants had detrusor sphincter dyssynergia: urinary incontinence (n=13), difficult urination (n=12), mixed urinary incontinence and difficult urination (n=30).</p> <p>Intervention: Participants treated with urethral sphincter injection of 100U of BTX-A (n=33) or detrusor injection of 200U of BTX-A (n=22).</p> <p>Outcome Measures: Urodynamic parameters (cystometric bladder capacity (ml), voiding pressure (cmH₂O), maximum flow rate (ml/s), postvoid residual (PVR, ml), Quality of</p>	<ol style="list-style-type: none"> Urodynamic parameters showed significant improvements in both groups; in the urethral BTX-A group, voiding pressure and PVR decreased, but bladder capacity remain unchanged whereas in the detrusor BTX-A group, bladder capacity and PVR increased, while voiding pressure and maximum flow rate decreased and detrusor overactivity disappeared in 50% of the participants.

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	life (QoL) via UDI-6 and IIIQ-7; satisfaction of treatment.	<ol style="list-style-type: none"> 2. Satisfaction post-treatment was perceived in 60.6% of the urethral BTX-A group and 77.3% of the detrusor BTX-A group. 3. For the urethral BTX-A group QoL, there was significant improvements in IIIQ-7 scores, but no significant change in UDI-6 scores whereas for the detrusor BTX-A group both IIIQ-7 and UDI-6 scores showed significant improvement. 4. The changes of IIIQ-7 and UDI-6 in the detrusor BTX-A group were significantly greater than those in the urethral BTX-A group. 5. Major causes of dissatisfaction with treatment were increased incontinence grade (n=16, 48.5%) and increased urgency (n=5, 15.2%) for the urethral group and increased PVR (n=11, 50%), and difficulty urinating (n=11, 50%) for the detrusor group.
Hikita et al. 2013 Japan Pre-Post N=11	<p>Population: Participants with NDO as a result of SCI or multiple sclerosis: Mean age: 48.8 yr (range 23-75 yr); Gender: males=5, females=6.</p> <p>Intervention: 300 U intradetrusor onabTx injections.</p> <p>Outcome Measures: King's Health Questionnaire (KHQ); maximum cystometric capacity; bladder compliance; incontinence episodes.</p>	<ol style="list-style-type: none"> 1. There were significant reductions in eight of the nine KHQ scores at the 8 wk follow-up. 2. The mean maximum cystometric capacity increased significantly in all participants at 8 wk follow-up (p<0.001). 3. Bladder compliance at maximum cystometric capacity also increased significantly in all participants at 8 weeks from baseline (p<0.001). 4. The number of incontinence episodes/d decreased significantly at the 8 wk follow-up (p<0.001). 5. The treatment stopped working at a mean of 7.15 mo post-treatment.
Chen et al. 2011 Taiwan Pre-Post N=38	<p>Population: Individuals with chronic suprasacral SCI with neurogenic detrusor overactivity or detrusor sphincter dyssynergia: Mean age: 40.1 yr (range 20-72); Gender: males=17, females=21; Median duration of SCI: 10.3 yr (range 1-35).</p>	<ol style="list-style-type: none"> 1. A satisfactory response to treatment was found in 23 participants (60%). 2. Significant increases were found in UDI-6 scores, QoL, cystometric bladder capacity and post-void residual, post-

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
	<p>Intervention: 200U of Botulinum Toxin A injected into 40 detrusor sites. A repeat of 300U was given when participants felt the therapeutic effects of the first 200U injection wore off. The time gap between the two injections was 6 mo.</p> <p>Outcome Measures: Urogenital Distress Inventory 6-item short form (UDI-6) questionnaire; QoL index; detrusor pressure at maximum flow rate (Pdet.Qmax); cystometric bladder capacity; post-void residual</p>	<p>treatment at 3 and 6 month follow-up.</p> <ol style="list-style-type: none"> 3. Pdet.Qmax significantly decreased post-treatment. 4. Neurogenic detrusor overactivity disappeared in 10 participants (23%) post-treatment. 5. Participants with a high baseline Pdet.Qmax (>40 cmH₂O) had significantly greater reductions in detrusor pressures than participants with a lower baseline Pdet.Qmax post-treatment at 3 and 6 month follow-up (p<0.001, p=0.007).
Chen & Liao 2011 China Pre-Post N=108	<p>Population: SCI participants with NDO: Mean age: 40.1 yr (range 16-78); Gender: males=81, females=27; Level of injury: C=29, T=58, L=21; Injury severity: complete=85, incomplete=23.</p> <p>Intervention: 300 IU of Botulinum Toxin A injected cystoscopically into the detrusor muscle at 30 different sites.</p> <p>Outcome Measures: Continence, quality of life (QoL), urodynamic parameters (mean cystometric capacity, mean reflux volume, mean voiding pressure).</p>	<ol style="list-style-type: none"> 1. 80 out of the total participant population were incontinent pre-treatment, post-treatment 51 (63.75%) became continent. 29 of the remaining incontinent individuals (36.25%) had a reduced degree of urinary incontinence post-treatment. 2. Pre-treatment 80 participants used anti-cholinergics daily, post-treatment 43 (53.75%) of participants stopped using anticholinergics, while an additional 28 (35%) reduced their daily requirement. 3. Both mean cystometric capacity and mean reflux volume increased significant (p<0.05). 4. Mean voiding pressure decreased QoL of life significant increased post-treatment (p<0.001).
Kuo & Liu 2011 Taiwan Pre-Post N=33	<p>Population: SCI participants all with detrusor sphincter dyssynergia: Mean age: 37 yr (range 2-23); Level of injury: C=7, T=15, L/S=11; ASIA impairment: A=19, B=10, C=4.</p> <p>Intervention: Repeated detrusor 200U onabTX injections repeated every 6 mo up to 4 times.</p> <p>Outcome Measures: Incontinence grade, mean bladder capacity, mean detrusor pressure, mean glomerular filtration rate (GFR), end-filling</p>	<ol style="list-style-type: none"> 1. 30/33 (90.9%) of participants reported improvements in incontinence, whether it was an improvement in their incontinence grade (n=18) or they became completely dry (n=12) following initial and subsequent onabTX injections. 2. UDI-6, IQ-7, and QoL indices significantly improved at all-time points, improvements

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	intravesical pressure, bladder compliance, frequency of clean intermittent catheterization (IC), Quality of Life (Urogenital Distress Inventory 6-item short form (UDI-6), Incontinence Impact Questionnaire 7-item short form (IIQ-7) and self-assessed QoL indices).	were cumulative and persistent following multiple injections. 3. Mean bladder capacity increased significantly (207ml to 412ml); mean detrusor pressure decreased significantly (39.8 cmH ₂ O to 20.6 cmH ₂ O) post-treatment (all p<0.05). 4. Bladder compliance also increased significantly (26.9 versus 40.1, p=0.035). 5. Frequency of IC decreased from 6.5 to 4.3 times per d (p<0.001) for all participants post-treatment. 6. A significant reduction in GFR was noted in participants with bladder compliance that increased by<10 cmH ₂ O (p=0.002), and in participants with detrusor pressure<10 cmH ₂ O post-treatment (p=0.036).
Wefer et al. 2010 Germany Pre-Post N=214	Population: Individuals with SCI (81%), myelomeningocele (14%), and MS (5%) all with NDO: Mean age: 38 yr; Gender: males=145, females=69. Intervention: Intravesical botulinum toxin A Outcome Measures: Maximum detrusor pressure, maximum cystometric capacity, detrusor compliance, incontinence episodes, urinary tract infections, incontinence aids	1. The following urodynamic parameters increased significantly following treatment: maximum detrusor pressure (p=0.004), maximum cystometric capacity (p=0.002), and detrusor compliance (p=0.0001). 2. The following decreased significantly post-treatment compared with baseline: urinary tract infections (68%-28%, p<0.05), incontinence episodes (63%-33%, p<0.05), and incontinence aids (58%-28%, p<0.05)
Alvares et al. 2010 Brazil Pre-Post N=22	Population: Individuals with SCI all with neurogenic incontinence: Mean age: 33.6 yr (range 13-61); Gender: males=19, females=3; Level of impairment: paraplegic=16, tetraplegic=6. Intervention: Botulinum-A-Toxin injections into the detrusor, sparing the trigone. Outcome Measures: maximum cystometric capacity, bladder reflex volume, maximum detrusor pressure, bladder compliance, and continence.	1. Maximum cystometric capacity (219 ml to 404 ml, p=0.01) and bladder reflex volume (175ml to 312ml, p=0.001) both increased significantly post-treatment. 2. Bladder compliance (30.6 ml/cm to 22.2 ml/cm, p=0.067) and maximum detrusor pressure (78 cmH ₂ O to 49 cmH ₂ O) both decreased post-treatment. 3. 13 participants (59%) achieved continence, however only 9

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
		participants (41%) remained continent at the 6-months followup.
Giannantoni et al. 2009 Italy Pre-Post N=17	<p>Population: SCI, NDO; Mean age: 39.7yr; Gender: Males=11, Female=6; Severity of injury: AIS A=11, B=6; Levels of injury : T1-2=1, T4-5=3, T9-10=2, T11-12=7; C=4</p> <p>Intervention: Participants who previously received intradetrusor BTX for NDO were followed up after about 6 yr.</p> <p>Outcome Measures: Number of catheterizations; number of incontinence episodes, UDC first volume, UDC maximum pressure, maximum cystometric capacity, quality of life (QoL), urinary tract infections (UTIs) were measured at baseline, 4 mo, 1 yr, 3 yr and 6 yr follow ups.</p>	<ol style="list-style-type: none"> 1. A significant decrease was seen in daily incontinence episodes and mean catheterization 4 months post treatment ($p<0.001$). 2. Improvement in all outcomes were seen at the 6 yr follow-up: <ul style="list-style-type: none"> • Number of catheterizations/d, $p=0.01$ • Number of incontinence episodes/d, $p=0.01$ • UDC first volume, $p=0.001$ • UDC maximum pressure, $p=0.01$ • Maximum cystometric capacity, $p=0.001$ • UTIs/yr=0.001 • Mean QoL index increased significantly at 3 yr and 6 yr follow ups ($p<0.001$).
Hori et al. 2009 UK Pre-Post N=72	<p>Population: Mean age: 45.4 yr; Gender: males=43, females=29</p> <p>Intervention: Individuals with SCI who received intradetrusor aboBTx injections previously were evaluated for overall treatment satisfaction</p> <p>Outcome Measures: Satisfaction.</p>	<ol style="list-style-type: none"> 1. 48 participants previously receiving aboBTx injection for NDO remained on the treatment, while 24 discontinued treatment due to its ineffectiveness. 2. Decrease in dosage from 1000 IU to 750 IU resulted in a halt in episodes of muscular weakness in participants previously presenting. 3. 36-68 participants were satisfied or very satisfied with aboBTx treatments with a mean satisfaction score of 6.2. 4. Younger participants were more likely to consider a permanent surgical solution than older participants ($p=0.02$).
Del Popolo et al. 2008 Italy Pre-Post N=199	<p>Population: SCI participants with NDO: Mean age: 42.5 yr (range 18-74); Mean follow-up: 48 mo (range 16-91).</p> <p>Intervention: Repeated intradetrusor injections of aboBTxA at doses of 1000, 750, 500 U.</p> <p>Outcome measures: Incontinence measured by an incontinence episode frequency (IEF) test, maximum cystometric bladder capacity (MCBC),</p>	<ol style="list-style-type: none"> 1. There was no significant difference in the clinical efficacy duration between treatment doses ($p=0.5274$). 2. MCBC, RV, and BC improved significantly after treatment compared with baseline values ($p<0.001$), and there were no significant changes in these

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	reflex volume (RV), bladder compliance (BC), number of pads/condoms, antimuscarinic drug consumption, short and long term side-effects, quality of life (QoL) measured with visual analogue scale (VAS).	<p>parameters after retreatment ($p>0.05$).</p> <ol style="list-style-type: none"> There was a significant improvement in participant satisfaction and QoL after each retreatment as expressed on the VAS ($p<0.001$). There was a significant reduction in IEF scores and pads/condom use in the first 4 weeks after each treatment ($p<0.0001$).
Kuo 2008 Taiwan Pre-Post N=50	<p>Population: Detrusor sphincter dyssynergia or detrusor overactivity from SCI=43, MS=2, transverse myelitis=5. Median age: 43 yr (range 25-67); Gender: male=32, female=18; Injury etiology: SCI=43, MS=2, transverse myelitis=5; all participants had urinary tract dysfunction (detrusor sphincter dyssynergia or detrusor overactivity); Level of injury: cervical (n=7), thoracic (n=28), lumbar (n=8); Median duration of SCI: 4.5 yr (range 2-25 yr).</p> <p>Intervention: 200 U of onaBTx into the detrusor</p> <p>Outcome Measures: Postvoid residual volume (PVR); Cystometric capacity; detrusor pressure at maximal flow rate (Pdet Qmax); Quality of life (Urogenital Distress Inventory 6-item short form (UDI-6), Incontinence Impact Questionnaire 7-item short form (IIQ-7)).</p>	<ol style="list-style-type: none"> 78% of participants reported treatment satisfaction; where decreases in incontinence grade and urgency episodes contributed the most to satisfaction. Maximal bladder capacity increased significantly after treatment (221ml to 432 ml, $p=0.000$). PdetQmax decreased significantly after treatment (43.5cmH2O to 12.6 cmH2O). PVR increased significantly after treatment (121ml to 325ml, $p=0.000$). Individuals had significant improvement in QoL after treatment (UDI-6: 11.7 versus 4.1, $p=0.01$, IIQ-7: 16.3 versus 11.7, $p=0.03$). Factors that contributed to dissatisfaction included: increased difficulty with urination and need for catheterization.
Mascarenhas et al. 2008 Brazil Pre-Post N=21	<p>Population: Mean age: 35.4 yr (range; 15-78 yr); Gender: male=10, female=11. Injury etiology: SCI=12; viral myelitis=8, MS=1 with neurogenic urinary dysfunction:</p> <p>Intervention: 300U of onaBTx in the trigone on the antireflux mechanism.</p> <p>Outcome Measures: Incontinence (vesicoureteral reflex), cystometric capacity, reflex volume, maximum detrusor pressure.</p>	<ol style="list-style-type: none"> 20/21 (95.2%) participants had no vesicoureteral reflex post-treatment (9 (42.8%) remained completely dry, 11 (52.4%) had significant improvement with occasional leaks). Significant increases from baseline were noted in both cystometric capacity (271.1ml to 390.1 ml, $p=0.002$) and reflex volume (241ml to 323.1 ml, $p=0.02$). Maximum detrusor pressure was significantly reduced post-

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		treatment (66.1 cmH ₂ O to 38.5 cmH ₂ O, p<0.001).
Reitz et al. 2007 France Pre-Post N=20	<p>Population: Median age: 41.1 yr (IQR: 22.2-67.5); Gender: male=13, female=7; Injury etiology: SCI paraplegia=15, tetraplegia=1, non-traumatic SCI=2, MS=2; all individuals had NDO.</p> <p>Intervention: Five intradetrusor injections of 300 U of onaBTx injected into 30 different sites.</p> <p>Outcome Measures: Continence, reflex volume, maximum cystometric capacity, maximum detrusor pressure, median compliance.</p>	<ol style="list-style-type: none"> 1. Continence improved significantly after the first injection and remained consistently improved after repeat injections. 2. The median reflex volume increased significantly (median values: 200ml to 440-500ml). 3. The presence of neurogenic detrusor overactivity decreased significantly by 60-75%. 4. Maximum cystometric capacity increased significantly 2,3-fold. 5. Maximum detrusor pressure decreased significantly (70 cmH₂O to 20 cmH₂O). 6. Median compliance at baseline did not change significantly.
Tow et al. 2007 Singapore Pre-Post N=15	<p>Population: Mean age: 49.9 yr; Gender: males=10, females=5; Level of injury: paraplegic=6; tetraplegic=9; Severity of injury: complete=11, incomplete=4; Mean follow-up time=7.1 yr.</p> <p>Intervention: 300 units of onaBTx diluted in 30mL of normal saline solution. 30 injections of 1 ml each were given intramuscularly into the detrusor, sparing the trigone. Participants were asked to reduce anticholinergic drugs after treatment.</p> <p>Outcome Measures: Mean number of leakages, maximal catheterizable volume, catheterisation frequency, means reflex volume, mean cystometric bladder capacity, maximal detrusor pressure, and mean duration of contraction. A post-treatment assessment was conducted 6 and 26 weeks after injection and a 3 d voiding diary was kept at 2 weeks and 6 weeks.</p>	<ol style="list-style-type: none"> 1. Mean number of leakages decreased significantly at 6 and 26 weeks post-injection (p<0.05). Catheterization frequency was significantly reduced 6 weeks post-injections (p=0.029) but not 26 weeks and 39 weeks post-injection. 2. Maximal catheterized volume increased at 6 weeks (p=0.003), 26 weeks (p=0.006), and 39 weeks (p=0.0296) post injection. 3. Mean reflex volume improved 6 weeks (p=0.0019) and 26 weeks (p=0.0172) post-injection. 4. Mean cystometric bladder capacity improved at 6 week post-injection (P=0.00007) and at 26 weeks post-injection (p=0.0117). 5. Maximal detrusor pressure decreased at 6 weeks (p=0.00007) and 26 weeks (p=0.0117) post-injection. 6. The duration of contraction showed no significant difference from pre-injection to 6 and 26 weeks post-injection.
Karsenty et al. 2006 France	<p>Population: Injury etiology: SCI=16, MS=1, with NDO and incontinence.</p>	<ol style="list-style-type: none"> 1. The mean number of injections per participant was 5.4 injections, no systemic side

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Pre-Post N=17	<p>Intervention: Repeated injections of 300 U of onaBTx injected into the detrusor muscle at 30 sites.</p> <p>Outcome Measures: Incontinence episodes, maximal cystometric bladder capacity, reflex volume, maximal detrusor pressure, compliance.</p>	<p>effects were observed after any of the total 91 injections.</p> <ol style="list-style-type: none"> The mean number of incontinence episodes/d decreased from 2.6 at baseline to 0 after the first injection, and remained at 0 after the participants' last injection. Maximal cystometric bladder capacity increased significantly after the first injection from baseline (mean capacity: 348.8ml to 499.1ml, $p<0.0002$). Repeated injections did not induce greater increases in the maximal cystometric bladder capacity than after the first injection ($p=0.06$). A significant decrease in maximal detrusor pressure after treatment was noted (75.5cm to 28.8cm, $p<0.0001$). The reflex volume increased significantly from baseline after the first injection (205.9ml to 351.2ml, $p<0.0005$). No difference in compliance was reported from baseline to the first or last injection.
Patki et al. 2006 UK Pre-Post N=37	<p>Population: Mean age: 39.4yr; Gender: males=24, females=14; Level of injury: C=10, T=24, L=3; Severity of injury: complete=25, incomplete=12</p> <p>Intervention: Individuals with SCI and drug resistant NDO were administered 1000 U aboBTx into the detrusor muscle and followed.</p> <p>Outcome Measures: Maximum detrusor pressure (MDP), maximum cystometric capacity (MCC), incontinence, QoL.</p>	<ol style="list-style-type: none"> Significant increase in mean MCC ($p<0.001$) was seen post aboBTx injection. MDP decreased significantly post injection ($p<0.001$). 3 months post injection, 28 participants had no unstable contractions. 26 participants previously incontinent were continent post injection. QoL questionnaire showed favorable response towards aboBTx injection in 32 participants. Symptoms began to recur at 8 weeks to 3 months.
Kuo et al. 2006 Taiwan Pre-Post N=24	<p>Population: Spinal Cord Lesions (SCL) Mean Age: 38.6yr; Gender: males=11, females=1; CVA Mean Age: 72.4yr; Gender: males=6, females=6</p> <p>Intervention: Participants with neurogenic detrusor overactivity were administered suburothelial onaBTx</p>	<ol style="list-style-type: none"> 4 individuals with SCL, without prior history of using ICC, had urinary retention in the 1st post operative week. Voiding pressure decreased significantly at 1 month compared to baseline in

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
	<p>injection (200U) and assessed for efficacy.</p> <p>Outcome Measures: Urinary retention, voiding pressure, bladder capacity, PVR, incontinence.</p>	<p>participants with a SCL (p=0.002).</p> <ol style="list-style-type: none"> From 1 month to 3 month followup an increase was seen in <ul style="list-style-type: none"> IDC volume Bladder capacity PVR From baseline to 3 month follow up: <ul style="list-style-type: none"> A decrease in incontinence grade was seen An increase in grade of difficulty urinating was seen. 22 participants with SCL reported successful results at 3 months.
<p>Klaphajone et al. 2005 Thailand Pre-Post N=10</p>	<p>Population: Mean age: 32.5yr; Gender: males=6, females=4; Level of injury: C=1, T=9; Severity of injury: AIS A=7, B=2, C=1</p> <p>Intervention: Individuals with SCI and neurogenic detrusor overactivity were injected with 300 U onaBTx into the detrusor muscle.</p> <p>Outcome Measures: Bladder compliance, functional bladder capacity, volume at first reflex, detrusor contraction, adverse events.</p>	<ol style="list-style-type: none"> At 6 weeks post injection, significant increase was seen in mean bladder compliance (p=0.012), mean functional bladder capacity (p=0.008) and mean volume at first reflex (p=0.045). Mean maximum detrusor contraction decreased significantly (p<0.001) 6 weeks post injection. These effects lasted up till 16 weeks, with levels returning to baseline by week 36. No adverse effects were seen.
<p>Hajebrahimi et al. 2005 Canada Pre-Post N=10</p>	<p>Population: Mean age: 41yr; Gender: males=6, females=4; Level of injury: tetraplegia=3, paraplegia=7; Severity of injury: complete=6, incomplete=4: AIS A=6, B=2, C=2.</p> <p>Intervention: Individuals with SCI and detrusor overactivity who failed to respond to anticholinergic medications were administered 400 U onaBTx injections into the bladder and followed.</p> <p>Outcome Measures: Reflex capacity, MDP, satisfaction.</p>	<ol style="list-style-type: none"> An increase of 63.08% was seen in average reflex capacity post injection, p<0.02. A decrease in MDP of 15.52% was seen post injection however, this was not significant. Participants reported 90% satisfaction rate.
<p>Bagi & Biering-Sorensen 2004 Denmark Pre-Post N=15</p>	<p>Population: Mean age: 32 yr (range 24-67); Gender: males=12, females=3; Mean time with SCI=9 yr; Level of injury=C5-L1.</p> <p>Intervention: 300 IU of Botulinum Toxin A injected cystoscopically into</p>	<ol style="list-style-type: none"> 13 out of 15 participants (87%) reported continence post-treatment and the volume of leakage was significantly reduced in the 2 incontinent participants.

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
	the detrusor muscle, excluding the trigone region. Outcome Measures: Continence, maximum detrusor pressure, maximum volume at a detrusor pressure of <40 cmH ₂ O, maximum bladder capacity.	<ol style="list-style-type: none"> 2. In all participants; maximum detrusor pressure was significantly reduced ($p<0.0005$) and the maximum volume at a detrusor pressure of <40 cmH₂O was significantly increased ($p<0.0005$). 3. Maximum bladder capacity was increased but the increase was not significant compared to baseline. 4. Participants remained continent post-treatment at a median of 7 months (range 4-12 months).
Schurch et al. 2000 Switzerland Pre-Post N _{initial} =21; N _{final} =19	Population: SCI: Age range 15-59 yr; Gender: males=14, females=7. Intervention: Outindividual intradetrusor OnaBTx injection under cystoscopic control. Outcome Measures: Continence level achieved, dose of anticholinergic medication, reflex volume, max detrusor pressure during voiding, detrusor compliance, max cystometric bladder capacity and individual satisfaction.	<ol style="list-style-type: none"> 1. Significant increase in reflux volume, maximum cystometric bladder capacity ($p<0.016$). 2. Increase in post void residual urine volume. 3. Non-significant voiding pressure change. 4. At the 6-wk followup complete continence was restored in 17 of 19 cases in which anticholinergic medication was markedly decreased or withdrawn. 5. 11 participants at 16 & 36 wks follow-up continued to show bladder function improvement.
Leitner et al. 2016 Switzerland Post Test N=52	Population: NDO; Mean age: 40 yr; Gender: males=24, females=24; Cause of NDO: SCI=32, Spina bifida=8, MS=7, Other=5; Treatment: All participants received intradetrusor onabotulinumtoxinA (OnaBTX) before 2011 (300 U) and after 2011 (200 U). Outcome Measures: Primary outcome measures was eligibility to continue OnaBTX injections. Prerequisites to do so included appropriate clinical and urodynamic effect. Secondary outcome measures were maximum cystometric capacity, compliance, bladder volume, detrusor overactivity, maximum detrusor pressure.	<ol style="list-style-type: none"> 1. Based on positive clinical and urodynamic effects, 60% of participants continued on with OnaBTX treatment. Nine participants did not continue on with treatment in favor of pursuing other treatment options despite having positive outcomes. 2. There were no significant differences in secondary urodynamic parameters between participants continuing treatment and those discontinuing treatment.
Gutierrez-Martin et al. 2015 Spain Case Series N=70	Population: NDO; Mean age: 39; Gender: males=40, females=30; Level of injury: C1-C8=32, D1-D4=10, D5-L1=28; Mean time post-injury: 167 mo.	<ol style="list-style-type: none"> 1. Significant increases in CC ($p=0.002$), IVC ($p=0.003$), and PVR ($p=0.002$) were seen post-treatment compared to baseline.

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
	<p>Treatment: Participants had received a 300 IU injection of onabotulinumtoxin (OnaBXT) into the detrusor and were followed-up with 6 mo post-injection.</p> <p>Outcome Measures: Cystomanometric bladder capacity (CC), first involuntary bladder contraction volume (ICV), maximum pressure of voluntary contraction (IC maxP), the filling pressure (fillP), maximum detrusor voiding pressure (maxP), maximum urinary flow (Qmax), post-void residual (PVR), and index of urethral resistance (BOOI)</p>	2. No other significant differences were found.
Caremel et al. 2011 Canada Case Series N=11	<p>Population: Mean age: 29 yr (range=21-40); Gender: males=11, females=0; Level of injury: C5 to T6, complete SCI (AIS A) Mean time post-injury: 74 mo (range 18-163).</p> <p>Intervention: Participants received intradetrusor botulinum neurotoxin A (BT) injections of 300 units of onaBTx (N=10) or 1000 units of aboBTx (N=3) (2 participants received 2 BT injections at 7 mo intervals using a different dosage), each injection=0.2ml, number of injection sites=10 (N=2), 20 (N=9) or 30 (N=2), on average BT injections were performed 57 d after the pre-ejaculation test (range 2 – 240 d) and 59 d prior to the post-ejaculation test (range 9 – 154 d).</p> <p>Outcome Measures: Detrusor overactivity, urinary incontinence, void volume.</p>	<ol style="list-style-type: none"> 1. BT treatment was effective in improving bladder function (overactivity and urinary incontinence) in 11 of 13 cases (85%) 2. In 10 of 13 cases (77%) amplitude of detrusor contractions decreased. 3. When compared with pre-BT treatment, there was a lower number of anterograde ejaculations post-BT (77% versus 54%) yet a higher number of retrograde ejaculations (23% versus 46%).
Pannek et al. 2009a Switzerland Case Series N=27	<p>Population: Mean age: 34.5; Gender: male=15, female=12; Severity of injury: complete=15, incomplete=12; mean time between injury and first OnaBTx treatment=62.9 mo.</p> <p>Intervention: 300 IU of OnaBTx in 30ml saline solution injected into the detrusor muscle</p> <p>Outcome Measures: the Qualiveen questionnaire, continence rate and treatment success rate</p>	<ol style="list-style-type: none"> 1. Urodynamic variables including bladder capacity, reflex volume and detrusor compliance significantly improved. 21 of 23 participants became continent after first OnaBTx treatment. 2. No significant differences in terms of urodynamic variables were reported between first and final treatment, however incontinence rate increased from 2 to 7 participants at final treatment. 3. Long term success rate for incontinence was 74%. There is a significant decrease in improvement in maximum

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		<p>detrusor pressure before the 2nd and the final treatment, suggesting that detrusor contraction strength did not completely recover after the injection.</p> <p>4. Four participants reported mild temporary muscular weakness and 1 participant dropped out of treatment due to severe side effects.</p>
<p>Akbar et al. 2007 Germany Case Series N=44</p>	<p>Population: Mean age: 34.34 yr; Gender: males=10; females=15; Level of injury: paraplegic=15, tetraplegic=10. Intervention: aboBTx injected intramuscularly into 20 detrusor sites for pediatric participants and 40 sites for adults. Participants were re-injected when there was a substantial return to baseline measures. Outcome Measures: Detrusor compliance, bladder capacity and detrusor pressure. Follow-up was 3-5 yr from the study.</p>	<p>1. After 1, 2, and 3 injections significant improvement ($p<0.001$) in:</p> <ul style="list-style-type: none"> • Detrusor compliance • Maximum detrusor pressure • Bladder capacity. <p>2. Prolonged efficacy of repeated injections in participants with neurogenic bladder function was seen over an average of 4.5 yr.</p> <p>3. No drug tolerance or changes in morphological appearance of the bladder was seen.</p> <p>4. Side effects were seen in 3 participants receiving a dose of 1000 U aboBTx, which was resolved by reducing the dose to 750 units.</p>
<p>Reitz et al. 2004 Switzerland Case Series N_{initial}=231; N_{final}=200</p>	<p>Population: Neurogenic detrusor overactivity. Gender: males=131, females=69. Intervention: Participants from 10 European medical centers who previously received 300 units of onaBTx into the detrusor were assessed. Outcome Measures: Mean cystometric bladder capacity, reflex volume, bladder compliance, mean voiding pressure were assessed at 12 and 36 weeks post injection.</p>	<p>1. Significant improvement in mean cystometric bladder capacity, reflex volume, bladder compliance and mean voiding pressure was seen at about 12 weeks post injection ($p<0.0001$).</p> <p>2. Complete continence was achieved in 132 of the 180 individuals with incontinence pretreatment.</p> <p>3. At 36 week follow-up, improvements in mean cystometric bladder capacity ($p<0.0001$), reflex volume ($p<0.01$) and mean voiding pressure ($p<0.0001$) remained.</p>

Discussion

In 2013, Mehta et al. published a large systematic review and meta-analysis examining the effect of botulinum toxin A on improving bladder function post SCI. In

total, fourteen studies met inclusion criteria including one RCT (Schurch et al. 2005), one case-control (Grosse et al. 2009), and 12 pre-post studies (Schurch et al. 2005, Del Popolo et al. 2008, Game et al. 2007, Giannantoni et al. 2009, Klaphajone et al. 2005, Kuo et al. 2006, Kuo et al. 2008, Pannek et al. 2009, Tow et al. 2007, Wefer et al. 2010; Akbar et al. 2007, Patki et al. 2006). Ten studies examined OnaBTx and four studies examined aboBTx. The meta-analyses revealed large effect sizes and a significant increase in reflex detrusor volume (1, 3, 6 months, $p < 0.001$ for all), bladder capacity (1, 3, 6, 12 months, $p < 0.001$ for all), bladder compliance (1, 3, 6, 12 months, $p < 0.001$ for all), and post-residual urine volume (1, 3, 6 months, $p < 0.001$ for all). There was also a mean decrease in catheterization frequency ($p < 0.001$) and number of incontinence episodes post treatment. Finally, Mehta et al. (2013) reported that there was no significant deterioration in maximum flow rate observed as a result of treatment ($p = 0.403$). Three mild adverse effects were reported: hypertension (Tow et al. 2007), muscular weakness (Akbar et al. 2007), and stress urinary incontinence (Del Popolo et al. 2008). While this systematic review reported optimistic findings, it was unable to assess comparisons of botulinum toxin A type, different dosing schedules, control groups, or location sites. Unfortunately, many large randomized controlled trials were excluded from the meta-analyses due to having more individuals with MS than SCI individuals, even if they contain large numbers of individuals with SCI.

Seven RCTs were published between 2007 and 2016 addressing the effectiveness of botulinum toxin for NDO post SCI; which were not included in the aforementioned systematic review and meta-analysis by Mehta et al. (2013). In a placebo-controlled RCT, Herschorn et al. (2011) examined the effect of 300U onaBTX injections into the intradetrusor to improve NDO. The authors found that onaBTX reduced incontinence episodes and maximum detrusor pressure during filling compared to controls ($p < 0.001$ for both) at 6, 24, and 36 week follow-up. Similarly, void volume and cystometric capacity increased more for the treatment group compared to controls ($p < 0.001$ for both). The authors reported minimal adverse effects such as muscle weakness and UTI. In three RCTs (Abdel-Meguid et al. 2010; Hui et al 2016; Huang et al 2016), subjects were randomized to receive onaBTX into either the intradetrusor only or both the intradetrusor plus intratrigoanal. Abdel-Meguid et al (2010) reported improvements in all urodynamic parameters (incontinence episodes, complete dryness, reflex volume, cystometric capacity and maximum detrusor pressure) among both groups; however, only improvements in incontinence episodes, complete dryness and reflex volume were significantly greater in the combined group compared to the detrusor-only group ($p < 0.001$ for all). Although Hui et al (2016, $n = 96$) and Huang et al (2016, $n = 80$) both found higher rates of complete dryness in the combined group and that secondary urodynamic parameter (UI/day, voiding volume) improvements were more dramatic for the control group; they reported divergent I-QoL results for the experimental group. It is important to note both Huang et al. 2016b and Hui et al. 2016 found that injecting onabotulinum toxin 40 units to trigone, and 160 units to detrusor did not lead to more VUR compared to 200 units to trigone alone, and yet doing so decreased leak point pressure. It is not clear, however, what individual groups were tested and how many were already on IC versus voluntary emptying with spontaneous void, and how many had improvement with emptying with voluntary spontaneous void. The latter would have been the main reason to decrease leak point pressure as

decreasing detrusor leak point pressure (DLPP) in individuals performing IC would not be beneficial.

Despite these beneficial effects, Leitner et al (2016) reported that almost 40% of individuals discontinue onabTX usage over time. Twenty-one percent of individuals discontinued due to lack of clinical and/or urodynamic response and 19% preferred to switch to another treatment (antimuscarinics and/or neuromodulation). Discontinuation likely is not related to effects on cardiac function. A pre-post study (Fougere et al. 2016, n=17) found that intradetrusor injections of 200 units onabotulinumtoxin actually reduced episodes of autonomic dysreflexia and elevations in blood pressure during urodynamic studies. Another case series of 99 individuals (Soler et al 2016) also confirmed the disappearance or improvement of autonomic dysreflexia in 70% of individuals treated successfully for detrusor sphincter dyssynergia (DSD) resulting from NDO.

A small RCT by Krhut et al. (2012) compared the efficacy of onabTX administered to the detrusor versus suburothelium for NDO secondary to SCI. There was no significant differences between groups for number of incontinent episodes, frequency of catheterizations, maximum detrusor pressure, void volume, cystometric capacity, and volume at first involuntary detrusor contraction. Krhut et al. (2012) reported favouring the suburothelial injections over the intradetrusor since injections could be better localized.

Two RCTs demonstrated that onabTX injected into the detrusor in either 200U or 300U produce similar improvements in CBC, PVR, Qmax (Chen et al 2014) and quality of life (QoL) was reported as equivocal for both doses by Chen et al (2014) and improved over the placebo group as reported by Schurch et al. 2007. Additional pre-post studies of individuals refractory to antimuscarinic agents for the treatment of NDO reported onabTX related improvement in both clinical efficacy (Chen & Kuo 2015) and QoL for more than eight months (Al Taweel et al 2015, n=103). This latter study also reported a reduction or discontinuation in oral anticholinergic use as a result of onabTX administration. OnabTX was also effective in individuals refractory to intravesical oxybutynin administration. (Alvares et al, 2014). Additional pre-post studies (Yang et al 2015; Ge et al 2015) and case series (Gutierrez-Martin et al 2015) add to the body of evidence for improved bladder function following onabTX administration; even in the event of a first failed injection (Peyronnet et al 2016).

In a retrospective study by Anquetil et al. 2016 comparing intradetrusor botulinum toxin to augmentation cystoplasty, botulinum toxin resulted in fewer complications and improved quality of life; however, augmentation cystoplasty was slightly better for decreasing incontinence and improving cystometric capacity.

Two important RCTs (Cruz et al. 2011; Ginsberg et al. 2012) served as the basis for the regulatory approval of BTX-A in Canada, the US, and Europe; however, the study populations included individuals with both SCI and multiple sclerosis. While these studies did not meet SCIRE inclusion criteria, it was nevertheless important to note these two RCTs as they have been pivotal in influencing the use of this treatment both in clinical practice and research. Ginsberg et al. (2013) reported the SCI

subanalysis of these studies (Cruz et al. 2011; Ginsberg et al. 2012); which form the largest analysis of double-blind placebo-controlled trials for NDO in SCI. Results confirmed a dramatic improvement in continence and quality of life following the administration of onabotulinum toxin.

Conclusion

There is level 1a evidence (from several RCTs: Abdel-Meguid et al (2010); Kruhut et al 2012; Hui et al 2016; Huang et al 2016; Ginsberg 2012) that supports the injection of onabotulinum toxin A into the detrusor muscle to provide targeted treatment for SCI – related neurogenic detrusor overactivity resistant to oral anticholinergic treatments. Benefits include decreased incontinence, improved bladder capacity, decreased detrusor pressure, improved quality of life, amongst other findings. Numerous level 3 and 4 studies confirm the efficacy and safety.

Dosages of 200U versus 300U onaBTX are non-superior for symptom and QoL improvement secondary to NDO; as supported by level 2 evidence from 2 less rigorous RCTs (Schurch et al 2007; Chen et al 2014). There are higher retention rates with 300U, thus 200U is the recommended dosing (Ginsbger et al. 2012).

The superiority of Intradetrusor botulinum toxin compared to augmentation cystoplasty is supported by level 2 evidence. Advantages of intradetrusor botulinum include fewer complications and better quality of life; even though augmentation cytoplasty was better at decreasing incontinence and improving cystometric capacity.

There is level 4 evidence that onaBTX may improve NDO in individuals that are refractory to anticholinergics (Chen & Kuo 2015; Al Taweel et al 2015; Alvarez et al 2014).

Level 4 evidence is available for onaBTX administration as the basis for reducing (Soler et al 2016) or eliminating (Fougere et al 2016; Soler et al 2016) autonomic dysreflexia while improving NDO symptoms.

There is level 4 evidence from one pre-post study and one case series (Klaphajone et al. 2005; Caremel et al. 2011) that detrusor contractility may be decreased through repeated BTX-A injection.

Onabotulinum toxin type A injections into the detrusor muscle improve neurogenic destrusor overactivity, intradetrusor pressures, bladder capacity and urge incontinence; it may also reduce destrusor contractility.

4.1.2.2 Capsaicin and Resiniferotoxin

Capsaicin (*trans*-8-methyl-*N*-vanillyl-6-nonenamide) is the main compound in hot peppers (e.g., red chili, jalapeños, and habaneros). It works as a temporary topical analgesic and is sold as an ointment world-wide and as a topical patch in Europe for allodynia. Capsaicin (CAP) induces localized and reversible anti-nociception from first C-fibre activation then subsequent neuropeptide release inactivation (Dray 1992). The initial C-fibre activation can be extremely painful and, in some individuals, intolerable. Although C-fibers are not involved prominently in normal voiding, neuroplastic changes to C-fiber bladder afferent expression after spinal cord injury account for an overactive C-fiber mediated voiding reflex (i.e., spinal detrusor hyperreflexia). Given the over-expression of C-fibers after SCI, the instillation of capsaicin into the bladder has been explored as a therapeutic approach. This, however, can be very painful and thus has not become clinically popular despite the initial work done in this area over 2 decades ago.

Resiniferatoxin (RTX) is an alternative vanilloid which has also been studied for its similar beneficial effects. Resiniferatoxin is less irritating to the bladder and is therefore better tolerated. By chemically reducing C-fiber bladder afferent influence with intravesical vanilloids (i.e., CAP, RTX), bladder contractility is decreased and bladder capacity is increased (Evans 2005). Unfortunately, despite the promising results presented below, it is not commercially available due to difficulty with formulation.

Table 3 Capsaicin

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
Silva et al. 2005 Portugal RCT PEDro=8 N=28	<p>Population: Neurogenic detrusor overactivity. Mean age: 38 yr; Gender: males=15, females=13.</p> <p>Intervention: Individuals were randomly placed in a treatment group receiving 50nM resiniferatoxin or a placebo group.</p> <p>Outcome Measures: First detrusor contraction (FDC), maximal cystometric capacity (MCC). Measures were assessed 1 month and 1 week pre-treatment and 1 and 3 months post treatment.</p>	<ol style="list-style-type: none"> 1. FDC and MCC increased significantly in the treatment group compared to the placebo group ($p=0.03$, $p=0.02$). 2. No significant difference was seen in FDC and MCC in the treatment group between month 1 post treatment and month 3. 3. Individuals in the RTX instillation group reported a non-significant increase in discomfort compared to the placebo. Otherwise similar side effects were seen between RTX and placebo. 4. A significant decrease in daily incontinence was seen in the treatment group ($p=0.03$).
deSeze et al. 2004 France RCT PEDro=10 N=39	<p>Population: SCI (n=18); MS (n=21); Mean age: 47 yr; Gender: males=17, females=22; Level of injury: paraplegia=14, tetraplegia=4; Severity of injury: AIS: A, B; Bladder</p>	<ol style="list-style-type: none"> 1. No significant difference between groups in MCC ($p=0.4$); both resulted in clinical and urodynamic improvement at d

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
	<p>management method: IC=23, reflex or voluntary voiding=8, suprapubic percussion=2, spontaneous voiding=14.</p> <p>Intervention: 100ml 100nMol/l resiniferatoxin (RTX) in 10% ethanol or 1mmol/l capsaicin (CAP) diluted in glucidic solvent.</p> <p>Outcome Measures: Clinical: daily voids/catheterization, leakage episodes with urgency/ leakage delay. Primary outcome measure: Maximum Cystometric Capacity (MCC).</p>	<p>90 (Improvement in MCC: 68% of RTX and 86% in CAP groups).</p> <ol style="list-style-type: none"> Persistent clinical improvement 94% versus 60% in favour of RTX but the difference was not significant. Side effects were similar between groups except clinically tolerable/brief suprapubic pain significantly higher in CAP group ($P<0.04$).
<p>Kim et al. 2003 USA RCT PEDro=8 N=36</p>	<p>Population: SCI=20, MS=7, Other=9 with detrusor hyperreflexia and intractable UTIs despite previous anticholinergic drug use; Gender: males=22, females=14.</p> <p>Intervention: Double-blind dose escalation of single instillation of 100mL intravesical resiniferatoxin (RTX) (0.005, 0.025, 0.05, 0.10, 0.2, 0.5, or 1.0 microM of RTX; n=4/group) or placebo (n=8).</p> <p>Outcome Measures: A visual analog pain scale (VAPS), bladder diary, mean cystometric bladder capacity (MCC) at wks 1, 3, 6 & 12 posttreatment, adverse events including autonomic dysreflexia (AD).</p>	<ol style="list-style-type: none"> VAPS: min. to mild discomfort with values of 2.85 and 2.28 for the 0.5-microM and 1.0-microM RTX treatment groups. No statistically significant changes in MCC or incontinence at lower doses of RTX. However in higher doses (0.5-microM & 1.0-microM) of RTX, MCC increased by 53% & 48% respectively at 3 weeks. Incontinence decreased by 51.9% & 52.7% for the 0.5-microM & 1.0-microM RTX. Intravesical RTX is well-tolerated but monitoring for autonomic dysreflexia is required.
<p>Petersen et al. 1999 Denmark RCT crossover PEDro=5 N=12</p>	<p>Population: Median age: 45 yr (range 28-68); Gender: males=6, females=6.</p> <p>Intervention: Individuals were initially randomized to either an intraversical saline (100ml left in the bladder for 30 minutes) or intravesical capsaicin (100 ml 1mmol/L left in the bladder for 30 minutes) group; cross-over to the alternative treatment took place after 4 weeks.</p> <p>Outcome Measures: Intravesical pressure during DH and bladder capacity, visual analogue scale (VAS).</p>	<ol style="list-style-type: none"> There were significant changes in the mean values of VAS scores during the study. VAS scores, mean volume and maximum pressure during DH was not significantly different between groups at follow-up. Bladder biopsies taken two weeks post treatment showed pronounced inflammation, superficial hemorrhage, and squamous epithelial metaplasia.
<p>deSeze et al. 1998 France RCT PEDro=10 N=20</p>	<p>Population: Age range 20-66 yr; Gender: males=11, females=9; Injury etiology: MS=12, SCI=8; Level of injury: paraplegia=17, tetraplegia=3; Severity of injury: complete=6, incomplete=14; Time post-injury=1-27 yr.</p>	<p>30 d after instillation, results favoured capsaicin over placebo:</p> <ol style="list-style-type: none"> Decrease in 24h voiding freq ($p=0.016$); Decrease in 24h leakages ($p=0.0008$).

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
	<p>Intervention: 30 mg capsaicin in 100mL 30% ethanol or 100ml 30% ethanol alone</p> <p>Outcome Measures: Clinical: voiding diary. Urodynamic: Maximum Cystometric Capacity (MCC), Maximum Detrusor Pressure (MDP).</p>	<ol style="list-style-type: none"> 3. Increase in MCC ($p=0.01$) 4. Decrease in MDP ($p=0.07$; not significant). 5. Similar side effects in each group.
George et al. 2007 India Prospective Controlled Trial N=18	<p>Population: Age range 20-53 yr; Gender: males=17, females=1.</p> <p>Intervention: Oxybutynin, propantheline, and capsaicin solution were instilled intravesically. Oxybutynin and propantheline were administered 3 times daily by a double blind method with a 6 d washout period between each drug. Individuals receiving propantheline or oxybutynin had urodynamic studies done before and 3 hours after the instillation of the third dose. The capsaicin instillation was not possible to blind and urodynamic studies were repeated 1 and 2 weeks after instillation of the drug.</p> <p>Outcome Measures: Reflex volume, detrusor leak point pressure, cystometric capacity, and urine leak frequency.</p>	<ol style="list-style-type: none"> 1. Overall capsaicin treatment resulted in significant change in: <ul style="list-style-type: none"> • Reflex volume ($p=0.018$). • Cystometric capacity ($p=0.0440$). • Leak volume ($p=0.000$). • Leak frequency ($p=0.009$). 2. Pre and post responses between intravesical oxybutynin, propantheline and capsaicin showed significant differences at 2 weeks with respect to leak volume ($p=0.017$) and leak frequency ($p=0.003$).
Shin et al. 2006 Korea Pre-Post N=15	<p>Population: Mean age: 27.2 yr; Gender: males=11, females=4; Severity of injury: AIS Impairment Score: A=10; B=5.</p> <p>Intervention: Conventional and ice provocative urodynamic studies were performed. Seven days later, 100 ml of resiniferatoxin solution (RTX; 100 nM) diluted in 10% ethanol was instilled into the bladder at an infusion rate of 30mL/min.</p> <p>Outcome Measures: Involuntary detrusor activity, reflex volume, maximal bladder capacity, compliance, DPmax, and reflex volume. Urodynamic changes were examined 30 days after the instillation.</p>	<ol style="list-style-type: none"> 1. Intravesical RTX instillation resulted in a significant increased reflex volume ratio ($p<0.05$). 2. No significant change was found after intravesical RTX instillation in: <ul style="list-style-type: none"> • Maximum bladder capacity. • Compliance • Maximal detrusor pressure. 3. Three cases showed complete suppression and 9 cases showed partial suppression of the unmyelinated C-fiber activities.
Watanabe et al. 2004 Japan Pre-Post N=16	<p>Population:</p> <p><u>Group 1:</u> Individuals with NDO from SCI ($n=7$) or transverse myelitis ($n=1$); Mean age: 30.9 yr (range 19-53); Gender: males=6, females=2.</p> <p><u>Group 2:</u> Individuals with NDO from SCI ($n=7$) or cerebral palsy ($n=1$); Mean</p>	<ol style="list-style-type: none"> 1. 6/8 individuals (75%) reported improvements in their incontinence grades and symptoms. 2. The mean bladder capacity increased significantly in both protocol groups (protocol 1:

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
	age: 28.1 yr (range 19-46); Gender: males=7, females=1. Intervention: Intravesical resiniferatoxin (RTX) (30 mL of 500 nM in protocol 1, 100ml of 1um in protocol 2). Outcome Measures: Incontinence, bladder capacity	138ml to 227.3ml, protocol 2:133.1ml to 247 ml, p<0.05).
Lazzeri et al. 1998 Italy Pre-Post N=7	Population: SCI individuals with detrusor hyperreflexia currently being treated with intravesical instillation of capsaicin: Mean age: 32.85 yr (range 19-54); Gender: males=2, females=5 Intervention: Resiniferatoxin (RTX) saline solution (30ml at 10 ⁻⁵ M) instilled into the bladders of all individuals and left for 30 minutes. Outcome Measures: Mean cystomanometric capacity (MCC); mean maximum bladder detrusor pressure (MDP), incontinence.	1. 15 days post-treatment: MCC significantly increased (190ml to 407.14 ml, p<0.01) and MDP decreased significantly. 2. Four weeks after RTX instillation, MCC remained significantly increased from its baseline value (421.66 ml, p value). 3. Incontinence was improved in 6/7 individuals (85.7%): improvements in their frequency, urgency and nocturia (n=3) or remained completely dry (n=3) post-treatment.
Dasgupta et al. 1998 UK Post Test N=20	Population: MS, SCI: Age range 40-70 yr; Gender: males=9, females=11. Intervention: Intravesical capsaicin. Outcome Measures: Histopathological examination of bladder biopsies, urodynamics to assess bladder capacity, cystoscopy in 2 individuals.	1. All biopsies were benign. Some reflected chronic inflammation (cystoscopy: 2 males with TM - transient inflammatory reaction to treatment). 2. Bladder capacity improvement at 6 weeks.
Das et al. 1996 USA Case Series N _{initial} =7; N _{final} =5	Population: Mixed group: Age range 23-52 yr. Intervention: Intravesical capsaicin treatment: 100uM, 500uM, 1mM, 2mM Outcome Measures: Symptomatic improvement, bladder capacity.	1. Symptomatic improvement: 3/5 completers. 2. Mean urodynamic bladder capacity increased (p<0.05).

Discussion

DeSeze et al. (1998) has provided level 1b evidence in support of the ability of capsaicin (CAP) to improve bladder function. The authors found that CAP installation was effective in decreasing 24h voiding frequency (p=0.016), decreasing 24h leakages (p=0.0008) and increasing maximal cystometric capacity (p=0.01) 30-days after installation compared to placebo. This study offers support to other small, non-RCT studies that reported significant CAP-induced increases in bladder capacity (Das et al. 1996; Dasgupta et al. 1998). However, a small RCT cross-over study did not find differences in bladder improvement between individuals receiving CAP versus placebo (Petersen et al. 1999).

George et al. (2007) described the use of a one time instillation of CAP and reported that its “efficacy” for cystometric capacity was significant. However, when evaluating the data, it seems the significant difference was actually a significant decline in capacity at 3 hours (pre=224.6 cc, 3 hr post=139.6 cc, $p=0.015$) and a non-significant decline at 1 week (174.2 cc at 1 week, $p=0.059$). The authors claim that there was a marked, progressive and overall improvement following CAP except for leak point pressure. But the statistical results do not support this claim, and only leak volume was improved statistically at 2 weeks. Autonomic dysreflexia, a significant side effect, was reported in 2 individuals following CAP. Although this study included blinded evaluations of oxybutynin versus propantheline instillation, CAP evaluations could not be blinded and therefore, a discussion of oxybutynin versus propantheline results was undertaken separately.

Dasgupta et al. (1998) confirmed the presence of metaplasia, dysplasia, and flat carcinoma in situ after treatment with intravesical CAP. All biopsies were determined to be benign but some showed signs of chronic inflammation; this finding has been supported by a small cross-over RCT by Petersen et al. (1999). Dasgupta et al. (1998) reported that neither papillary nor solid invasive cancer was detected after 5 years of follow-up. Further surveillance is required up to 10 years when chemical carcinogenic morphologies typically present.

DeSeze et al. (2004) established that RTX was similarly effective in increasing bladder capacity when compared to CAP. CAP was significantly more effective at increasing urgency delay ($p<0.01$) but there was only a trend to greater maximum bladder capacity in favour of CAP. The increase in persistent clinical improvements due to RTX over CAP at 90 days follow-up was not statistically significant. Although there was also a statistically significant increase in suprapubic pain with CAP, it was clinically tolerable and brief ($p<0.04$).

Despite non-significant findings reported in a small non-RCT by Shin et al. (2006), the efficacy of RTX has been confirmed in one RCT (Silva et al. 2005) and two pre-post studies (Watanabe et al. 2004; Lazzeri et al. 1998). Compared to placebo, Silva et al. (2005) found that RTX was responsible for significantly increased volume of first involuntary detrusor contraction ($p=0.03$), maximum cystometric capacity ($p=0.02$), decreased urinary frequency ($p=0.01$) and incontinence ($p=0.03$) with similar side effects compared to placebo. Kim et al. (2003) confirmed the improvements in SCI bladder function and further investigated the effect of RTX dosing. Despite the small sample size in each dose category, maximum cystometric capacity at 3 weeks post-treatment increased by 53% and 48% for doses of 0.5 μM and 1.0 μM , respectively. Similarly, incontinence episodes decreased by 51.9% and 52.7%, respectively.

Conclusion

There is level 1a evidence (four RCTs; Silva et al. 2005; deSeze et al. 2004; Kim et al. 2003; deSeze et al. 1998) and three level 4 studies that the use of vanilloid compounds (e.g., capsaicin, resiniferatoxin) increases maximum bladder

capacity and decreases urinary frequency, leakages, and pressure in NDO of spinal origin.

There is level 4 evidence (from one post test study; Dasgupta et al. 1998) that intravesical capsaicin instillation in bladders of individuals with SCI does not increase the rate of common bladder cancers after 5 years of use.

Vanillanoid compounds such as capsaicin or resiniferatoxin increase maximum bladder capacity, and decrease urinary frequency, incontinence, and intradetrussor pressure in neurogenic detrusor overactivity.

Intravesical capsaicin instillation in bladders of individuals with SCI does not increase the rate of common bladder cancers after 5 years of use.

4.1.2.3 Nociception/Orphanin Phenylalanine Glutamine

Nociceptin/orphanin phenylalanine glutamine (N/OFG) is a heptadecapeptide (Meunier et al. 1995; Reinscheid et al. 1995) that affects the sensory innervation of the lower urinary tract in a similar fashion to CAP and RTX. It activates the G protein coupled receptor nociceptin orphan peptide and thus has an inhibitory effect on the micturition reflex in the rat (Lecci et al. 2000).

Table 4 Nociception/Orphanin Phenylalanine Glutamine

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
Lazzeri et al. 2003 Italy RCT PEDro=10 N=14	<p>Population: SCI subjects with neurogenic detrusor overactivity: Mean Age (treatment): 43.7 yr; Mean age (placebo): 41.4 yr; Gender: males=6, females=8; Level of Injury: T4-L2; Cause of injury: trauma=10, non-trauma=4 (ratio 5:2 per group); Time post-injury (treatment): 8.7 yr; Time post-injury (control): 7.0 yr.</p> <p>Intervention: A randomized placebo double blind study evaluating the neuropeptide nociceptin/orphanin (N/OFG) versus placebo.</p> <p>Outcome Measures: Bladder capacity, volume threshold for the appearance of detrusor overactivity (DO), and maximal bladder pressure during involuntary bladder contractions.</p>	<ol style="list-style-type: none"> 1. N/OFG resulted in significant increase in: <ul style="list-style-type: none"> • Capacity (p<0.001) • DO volume threshold (p<0.01). 2. N/OFG resulted in a non-significant decrease in: <ul style="list-style-type: none"> • Max bladder pressure 3. No difference between N/OFG and Placebo in: <ul style="list-style-type: none"> • No phasic contractions or autonomic dysreflexia • Incomplete individuals - no suprapubic or urethral sensation • Vital signs unchanged. 4. N/OFG (but not placebo) elicits robust acute inhibitory effect on micturition reflex in

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
		individuals with neurogenic bladder.
Lazzeri et al. 2006 Italy RCT PEDro=8 N=18	<p>Population: Neurogenic detrusor overactivity. Treatment: Mean age: 37.1 yr; Gender: males=4, females=5; Placebo: Mean age: 44.9 yr; Gender: males=4, females=5</p> <p>Intervention: SCI individuals were randomly placed into the treatment group receiving 1 mg of nociceptin/orphanin FQ/d for 10 days or placebo.</p> <p>Outcome Measures: Bladder pressure, Incontinence Episode Frequency (IEF), Voiding Diary-Bladder Capacity (VD-BC).</p>	<ol style="list-style-type: none"> 1. Post-treatment, mean bladder pressure and IEF decreased significantly ($p<0.05$) in the treatment group; however, no such change was seen in the placebo group. 2. No significant difference was seen in the bladder capacity and VD-BC post treatment.

Discussion

Following a successful preliminary human study, Lazzeri et al. (2003) confirmed that N/OFG versus placebo is responsible for a significant increase in bladder capacity ($p<0.001$) and threshold volume of detrusor overactivity ($p<0.001$), and a non-significant decrease of maximum bladder pressure of the dysfunctional neurogenic bladder. These results were verified in an additional small-scale RCT ($n=18$) of a 10 day course of N/OFG treatment versus placebo (saline). Statistically significant improvements to bladder capacity (assessed by daily voiding diary) and urine leakage episodes were seen in the treated group but not with placebo (Lazzeri et al. 2006). The authors conclude that this inhibition of the micturition reflex supports nociceptin orphan peptide receptor agonists as a possible new treatment for neurogenic bladders of SCI individuals.

Conclusion

There is level 1a evidence (from two RCTs; Lazzeri et al. 2003; Lazzeri et al. 2006) that supports the use of nociceptin/orphanin phenylalanine glutamine, a nociceptin orphan peptide receptor agonist for the treatment of neurogenic bladder in SCI.

Nociceptin/orphanin phenylalanine glutamine, a nociceptin orphan peptide receptor agonist, may be considered for the treatment of neurogenic bladder in SCI.

4.1.3 Intravesical Instillations for SCI-Related Detrusor Overactivity

Intravesical instillations are intended as a means for increasing bladder capacity, lowering pressures, and decreasing incontinence, with the potential for decreased systemic side effects compared to oral medications. Capsaicin and resiniferotoxin have been discussed above in toxins. Other medications used as intravesical installations are anticholinergics such as oxybutynin and propantheline which are presented below. Most of these protocols consist of dissolving the medication in a liquid solution and instilling the medication after emptying the bladder by IC, then leaving it in place until the next scheduled intermittent catheterization.

Table 5 Intravesical Instillations for SCI-Related Detrusor Overactivity

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
George et al. 2007 India RCT PEDro=3 N=18	Population: Age range 20-53 yr; Gender: males=17, females=1. Intervention: Oxybutynin, propantheline, and capsaicin solution were instilled intravesically. Oxybutynin and propantheline were administered 3 times daily by a double-blind method with a 6 d washout period between each drug. Urodynamic studies done at baseline and 3 hours after the instillation of the third dose. A capsaicin instillation was also administered and urodynamic studies were repeated 1 and 2 weeks after instillation of the drug. Outcome Measures: Reflex volume, detrusor leak point pressure, cystometric capacity, and urine leak frequency.	1. Pre and post responses between intravesical oxybutynin, propantheline, and capsaicin showed significant differences at 2 weeks with respect to leak volume ($p=0.017$) and leak frequency ($p=0.003$). 2. However, individually, only propantheline had significant improvement in leak frequency ($p=0.039$), and neither had significant changes in the other parameters.
Ersoz et al. 2010 Turkey Pre-Post N=25	Population: Mean age: 30.2 yr; Gender: male=16, female=9; Mean time post-injury: 40.7 mo; Severity of injury: tetraplegia=2, paraplegia=21. Intervention: intravesical oxybutynin hydrochloride treatment. Outcome Measures: Urodynamic variables and adverse events.	1. The bladder volumes improved significantly post-treatment ($p=0.024$). The increase in bladder volume was 82% (mean=124.1mL). 2. 10 individuals discontinued treatment due to UTI, procedure difficulty and economic difficulty. 3. 6 of 9 individuals shifted from indwelling catheters to intermittent catheterization after the treatment
Haferkamp et al. 2000 Germany Pre-Post N=32	Population: SCI (n=17), myelomeningocele (n=15); all individuals had neurogenic bladders with detrusor hyperflexia. Mean age: 12 yr (range 1-34 yr); Gender: male=18, female=14; Level of impairment: tetraplegic=10, paraplegic=22.	1. 21 individuals became completely continent using just the standard dose of treatment. 2. Of the 21 individuals there was a significant decrease in median MDP ($p<0.01$), a

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
	<p>Intervention: A standard dose of intravesical oxybutynin (0.3 mg/kg daily) or increasing dose of 0.2mg/kg/d up to 0.9 mg/kg.</p> <p>Outcome Measures: Continence, age-adjusted bladder capacity (ABC), compliance, maximal detrusor pressure (MDP).</p>	<p>significant increase in both the median compliance and median ABC ($p<0.01$).</p> <p>3. In the remaining 11 individuals: 7 out of 11 individuals became continent with increased dosage (0.7 mg/kg was the median dose required). In these 7 individuals median MDP significantly decreased ($p<0.05$), and both median compliance and median ABC increased significantly ($p<0.05$).</p>
<p>Pannek et al. 2000 Germany Pre-Post N=25</p>	<p>Population: All individuals had SCI and had either a detrusor storage pressure greater than 40 cmH₂O (n=20) or dysreflexia (n=5) despite oral oxybutynin treatment (5 mg four times daily); Mean age: 36.7 yr (range 18-64 yr); Gender: males=19, females=6, Level of SCI: cervical (n=14), thoracic (n=11); Time from lesion to treatment: 5.2 yr (range 0.3-20.9 yr).</p> <p>Intervention: Intravesical oxybutynin (15 mg) three times daily.</p> <p>Outcome Measures: Bladder storage volume, maximum storage pressure, detrusor storage pressure.</p>	<ol style="list-style-type: none"> 1. Intravesical treatment increased bladder storage volume (349ml- to 420 ml). 2. Mean maximum storage pressure significantly reduced from 54 to 26.5 cmH₂O ($p<0.00001$). 3. In the individuals with elevated detrusor storage pressures, 18 out of 21 had detrusor pressures return to less than 40 cmH₂O (mean pressure 18 cmH₂O). 4. 19 individuals were incontinent pre-treatment, 15 (79%) achieved continence post-treatment. 5. 9 out of the 25 individuals had chronic urinary tract infections pre-treatment; urinary tract infections were resolved in all 9 individuals post-treatment.
<p>Vaidyananthan et al. 1998 England Pre-Post N=7</p>	<p>Population: SCI; Age range 22-69 yr; Level=C6-T12; Time post-injury=6-38 yr.</p> <p>Intervention: Intermittent catheterization (IC) 5-6/d alone first then with intra-vesical instillation of oxybutynin (5mg in 30mL) 1-3 times/d for 14 to 30 mo in individuals originally managed by condom catheterization.</p> <p>Outcome Measures: Customized scales of urinary continence, sexuality, quality of life (QoL) and monitoring of side effects.</p>	<ol style="list-style-type: none"> 1. All subjects showed increased continence with IC and much more so with oxybutynin added. 2. 6 subjects reported increased sexuality with IC and all subjects had higher ratings with oxybutynin added. 3. Mixed results with QoL with IC but consistently increased QoL when added oxybutynin. 4. Decreased UTIs with IC and oxybutynin.
<p>Szollar & Lee 1996 USA Pre-Post N=13</p>	<p>Population: SCI individuals with neurogenic bladder dysfunction; Mean age: 41 yr (range 20-68 yr);</p>	<ol style="list-style-type: none"> 1. Mean bladder capacity and volume at first contraction both increased (bladder: 344-400 cc; volume: 167-184 cc) at the 3 mo

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
	Level of injury: C5-L1; Time post-injury: 8.7 yr (range 1-26 yr). Intervention: Intravesical oxybutynin; videourodynamic study. Outcome Measures: Bladder capacity, leak point pressure, volume at first urge to void.	follow-up, but this improvement was not significant. 2. Leak point pressure significantly decreased (65-47 cmH ₂ O).
Singh & Thomas 1995 UK Pre-Post N=6	Population: Mean age: 36 yr; Gender: males=6, females=0. Intervention: Oxybutynin hydrochloride (10mg) was instilled through the urethral catheter and left in the bladder for 60 minutes. Outcome Measures: Maximum Detrusor Pressure (DPmax), peak flow rate. Video urodynamic assessment was conducted before and after oxybutynin instillation.	1. No significant difference was seen before and after oxybutynin instillation in: • DPmax (p=0.2). • Peak flow rate (p=0.54). 2. Urinary residual did not increase after oxybutynin instillation.
Prasad & Vaidyanathan 1993 India Pre-Post N=14	Population: Injury etiology: SCI (n=8), myelomeningocele (n=2), transverse myelitis (n=1), post-rabies vaccine polyradiculopathy (n=1), prolapsed intervertebral disc (n=1), retroperitoneal neuroblastoma (n=1); all individuals practiced clean intermittent catheterization and their maximum cystometric capacity was below 250 ml or vesical compliance was less than 5. Intervention: Intravesical oxybutynin chloride (5 mg tablet) Outcome Measures: Bladder capacity, and vesical compliance.	1. No local or systemic side effects were observed during follow-up (6-12 mo) in the majority of individuals; one individual however could not retain the drug intravesically and was excluded, while one was lost to follow-up. 2. The remaining 12 individuals demonstrated increases in maximum cystometric capacity and vesical compliance.

Discussion

George et al. (2007) described results of a double-blind crossover (6 day washout) trial comparing propantheline (15mg) and oxybutynin (5mg) solutions (10ml) for thrice daily intravesical instillation in 18 individuals with SCI that managed their neurogenic bladder dysfunction with clean IC. Capsaicin was also included as a comparator but because instillation required local anesthesia to prevent hyperreflexia, CAP treatment could not be blinded. Although the study suggests that all of the intravesical agents exhibited effective attributes as adjuvant treatments, more subjects demonstrated improvement with propantheline (vs. oxybutynin) for residual volume, detrusor leak point pressure and clean IC volume. However, there was a significant worsening of leak frequency (p=0.039) for propantheline versus oxybutynin. Conversely, the pre-post CAP results revealed significant improvement for leak volume and leak frequency and significant worsening for residual volume and cystometric capacity. Two of the individuals with the oxybutynin instillations developed systemic side effects (e.g., dry mouth) typical

of those on oral oxybutynin. Two individuals experienced autonomic dysreflexia following CAP instillation.

Vaidyanathan et al. (1998) reported a pre-post trial (n=7) for which individuals originally managed by condom catheterization were switched to IC. Oral oxybutynin was provided to five study participants to overcome mild to moderate urine leakage between intermittent catheterizations. As a result of unacceptable side effects, oral oxybutynin was replaced with intravesical instillation to overcome the unacceptable side effects of the oral formulation. However, despite daytime continence, reduced UTI frequency and cessation of dry mouth, three of the five study participants reported continued nocturnal leaking 1-2 times per week when IC was accompanied by intravesical instillation. In all seven individuals, QoL scores were mixed with IC alone but showed a definite improvement when oxybutynin was added.

Ersoz et al. (2010) studied individuals who used indwelling catheters and were treated simultaneously with oral and intravesical oxybutynin. With this combination treatment, significantly improved bladder volumes were reported, however, 52.6% of individuals were lost to attrition and reports of difficulty with intravesical instillation of oxybutynin were common.

Haferkamp et al. (2000) studied the addition of intravesical oxybutynin instillation in individuals who performed IC five times daily and who were not adequately treated with oral anticholinergic medication (n=15) and/or experienced intolerable side effects from the oral medication (n=13). Four additional pediatric participants were included who had difficulty swallowing oxybutynin tablets. Of the 32 participants with SCI and neurogenic bladder function, twenty-one became continent with a standard dosage (0.3-0.7mg/kg/day) and eleven required a higher dosage (0.9mg/kg/day). Two participants treated with the higher dose complained of constipation and dryness of the mouth; none of the participants withdrew from treatment.

Intravesical oxybutynin (15mg TID) treatment was combined with oral treatment (5 mg four times daily) in a group of 25 individuals with SCI that had detrusor storage pressures greater than 40cm H₂O (n=21) or persistent autonomic dysregulation (n=5) for at least 3 months (Pannek et al. 2000). All participants performed clean IC and 8 of 25 participants also received desipramine treatment. Although detrusor storage pressure responded well and no participants discontinued treatment as a result of side effects, autonomic dysregulation was not resolved with the combination treatment. This study reported that surgical intervention for detrusor hyperreflexia was avoided in 80% of individuals as a result of combination treatment with intravesical and oral oxybutynin. When combined therapy proved successful, a structured reduction of oral oxybutynin was undertaken in 11 of 25 participants and this likely contributed to the lack of side effects reported in this study.

Intravesical instillation of oxybutynin (5 mg suspended in 10 ml water) combined with clean IC was reported to increase bladder capacity in a group of 12 individuals (SCI n=8) with neurogenic bladder dysfunction (Prasad & Vaidyanathan 1993). Six to 12 months of follow-up revealed significantly improved maximum cystometric

capacity and vesical compliance (both $p < 0.001$) and decreased clean IC frequency ($p < 0.05$). Notably, no local or systemic side effects were reported.

Szollar & Lee (1996) also reported significantly decreased leak point pressure and improved mean bladder capacity and mean volume at first contraction, for 10 of 13 individuals (including an initial non-responder) with SCI treated with intravesical oxybutynin (5 mg diluted in 30 ml saline, tid for 3 months). Participants were selected if they practiced clean IC but were intolerant to 5 mg TID oral oxybutynin. After 3 months of treatment, no local or systemic side effects were reported. An initial non-responder continued to experience incontinence after augmentation cystoplasty but did eventually respond positively to oxybutynin instillation post-operatively.

In contrast, Singh and Thomas (1995) presented a pre-post study with oxybutynin instillations (10 mg) in 6 male participants with SCI who had Brindley anterior root stimulators implanted and who failed to demonstrate significant improvements in peak detrusor pressure during voiding and peak flow rate. During implantation of the Brindley anterior root stimulator, sacral dorsal rhizotomies are performed. Considering oxybutynin's effectiveness in individuals who manage their neurogenic bladder dysfunction with catheterization; the lack of efficacy in the above study could be attributable to the absence of an intact sacral arc and therefore may provide additional insight into the mechanism of action for oxybutynin.

Conclusions

There is level 2 evidence (from one RCT; George et al. 2007) advocating for propantheline and oxybutynin intravesical instillation as adjuvant therapy for neuropathic bladder dysfunction managed with clean intermittent catheterization; with propantheline being superior in more cystometric parameters.

There is level 4 evidence (from a pre-post study; George et al. 2007) supporting the use of capsaicin intravesical instillation in reducing leak volume and frequency. However, this study also revealed that capsaicin intravesical instillation increased residual volume and decreased cystometric capacity, and can induce hyperreflexia in individuals with SCI and neurogenic bladder dysfunction.

There is level 4 evidence (from three pre-post studies; Vaidyanathan et al. 1998; Szollar & Lee 1996; Parsad & Vaidyannathan 1993) that intermittent catheterization combined with intravesical oxybutynin instillation is effective for the treatment of neuropathic bladder dysfunction following SCI.

There is level 4 evidence (from three pre-post studies; Haferkamp et al. 2000; Pannek et al. 2000; Ersoz et al. 2010) that the intravesical instillation of oxybutynin is an effective adjuvant therapy for individuals with SCI who manage their neurogenic bladder dysfunction with intermittent catheterization and oral oxybutynin.

There is level 4 evidence (from one pre-post study; Singh & Thomas 1995) that intravesical oxybutynin instillation is not effective in males with SCI following the surgical implantation of a Brindley anterior root stimulator.

Both propantheline and oxybutynin intravesical instillations improve cystometric parameters in individuals with SCI and neuropathic bladder, but propantheline provides superior improvement in more parameters.

Catheterization combined with intravesical instillation of oxybutynin alone or in addition to oral oxybutynin is effective in improving the symptoms of neuropathic bladder in individuals with SCI.

For individuals with SCI and neuropathic bladder, capsaicin can decrease leak volume and frequency but can also increase residual volume and cystometric capacity as well as induce hyperreflexia.

Intravesical instillation of oxybutynin is ineffective for male individuals with SCI who have an implanted Brindley anterior root stimulator.

4.1.4 Other Pharmaceutical Treatments for SCI-Related Detrusor Overactivity

There are other therapies reported to decrease NDO that have not been mentioned nor fit into the categories noted above. In particular, medications that have been traditionally used for treating spasticity of skeletal muscles following SCI (e.g., intrathecal baclofen and clonidine) have been reported to be helpful for decreasing spasticity of the bladder in the same population. Intrathecal administration of medications has been used since the early 1990s for treating spasticity, and better spasticity control can be achieved with fewer systemic side effects compared to oral administration.

Table 6 Other Pharmaceutical Treatments for SCI-Related Detrusor Overactivity

Author Year Country Score Research Design Total Sample Size	Methods	Outcome
Phosphodiesterase-5 Inhibitors		
Gacci et al. 2007 Italy RCT PEDro=6 N=25	<p>Population: Mean age: 34.9 yr (range 24-60 yr); Gender: males=25, females=0; ASIA severity: A=18, B=n=7.</p> <p>Intervention: Subjects received either a 20 mg vardenafil injection (n=15) or placebo (n=10).</p> <p>Outcome Measures: Maximum detrusor pressure (MDP), maximum</p>	<ol style="list-style-type: none"> 1. Compared to placebo, vardenafil significantly decreased MDP and VDO ($p<0.001$ for all). 2. There was an improvement of MCC observed ($p<0.001$).

Author Year Country Score Research Design Total Sample Size	Methods	Outcome
Phosphodiesterase-5 Inhibitors		
	cystometric capacity (MCC), detrusor overactivity volume (VDO).	
Taie et al. 2010 Iran Pre-Post N=20	Population: Males with supra sacral SCI Intervention: 20mg of oral tadalafil Outcome Measures: Urodynamic variables	1. A significant increase in bladder compliance ($p<0.001$) and bladder capacity ($p<0.001$) was observed. 2. Maximum voiding detrusor pressure ($p<0.001$) and maximum detrusor filling pressure ($p<0.001$) decreased significantly after a single dose.
Intrathecal Baclofen		
Steers et al. 1992 USA PEDro=8 RCT N _{initial} =10; N _{final} =9	Population: SCI: Age=24-61 years; Gender: males=7, females=3; Time since injury=1-12 years. Intervention: Intrathecal bolus of baclofen or saline at L3 to L4. Outcome Measures: Reduction in spasticity, urodynamics.	1. Post bolus intrathecal: <ul style="list-style-type: none"> Increase in bladder volume at first sensation and bladder compliance at 2 hrs ($p<0.05$). Ashworth decrease >2. 2. Pre-Post continuous intrathecal baclofen: <ul style="list-style-type: none"> Increased volume, volume at first sensation, compliance, residual volume: $p<0.05$ Decreased maximum urethral pressure, voiding pressure: $p<0.05$. Change in bladder symptoms reported at or after 48 hours. Dosages ranged from 94- 372 ug (mean 220ug) and followup ranged from 12-23 months (mean 18).
Clonidine		
Chartier-Kastler et al. 2000a France Case Series N=9	Population: Gender: males=6, females=3; Level of injury: paraplegia; Severity of injury: complete, incomplete. Intervention: All underwent surgery to have a catheter implanted allowing intrathecal injections of clonidine. Outcome Measures: Complications.	1. No statistical results reported. 2. 6 of 9 subjects elected to have permanent pump implantation for the treatment of severe detrusor hyperreflexia. 3. No complication or infections reported.
Mirabegron		
Wollner et al. 2016a Switzerland Pre-Post N=15	Population: Neurogenic detrusor overactivity; Mean age=45 yr; Gender: males=11, females=4; Level of injury: cervical=3, thoracic=8, lumbar=2, none=2; ASIA classification: A=8, B=0, C=1, D=4;	1. Post-intervention, there was a significant decrease in maximum detrusor pressure ($p=0.018$).

Author Year Country Score Research Design Total Sample Size	Methods	Outcome
Phosphodiesterase-5 Inhibitors		
	<p>Injury etiology: traumatic=12, myelomeningocele=1, multiple sclerosis=1; encephalomyelitis=1.</p> <p>Intervention: Mirabegron 25 mg/d and 50 mg/d after 2 wk.</p> <p>Outcomes: Maximum detrusor pressure, maximum cystometric capacity, compliance, frequency of 24 hr bladder evacuation, 24 hr incontinence episodes, satisfaction, side effects.</p>	<ol style="list-style-type: none"> Maximum cystometric capacity and compliance showed non-significant increases. The frequency of bladder evacuation per 24 hr ($p=0.003$) and incontinence episodes per 24 hr ($p=0.027$) were significantly reduced. Of the 15 participants, 9 were satisfied with the therapy and 4 reported side effects.

Discussion

With respect to bladder management, phosphodiesterase-5 inhibitors (PDE5) inhibitors are postulated to promote relaxation of the detrusor muscle, thereby decreasing overactivity and increasing capacity and compliance. This was confirmed in work by Taie et al. (2010) in male participants with suprasacral SCI where bladder compliance and capacity increased, and maximum voiding detrusor pressure and filling pressure decreased significantly following a single dose of 20mg oral tadalafil. An RCT by Gacci et al. (2007) examined the effect of vardenafil injections compared to placebo injections on maximum detrusor pressure, maximum cystometric capacity, and detrusor overactivity volume among 25 individuals with SCI. The authors reported significant improvements in the vardenafil group compared to the placebo group ($p<0.001$ for all).

Chartier-Kastler et al. (2000a) specifically used test bolus intrathecal injections of clonidine (ITC) to investigate its effects on SCI NDO in individuals otherwise resistant to a combination of oral treatment and self-IC. After the test bolus injection, 6 of 9 subjects elected to have permanent pump implantation for the treatment of severe detrusor overactivity. Confirmatory studies of this proposed alternative treatment are needed as the sample size was small and no objective outcome measures were used.

Steers et al. (1992) investigated the use of intrathecal baclofen specifically for the treatment of genitourinary function in 10 individuals with severe spasticity post SCI. Compared to placebo, involuntary bladder contraction induced incontinence was eliminated and one individual was able to convert from indwelling urethral catheterization to intermittent self-catheterization. Bladder capacity was increased by a mean of 72% while detrusor-sphincter dyssynergia was eliminated in 50% of individuals. Steers et al. (1992) recommend the use of intrathecal baclofen for SCI genitourinary dysfunction when oral pharmacological interventions are insufficient to improve bladder function. However, in light of the documented effectiveness of botulinum toxin described above, the relative ease and temporary nature of treatment with botulinum toxin, and the absence of significant adverse effects, it is

unlikely that clinicians would chose intrathecal treatments over toxin therapy except in cases when intrathecal therapy is indicated for other reasons (e.g., spasticity).

Mirabegron, a detrusor muscle relaxant (β -3 agonist) was shown to be effective in 9/15 individuals suffering from NDO (Woolner & Pannek 2016) after at least 6 weeks of administration. Four individuals reported side effects and the 2 remaining individuals were excluded due to missing data.

Conclusions

There is level 1b evidence (from one RCT and one pre-post study; Gacci et al. 2007; Taie et al. 2010) that phosphodiesterase-5 inhibitors may be beneficial in improving bladder function post SCI.

There is level 1b evidence (from one RCT; Steers et al. 1992) that intrathecal baclofen may be beneficial for bladder function improvement in individuals with SCI when oral pharmacological interventions are insufficient.

There is level 4 evidence (from one case series; Chartier-Kastler et al. 2000a) that the use of intrathecal clonidine improves detrusor overactivity in individuals with SCI when a combination of oral treatment and intermittent catheterization is insufficient.

There is level 4 evidence (from one retrospective chart analysis; Wollner & Pannek 2016a) that supports the use of mirabegron to improve the symptoms of NDO.

Tadalafil, vardenafil, intrathecal baclofen, clonidine and mirabegron may be beneficial for bladder function improvement but further confirmatory evidence is needed.

4.2 Enhancing Bladder Volumes Non-Pharmacologically

4.2.1 Electrical Stimulation to Enhance Bladder Volumes

Electrical stimulation, most notably anterior sacral root stimulation, has been used to enhance bladder volume and induce voiding (Egon et al. 1998; Brindley et al. 1982). Typically, this approach has involved concomitant dorsal sacral rhizotomy and implantation of a sacral nerve stimulator. The combined effect of this is a more compliant bladder, enhanced storage capacity under lower pressure, and triggered voiding resulting in reduced incontinence; without the need to catheterize. As the focus of many of the studies involving electrical stimulation is both increased bladder capacity and control of bladder emptying, we will describe the evidence for these and other methods of electrical stimulation for improving bladder outcomes

in a single subsequent subsection (see section 3.4.7 Electrical Stimulation for Bladder Emptying (and Enhancing Volumes)).

4.2.2 Surgical Augmentation of the Bladder to Enhance Volume

Bladder augmentation or augmentation cystoplasty is a surgical procedure that increases bladder capacity and prevents detrusor overactivity. It is typically considered when conservative approaches such as anticholinergics or intravesical botulinum toxin with IC have failed, or when there is a small capacity poorly compliant bladder (Chartier-Kastler et al. 2000b; Quek & Ginsberg 2003). Intolerable incontinence or renal deterioration are common reasons that may lead the clinician to consider definitive urological surgery. Several approaches have been described in the SCI literature with a common method being variations of the “clam-shell” ileocystoplasty in which the bladder is opened up like a clam and an isolated segment of intestine (ileum) is used to create a patch that is then sewn into the bladder to create a larger bladder (Chartier-Kastler et al. 2000a; Nomura et al. 2002; Quek & Ginsberg 2003; Chen & Kuo, 2009). Surgical techniques focused on urinary diversion from the bladder and subsequent drainage (e.g., cutaneous ileal conduit diversion) are discussed in the section addressing incontinent urinary diversion and drainage (see section 3.4.6 Continent Catheterizable Stoma and Incontinent Urinary Diversion).

Table 7 Surgical Augmentation of the Bladder to Enhance Volume

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
Anquetil et al. 2016 France Cohort N=30	<p>Population: Detrusor overactivity; Mean age: 41.9 yr; Gender: males=16, females=14; Level of injury: paraplegia=12, tetraplegia=18; Severity of injury: complete=23, incomplete=7; Mean time post-injury: 16.57 yr.</p> <p>Intervention: Study participants had received either at least two successive botulinum therapy injections (BT) or augmentation enterocystoplasty (AC).</p> <p>Outcome Measures: Method of bladder drainage, urinary incontinence, complications, maximum detrusor pressure, low compliance, maximum cystometric bladder capacity, Qualiveen-30.</p>	<ol style="list-style-type: none"> 1. In the BT group, 12 used clean intermittent self-catheterization, 2 used clean intermittent catheterization, and 0 used indwelling catheterization, while in the AC group, 14 used clean intermittent self-catheterization, 1 used clean intermittent catheterization, and 1 used indwelling catheterization. 2. Urinary incontinence occurred more frequently in BT than AC ($p=0.0187$). 3. Four AC participants had postoperative complications while there were no complications for BT participants. No significant differences between groups were observed in terms of urinary lower tract infections. 4. Two participants had a high maximum detrusor pressure and one participant had low

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
		<p>compliance in the BT group compared to none in the AC group.</p> <p>5. Maximum cystometric bladder capacity in BT group was 418 mL compared to 550 mL in AC group.</p> <p>6. The mean Qualiveen-30 score was significantly higher (worse) in BT group than in AC group ($p=0.037$).</p>
Reyblat et al. 2009 USA Case Control N=73	<p>Population: SCI=68; Mean age: 34 yr; Gender: males=55, females=18.</p> <p>Intervention: Charts were reviewed for individuals who had previously undergone extraperitoneal augmentation (n=49) and intraperitoneal augmentation (n=24) to assess effectiveness.</p> <p>Outcome Measures: Complication rate, operation time, bowel function, catheterization time.</p>	<p>1. Overall complication rate was similar in both groups (extraperitoneal 37% versus intraperitoneal 42%).</p> <p>2. Intraperitoneal group had a significantly higher operation time than the extraperitoneal group ($p<0.0001$).</p> <p>3. Bowel function returned earlier in extraperitoneal group than the intraperitoneal group ($p=0.0005$).</p> <p>4. No significant difference was seen between the groups in mean time to catheter removal.</p>
Krebs et al. 2016 Switzerland Pre-Post N=29	<p>Population: Neurogenic lower urinary tract dysfunction; Mean age: 34 yr; Gender: males=17, females=12; Level of injury: paraplegia=26, tetraplegia=3; Severity of injury: incomplete=13, complete=16; Injury etiology: trauma=12, non-trauma=6, myelomeningocele=11.</p> <p>Intervention: Participants had received supratrigonal cystectomy and augmentation ileocystoplasty.</p> <p>Outcomes: Continence, detrusor relaxation therapy, maximum detrusor pressure, reflex volume, bladder capacity, detrusor compliance, maximum detrusor pressure >40 cm H₂O, detrusor compliance <20 mL/cm H₂O, risk of renal damage, complications.</p>	<p>1. At a median follow-up of 2.4 yr post-operatively, compared to prior treatment, there was a significant increase in the number of continent participants ($p=0.001$) and a significant decrease in number of participants requiring detrusor relaxation therapy ($p=0.02$).</p> <p>2. Compared to prior treatment, participants receiving treatment had significant increases in reflex volume ($p=0.006$), bladder capacity ($p=0.001$), and detrusor compliance ($p=0.001$).</p> <p>3. Compared to prior treatment, there was a significantly lower number of participants with high detrusor pressure ($p=0.001$), low detrusor compliance ($p=0.001$), and risk of renal damage ($p=0.001$).</p> <p>4. Of the 29 participants, complications were observed in 11 participants, with 6 participants requiring surgical interventions to resolve the complications.</p>

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
Perrouin-Verbe et al. 2016 France Pre-Post N=29	<p>Population: Median age: 35 yr; Gender: males=7, females=22; Level of injury: cervical=17, thoracic=10, lumbar=2; Median time post-injury: 9 yr.</p> <p>Intervention: Individuals unable to perform intermittent self-catheterization through the native urethra received continent cutaneous urinary diversion with a concomitant supratrigonal and augmentation enterocystoplasty.</p> <p>Outcome Measures: Postoperative complications, duration of hospitalization, long-term complications, urethral continence, antimuscarinics, onabotulinum toxin A, detrusor overactivity, low bladder compliance, maximal cystometric capacity, maximal detrusor pressure, creatinine clearance, upper urinary tract dilation, quality of life.</p>	<ol style="list-style-type: none"> 1. During the first month post-surgery, there were three minor complications, two major complications and no deaths. 2. The overall complication rate was 44.8% and the total reoperation rate was 24.1%. 3. Compared to before surgery, the number of participants with urethral incontinence ($p=0.013$), using antimuscarinics, using onabotulinum toxin A, with detrusor overactivity ($p=0.0006$), with low bladder compliance ($p=0.05$), and upper urinary tract dilation significantly decreased. 4. There was a significant increase for the median maximal cystometric capacity ($p=0.021$), a significant decrease for maximal detrusor pressure ($p=0.05$), and no significant difference in creatinine clearance. 5. Urethral continence was achieved in 96% of participants and quality of life was improved in 90%.
Gobeaux et al. 2012 France Pre-Post N=61	<p>Population: Mean age: 34.7 ± 11.2 yr (range=14-68); Gender: males=30, females=31; Level of injury: Above T6=18, T6-12=32, Below T12=11; Injury etiology: Traffic accident=41, Defenestration=7, Spinal cord surgery=6, Sport=3, Firearm=3, Other=1. Mean time post-injury: 9.7 ± 1.6 yr.</p> <p>Intervention: Participants underwent supratrigonal cystectomy with Hautmann pouch surgery.</p> <p>Outcome Measures: Total continence rate, surgery success, maximum cystometric capacity (MCC), mean compliance (MC), mean detrusor pressure (MDP), neurogenic detrusor overactivity (NDO), complication rate, incidence of bowel dysfunction.</p>	<ol style="list-style-type: none"> 1. Continence was significantly improved for 52 of the 58 participants (89.7% ($p<0.05$)) and total continence was achieved in 74.1% of cases ($N=43$). 2. Mean MCC and MC after treatment significantly increased ($p<0.05$). 3. MDP before versus after treatment significantly decreased from 54.1 to 19.1 cmH₂O resp. ($p<0.05$). 4. Persistent NDO was evident in 36 participants (59%) pre-surgery versus 12 participants (20.7%) post-surgery ($p<0.05$). 5. The overall surgery complication rate was 37.7% ($N=23$) of which 82.6% were \leq grade 2 ($N=19$).
Chen & Kuo 2009 Taiwan Pre-Post N=40	<p>Population: Mean age: 36.3 yr; Gender: males=36, females=4; mean follow up: 7.8 yr (range 1-14 yr); level of SCI - suprasacral: 33,</p>	<ol style="list-style-type: none"> 1. The bladder capacity improved from 115 to 513 mL postoperatively ($p<0.0001$). 2. Bladder compliance also improved significantly ($p<0.0001$).

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
	sacral: 7; 95% of participants had incontinence Intervention: Augmentation enterocystoplasty surgery Outcome Measures: Urodynamic variables; adverse events	Four participants could achieve continence while 29 required clean IC for bladder management.
Chartier-Kastler et al. 2000b France Pre-Post N=17	Population: Mean age: 36.5 yr; Gender: males=11, females=6; Level of injury: above T6=4, T6-T12=9, below T12=4; Severity of injury: complete=14, incomplete=3; Mean duration of SCI=7.5 yr. Intervention: Participants underwent partial cystectomy with enterocystoplasty or detubularized clam cystoplasty. Outcome Measures: Continence, maximal cystometric capacity, filling pressure, complications.	<ol style="list-style-type: none"> 15 participants were completely continent postoperatively. A significant increase in maximal cystometric capacity by 191% was seen ($p<0.05$). Maximal filling pressure decreased by 72% ($p<0.05$). No complications were encountered.
Gurung et al. 2012 UK Case Series N=19	Population: Mean age: 28.9 yr (range=12-52); Gender: male=12, female=7; Level of injury: Cervical=1, Thoracic=16, Lumbar=2; injury etiology: RTA (road traffic accident) (N=11), Fall (N=6), Gunshot (N=2); Mean time from injury to operation: 4.5 yr (range=0.3-22). Intervention: Participants underwent augmentation ileocystoplasty (AIC), with follow-up at 3 mo, 1 yr, 5 yr and <10 yr. Outcome Measures: Maximum cystometric capacity (MCC), Maximum detrusor pressure (MDP), Quality of life (QoL).	<ol style="list-style-type: none"> Of the 26 participants who had undergone AIC before 1998, only 19 participants were available for long-term follow-up/analysis. Two participants died from unrelated causes. Of the 17 participants, continence was reported in 15/17 participants (vs 0 before surgery). MCC at the latest follow-up at >10 yr post-surgery increased significantly from an estimated preoperative mean of 229ml to a mean of 494ml (range=387-601 ml) ($p<0.001$). MDP at the latest follow-up at >10 yr post-surgery, decreased significantly from a preoperative value of 81cmH₂O to a mean of 28cmH₂O (range=15-40 cmH₂O) ($p<0.001$). Of the 14 participants who completed the questionnaire survey, 13/14 were satisfied with the outcome such that they would consider undergoing the procedure again and would recommend it to someone else.
Quek & Ginsberg 2003 USA Case Series N=26	Population: Individuals with SCI and bladder augmentation: Mean age: 29 yr; Gender: males=18, females=8. Intervention: Bladder augmentation with a minimum of	<ol style="list-style-type: none"> There was a significant increase in bladder capacity from preaugmentation to postaugmentation ($p<0.001$).

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
	retrospective review of 4 yr. The majority of participants had this done in conjunction with various other continence or antireflux techniques. Outcome Measures: Bladder capacity, maximum detrusor pressure, subsequent operations, bowel function, UTI, complications, satisfaction. Mean follow up=8 yr.	<ol style="list-style-type: none"> Mean maximum detrusor pressure decreased significantly ($p<0.01$). No significant changes in bowel function were seen in 23 participants. 88% of participants with previous symptomatic urinary infections had significant improvement in the frequency of infections. Participants were very satisfied with the bladder augmentation and would recommend it to a friend.
Nomura et al. 2002 Japan Case Series N=11	Population: SCI: Mean age: 29.0 yr; Gender: males=10, females=1; Level of injury: thoracic=11; Severity of injury: complete=10, incomplete=1; Injury etiology: trauma=10, transverse myelitis=1; Mean time post-injury=73.5 mo. Intervention: Retrospective review of augmentation ileocystoplasty. Outcome Measures: Bladder capacity, continence, complications.	<ol style="list-style-type: none"> Bladder capacity increased significantly postoperatively ($p<0.001$). All participants showed improvement in urinary incontinence. Complications included: <ul style="list-style-type: none"> Transient paralytic ileus occurred in 4 participants. Wound infection occurred in 1 participant.

Discussion

Like most surgical approaches, the evidence for surgical augmentation of the bladder exists in the form of clinical experience from individual centres and is described in retrospective chart reviews (Nomura et al. 2002; Quek & Ginsberg 2003; Chen & Kuo 2009; Reyblat et al. 2009) or less often in prospective studies limited to pre-post (cohort) study designs (Chartier-Kastler et al. 2000b; Anquetil et al 2016; Krebs et al 2016; Perrouin-Verbe et al 2016). Long-term retrospective results associated with ileocystoplasty in persons with traumatic and non-traumatic SCI (or spina bifida) were reported over a mean period of 5.5, 8 and 14.7 years by Nomura et al. (2002; n=21), Quek and Ginsberg (2003; n=26), and Gurung et al. (2012; n=19), respectively. Chartier-Kastler et al. (2000b) conducted a prospective evaluation of 17 persons with longstanding traumatic SCI who underwent enterocystoplasty (i.e., ileocystoplasty) with systematic follow-up at 1, 3, 6, 12 months and then yearly for a mean follow-up of 6.3 years. Krebs et al (2016) monitored 29 individuals, pre and post supratrigonal cystectomy and augmentation ileocystoplasty for a median follow-up of 2.4 years. Similarly, Perrouin-Verbe et al. (2016) followed individuals who were unable to perform intermittent self-catheterization and subsequently underwent supratrigonal and augmentation enterocystoplasty. Anquetil et al. (2016) compared results after augmentation enterocystoplasty to repeated (at least 2 successive)

botulinum therapy injections. Chen and Kuo (2009) reported on 40 adults with SCI. Gobeaux et al. (2012) presented data on 61 persons with SCI individuals who underwent supratrigonal cystectomy with Hautmann pouch.

Augmentation ileocystoplasty with Mitrofanoff appendicovesicostomy or continent urinary diversions (such as Kock ilial reservoir, or Indiana pouch) are described by Zommick et al. (2003) as efficacious lower urinary tract reconstruction options for select tetraplegic individuals. In all cases, this was conducted in individuals with overactive bladder and/or detrusor-sphincter dyssynergia with reflex incontinence which failed to respond to conservative treatment. Across all these studies, significant resolution of incontinence occurred in the majority of individuals. Chartier-Kastler et al. (2000b) conducted systematic urodynamic investigations and showed a significant increase in maximal cystometric capacity by 191% (174.1 to 508.1 ml, $p < 0.05$) with a concomitant decrease in maximal filling pressure of 72% (65.5 to 18.3 cm H₂O, $p < 0.05$). These results are similar to those reported by Nomura et al. (2002) and Quek and Ginsberg (2003). Reyblat et al. (2009) compared an “extraperitoneal” approach (small peritoneotomy and standard ‘clam’ enteroplasty) vs. the standard intraperitoneal approach, and found that the extraperitoneal approach resulted in shorter operative time, shorter hospital stay, and eventual return of bowel function. Serious complications were absent across most studies, and other complications were noted in relatively few individuals (e.g., transient paralytic ileus, vesicoureteral reflux, wound infection, urethral stricture of unknown cause, recurrent pyelonephritis possibly due to non-compliance with IC and use of Crede maneuver) with the vast majority responding well to conservative treatment (Chartier-Kastler et al. 2000b; Nomura et al. 2002; Quek & Ginsberg 2003). Subsequent subjective assessment of satisfaction with the procedure was reported to be extremely high (Quek & Ginsberg 2003); consistent with other similar investigations of individuals with SCI (Khastgir et al. 2003; Zommick et al. 2003). Chen and Kuo (2009) noted, however, that issues which commonly follow ileoplasty (e.g., UTI, reservoir calculi, new onset upper-tract urolithiasis) still require treatment. In a retrospective chart review Reyblat et al. (2009) reported equivocal postoperative continence using an extraperitoneal (small peritoneotomy and standard ‘clam’ enteroplasty) versus standard intraperitoneal augmentation. The extraperitoneal approach resulted in shorter operative time, shorter length of stay, and more rapid return of bowel function. There was a potential for selection bias in this study that was mitigated with a subgroup analysis to control for a significant confounding variable of higher rates of prior abdominal surgery in the intraperitoneal group (Reyblat et al. 2009). The Gobeaux et al. (2012) study reported an impressive average 5.84 year follow-up result of 74% complete continence, decreased rates of infection and preserved upper tract function as measured through urodynamics. The presence of subsequent bowel dysfunction (e.g., new onset diarrhea and/or fecal incontinence resulting from the ileal resection) in 27.5% of individuals, however, indicates that candidates need to be counseled carefully before choosing this intervention as a treatment option. Gurung et al. (2012) reported that although bladder stones are a common complication following cystoplasty, the encouraging long-term individual-reported satisfaction counterbalances the increased risk of this treatable complication.

Conclusion

There is level 4 evidence (from six pre-post, one post-test, one cohort, three case series, and one case control; Gobeaux et al. 2012; Chen & Kuo 2009; Chartier-Kastler et al. 2000b; Anquetil et al 2016; Krebs et al. 2016; Perrouin-Verbe et al. 2016; Gurung et al. 2012; Quek & Ginsberg 2003; Nomura et al. 2002; Reyblat et al. 2009) that surgical augmentation of the bladder (ileocystoplasty) may result in improved continence in persons with SCI who failed to respond adequately to alternative approaches and interventions for neurogenic bladder dysfunction.

There is level 3 evidence (from one case control; Reyblat et al. 2009) that extraperitoneal compared to intraperitoneal augmentation enterocystoplasty produces equivocal postoperative continence with better early postoperative recovery.

Surgical augmentation of bladder may result in enhanced bladder capacity, lower filling pressure, and improved continence in persons with SCI.

Extraperitoneal compared to intraperitoneal augmentation enterocystoplasty may result in a quicker postoperative recovery.

4.3 Enhancing Bladder Emptying Pharmacologically

Pharmacological management of dysfunctional bladder emptying is based on understanding the neuroanatomy of the lower urinary tract. The normal coordinated effort of the lower urinary tract includes bladder storage and emptying. During the filling process, sympathetic adrenergic receptors (e.g., norepinephrine) facilitate the storage of urine in the bladder. These efferent nerves originate from T11 to L2 and offer inhibitory input to the bladder. Beta-adrenergic receptors populate the smooth muscle of the bladder and their stimulation relaxes the bladder wall. Conversely, the prevalence of alpha-adrenergic receptors is greater in the lower portion of the bladder including the sphincter and their stimulation increases bladder outlet resistance. In contrast, parasympathetic nerves are responsible for bladder contractions and emptying. The parasympathetic nerves originate from S2 to S4 and provide increased excitatory input to cholinergic (e.g., acetylcholine) receptors in the bladder wall in response to bladder filling. In individuals with SCI lesions, these pathways may be interrupted leading to impairments in urine storage and emptying (Hanno, 2001).

Enhancing bladder storage, as discussed earlier in the chapter, involves relaxing the detrusor muscle thereby allowing for increased bladder volumes. Individuals with impaired bladder emptying have either a sphincter that fails to fully relax or alternatively weak or nonexistent detrusor muscle contractions; both of which compromise emptying. These individuals can be treated pharmacologically with oral alpha-adrenergic blockers or botulinum toxin (injected into the sphincter). Both

interventions are intended to improve voiding by decreasing the resistance to outflow but may also increase incontinence; a point not highlighted in the studies presented below. However, in male individuals who already have incontinence and are using condom drainage, but have persistently elevated residuals, alpha blockers or botulinum toxin (injected into the sphincter) may improve emptying.

4.3.1 Alpha-Adrenergic Blockers for Bladder Emptying

A variety of alpha-adrenergic blockers have been used to treat SCI bladder dysfunction. These drugs target alpha adrenoreceptor blocker subtypes which may be implicated in a variety of mechanisms including bladder neck dysfunction, increased bladder outlet resistance, detrusor-sphincter dyssynergia, autonomic hyperreflexia or upper tract stasis.

Table 8 Summary of Alpha-Adrenergic Blockers

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
Abrams et al. 2003 UK Study 1: RCT PEDro=8 N _{initial} =263; N _{final} =244 Study 2: Pre-Post N _{initial} =186; N _{final} =134	Population: SCI: Mean age: 18 yr; Time since injury: 85-103 mo. Intervention: Subjects were randomized to one of three groups; the 0.4mg tamsulosin, the 0.8mg tamsulosin or the placebo group. Medication or placebo were given once daily (after breakfast). Assessment for the groups was 2 and 4 weeks after treatment. Outcome Measures: Urethral closure pressure.	1. No significant change-maximal urethral closure pressure. 2. Significant individual micturition diary change – 1) incontinence episode frequency and pad change freq reduced with tamsulosin: 0.04mg (p=0.009); 2) increase in mean void volume was seen in the 0.08mg group (p=0.003); however not in the 0.04 group.
Costa et al. 1993 France RCT PEDro=8 N=20	Population: SCI: Age range 18-60 yr; Gender: males=20, females=0; Time post-injury=4mo-7 yr. Intervention: Moxisylyte at 0.25 mg, 0.50 mg, and 0.75 mg or placebo on different days separated by 4 to 7 days. According to the balance incomplete block design (3 treatments/individual). Outcome Measures: Maximum urethral closure pressure (trapezoidal rule used on tracings); pre/post arterial blood pressure and heart rate; pharmacodynamic analysis.	1. Treatment effects at 10min (p=0.0106). 2. Decrease in diastolic blood pressure of 17.8%, 14%, and 5.2% after 0.75 mg, 0.50 mg, and 0.25 mg, respectively. 3. Significant heart rate increases at 5, 10*, 15, 20, 30, 60 min (p=0.0016; *max). 4. For 0.50 and 0.75 mg/kg, significant difference at 20min (p<0.02) but not at 15min (p=0.0598). 5. Urethral closure pressure dose related-max of 47.6% reduction at 10min after 0.75 mg/kg.
Al-Ali et al. 1999 Iraq Pre-Post N _{initial} =46; N _{final} =41	Population: SCI: Age range 13-49 yr. Intervention: Phenoxybenzamine 10mg daily increased to 10 mg/twice daily and then 10 mg/3x daily for 3 wks to 6 mos.	1. No statistically significant results reported. 2. Improved max urethral closure pressure in 19 participants with reflex bladders.

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
	Outcome measures: Urethral closure pressure.	3. Non-responders=22 (9=areflexive bladders; 13=reflex bladders).
Perkash 1995 USA Pre-Post N=28	Population: SCI: Age range 20-74 yr; Severity of injury: Frankel: A, C-D. Intervention: Terazosin for voiding. Outcome Measures: Subjective assessment and detrusor voiding pressure (urodynamics).	1. Subjective assessment –14 participants improved voiding, 14 participants no difference. 2. Occasional autonomic dysreflexia in 11 participants. 3. Decreased voiding pressure in 12 participants, no change in 10, and increased pressure in 6.
Linsenmeyer et al. 2002 USA Case Series N ₁ =10; N ₂ =7	Population: Study 1: Mean age: 28 yr; Gender: males=10, females=0; Severity of injury: AIS: A, B; Study 2: Gender: males=7, females=0. Intervention: Study 1: impact of alpha blockers on upper tract stasis. Study 2: the impact of alpha blockers on urodynamic parameters in those with and without resolution of stasis. Outcome Measures: Urodynamic parameters: mean changes in opening pressure, maximum detrusor voiding pressure and duration uninhibited contraction.	1. Pre-treatment: 6 subjects taking prazosin, 4 taking terazosin. 2. Three month treatment with alpha blockers resolves upper tract stasis (p<0.0003). 3. Study 2: Uninhibited bladder contraction duration decreased with alpha-blocker usage (p<0.001). 4. Mean arterial pressure during uninhibited contraction significantly decreased during alpha-blocker treatment (p<0.01).
Chancellor et al. 1993a USA Case Series N ₁ =15; N ₂ =9	Population: SCI: Age range 18-45 yr; Gender: males=15, females=0. Intervention: Once Detrusor External Sphincter Dysynergia (DESD) without obstruction of the bladder neck or prostate was documented, therapy with terazosin (5mg daily) was initiated. Outcome Measures: Voiding pressure.	1. No significant differences in DESD voiding pressure after 4-12 weeks initial terazosin treatment (p=.48) 2. Voiding pressure was reduced (p<0.001) after subsequent external sphincterotomy or sphincter stent placement. 3. Out of 9 subjects who experienced persistent voiding symptoms after sphincterotomy following initial terazosin treatment, subsequent terazosin treatment improved voiding in participants with only bladder neck obstruction while the other 4 who did not improve had obstruction only at the external sphincter.

Note: SCI=Spinal Cord Injury, AIS=ASIA Impairment Scale

Discussion

Relieving symptoms of neurogenic bladder dysfunction by decreasing outflow resistance is achieved with alpha-1 blockers. Protection against the complications of

chronic urinary retention is the primary intent of the therapeutic use of alpha-adrenergic blocking drugs for neurogenic bladder dysfunction.

Tamsulosin is an alpha-1 adrenoreceptor antagonist that has been used to treat SCI bladder neck dysfunction by relaxing smooth muscles in the bladder neck to improve urine flow rate. A large scale (n=263) study conducted by Abrams et al. (2003) provided evidence for decreased micturition frequency and improvement in urinary leakage parameters for individuals with SCI. The study was a 4-week RCT followed by an open-label period conducted over one year in persons with overactive bladder with or without dyssynergia. Maximal urethral pressure determined via urethral pressure profilometry demonstrated a significant reduction during the longer open-label period ($p < 0.001$), but not the one-month RCT. In the 1-year open-label investigation, tamsulosin was also associated with improvement in several cystometry parameters related to bladder storage and emptying, as well as increased mean voided volume values as reported in a individual diary. Given that positive outcomes were more apparent during the open-label phase, which consisted of a pre-post trial design, the study has been assigned as level 4 evidence.

Moxisylyte is an alpha adrenoreceptor blocker used commonly in the treatment of Raynaud's disease in which constriction of the blood vessels in the hands causes numbness and pain in the fingers. In a small RCT, Costa et al. (1993) investigated the off-label use of moxisylyte in the treatment of SCI bladder neck dysfunction due its property as a smooth muscle relaxant. A decrease in urethral closure pressure was found to be dose related and significant when compared to placebo, with the maximum reduction of 47.6% occurring 10 minutes following the administration of 0.75mg/kg in individuals with SCI.

Terazosin is most often used to treat hypertension. However, this alpha-adrenergic blocker can also be used to treating bladder neck dysfunction by relaxing the bladder neck and reducing resistance to outflow during the voiding process. Perikash et al. (1995) reported that although 82% of individuals (N=28) without detrusor sphincter dyssynergia perceived improvement in voiding, only 42% registered objective decreases in maximum urodynamic voiding pressure. Side effects and tolerance may be deterrents to the wide-spread adoption of terazosin as an treatment for bladder neck dysfunction following SCI. The specificity of terazosin's action on the bladder neck, exclusive of the external sphincter, was demonstrated by Chancellor et al. (1993a).

Phenoxybenzamine is an antihypertensive which is usually used to treat autonomic symptoms of pheochromocytomas such as high blood pressure or excess sweating. Al-Ali et al. (1999) undertook to utilize the autonomic effects of phenoxybenzamine to treat bladder dysfunction which is in part under autonomic control. Treatment with phenoxybenzamine resulted in a reduction of bladder outlet resistance, detrusor-sphincter dyssynergia and autonomic hyperreflexia in some subjects while no benefits were recorded for individuals with areflexive bladders. Phenoxybenzamine might therefore be beneficial as an adjunct treatment for neurogenic bladder dysfunction following SCI, when tapping or crede is unable to achieve satisfactory residual urine volumes of <100 mL. The lack of efficacy in those with bladder neck

dysfunction was specifically noted in this study. Since statistically significant results were not reported in this study, further appropriately-sized RCTs are needed to establish the efficacy of phenoxybenzamine for treating neurogenic bladder dysfunction following SCI.

The pyelourethral smooth muscle responsible for urethral peristalsis and movement of the urine from the kidneys to the bladder via the ureters is also a potential site of action for alpha 1-receptor antagonist therapy. In a small (n=10) retrospective chart review, Linsenmeyer et al. (2002) identified men with upper tract (i.e. kidneys and ureters) stasis secondary to SCI \geq T6 who used reflexive voiding to manage their bladders. After 6 months of alpha-1 blocker therapy, improvement in upper tract stasis was reported for 80% of the sample, as measured by significant decreases in duration of uninhibited bladder contractions. Firm conclusions about effectiveness and the optimum duration of treatment can only be validated with further RCTs.

Conclusion

There is level 1b evidence (from one RCT; Costa et al. 1993) that moxislyte decreases maximum urethral closure pressure by 47.6% at 10 minutes after an optimum dose of 0.75 mg/kg in individuals with SCI.

There is level 4 evidence (from one pre-post study; Abrams et al. 2003) that tamsulosin may improve bladder neck relaxation and subsequent urine flow in individuals with SCI.

There is level 4 evidence (from one pre-post and one case series study; Perlash 1995; Chancellor et al. 1993a) that supports terazosin as an alternative treatment for bladder neck dysfunction in individuals with SCI; provided that side effects and drug tolerance are monitored.

There is level 4 evidence (from one case series study; Al-Ali et al. 1999) that suggests that phenoxybenzamine might have a role as an adjunct treatment for neurogenic bladder dysfunction following SCI, when tapping or crede is insufficient to achieve residual urine volumes <100mL.

There is level 4 evidence (from one case series study; Linsenmeyer et al. 2002) that 6 months of alpha-1 blocker therapy may improve upper tract stasis in men with SCI by decreasing the duration of involuntary bladder contractions.

Tamsulosin may improve urine flow in SCI individuals with bladder neck dysfunction.

Mosixylyte is likely able to decrease maximum urethral closure pressure at a dose of 0.75mg/kg in individuals with SCI.

Terazosin may be an alternative treatment for bladder neck dysfunction in individuals with SCI; however, side effects and drug tolerance should be monitored.

Phenoxybenzamine may be useful as an adjunct therapy for reducing residual urine volumes in individuals with SCI who manage their neurogenic bladder dysfunction by performing crede or tapping maneuvers.

Six months of alpha 1-blocker therapy in men with SCI may improve upper tract stasis.

4.3.2 Botulinum Toxin for Bladder Emptying

Botulinum toxin is an exotoxin produced by the bacteria *Clostridium botulinum*. As noted previously (see 3.1.2 Toxin therapy for SCI-related Detrusor Overactivity), it has been used for many conditions associated with muscular overactivity and specifically for NDO. Among individuals with sphincter overactivity post SCI, botulinum toxin may be administered into the external urethral sphincter causing the muscle to relax resulting in improved drainage (DeSeze et al. 2002). The toxin works by inhibiting acetylcholine release at the neuromuscular junction and relaxing the muscle, an effect that gradually wears off over the months following injection. Injections of botulinum toxin A into the sphincter may improve emptying and possibly eliminate the need for catheterization.

Table 9 Bladder Emptying through Botulinum Toxin

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
DeSeze et al. 2002 France RCT PEDro=7 N=13	Population: Mean age: 45.5 yr; Gender: males=12, females=1; Level of injury: paraplegic=9, tetraplegic=4. Intervention: Participants were randomly placed into two groups: 1) botulinum A toxin group (BTX) received one injection of 100 IU onaBTX in 4 mL of 9% saline into the external urethral sphincter or 2) lidocaine group (LG) received an injection of 4mL of 0.5% lidocaine into the external urethral sphincter. Outcome Measures: Maximal urethral pressure, maximum detrusor pressure and detrusor sphincter dyssynergia. One month	<ol style="list-style-type: none">1. The BTX group showed significant decrease in post-voiding residual volume (PRUV; $p<0.01$) and maximal urethral pressure ($p<0.04$). However, no significant change was seen in the lidocaine group.2. After one month, autonomic dysreflexia disappeared in participants from BG but remained unchanged in the lidocaine group.3. Participants in the BTX group gave a significantly higher mean efficacy score compared to the LG group.

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
	after the injections, the efficacy and tolerance was assessed.	4. No significant difference was seen in tolerance between the two groups.
Dykstra & Sidi 1990 USA RCT PEDro=5 N=5	<p>Population: Mean age: 32 yr; Gender: males=5, females=0; Level of injury: cervical; Severity of injury: complete=4, incomplete=1; Mean time post-injury=14 yr.</p> <p>Intervention: Injection of 140 U of botulinum A toxin (or saline) into 3-4 sites of the external urethral sphincter via cystoscope followed by two more injections of 240 U.</p> <p>Outcome Measures: Cystometry to obtain post-void residual (PVR), urethral pressure profiles, bladder pressure on voiding obtained pre-post 3 week treatment periods.</p>	<ol style="list-style-type: none"> 1. OnaBTx reduced bladder flow obstruction as indicated by decreases in all measures. 2. A mean decrease from baseline to 3 weeks post injection was seen in: <ul style="list-style-type: none"> • Urethral pressure profiles: 22cm H₂O • Post void residual volume: 118cc • Bladder pressure: 25cm H₂O 3. No changes were seen with saline injections (n=2) for these parameters. 4. 3 of 5 participants noted mild, generalized upper extremity weakness that caused difficulty with transfers and some ADLs, gradually subsiding over 2-3 weeks. No other adverse events reported.
Dykstra et al. 1988 USA RCT PEDro=3 N=11	<p>Population: Mean age: 29 yr; Gender: males=11, females=0; Level of injury: C=10, T=1; Severity of injury: complete=11, incomplete=0.</p> <p>Intervention: Three protocols were created: 1) subjects were injected (into the urethra) 20 U of toxin initially and 40 U in the second week. All subsequent wk the participants were given 80 U doses. 2) The initial dose was 80 U and the second week dose was 160 U, followed by weekly doses of 240 U. 3) Participants were injected with 140 U of toxin the first week and all subsequent weekly doses were of 240 U.</p> <p>Outcome Measures: Urethral pressure, post-void residual urine volume, autonomic dysreflexia.</p>	<ol style="list-style-type: none"> 1. The urethral pressure decreased an average of 27cm after treatment. 2. Post-void residual urine volume decreased by an average of 146cc after the toxin injections. 3. However an increase in post-void residual volume and urethral pressure was observed as the effects of the toxin diminished. 4. No UTIs occurred as a result of the cystoscopic injections. 5. More than half the participants who suffered from autonomic dysreflexia noticed improvement in the dysreflexia after toxin injections.
Petit et al. 1998 France Prospective Controlled Trial N=17	<p>Population: Mean age: 35 yr; Gender: males=17, females=0; Level of injury: paraplegic=3, tetraplegic=8.</p> <p>Intervention: All participants received endoscopic injection of 150 IU BTx diluted to 4mL with 0.9% saline solution into the external urethral sphincter at 3 or 4 points.</p>	<ol style="list-style-type: none"> 1. One mo after BTx injection a significant decrease was seen in PRUV (p<0.001), urethral (p<0.001) and bladder pressure on voiding (p<0.01). 2. Modality of voiding was improved in 10 participants.

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
	Outcome Measures: Post voiding residual urine volume (PRUV), bladder pressure on voiding, urethral pressure, tolerance. Assessment was made after 15 d, 1 mo, 2 mo, 3 mo, 6 mo, and 1 yr.	3. The effect of BTx lasted from 2 to 3 mo in 3 participants and 3 to 5 mo in 2 participants.
Schurch et al. 1996 USA Prospective Controlled Trial N=24	Population: Mean age: 32.2 yr; Gender: males=24, females=0; Level of injury: paraplegic=11, tetraplegic=13; Mean time post-injury=40.6 mo. Intervention: Participants were divided into one of three treatment protocols: 1) 4 transurethral injections of 25 IU botulinum A toxin repeated 1 to 3 monthly; 2) 4 injections of 25 IU botulinum A toxin given monthly for 3 months and repeated after 6 or 12 months; 3) 1 transperineal injection of 250 IU botulinum A toxin per month for 3 months and then repeated after 6 or 12 months. Outcome Measures: Post void-residual (PVR), cultures of urine samples and complete urodynamic examination was performed.	1. Decreased PVR from 450 to 50 ml were seen in 9 out of 24 participants. 2. All groups showed significant improvement in: Maximum urethral pressure ($p<0.0001$), duration of detrusor sphincter dyssynergia ($p=0.02$), and basic urethral sphincter pressure ($p=0.01$). 3. Injection of botulinum A toxin improved vesicourethral function for only 2 to 3 mo, while repeated injections lasted 9 to 13 mo. 4. Transperineal injections were not as effective as transurethral injections on maximum urethral pressure.
Huang et al. 2016a China Pre-Post N=59	Population: DO and DESD; Mean age: 39.1 yr; Level of injury: cervical=28, thoracic=25, lumbar=6; ASIA classification: A=42, B=14, C=3; Mean time post-injury: 11.74 mo. Treatment: Participants received 200 U Botox (OnaBTX) injections in two sites, 30 mL into the detrusor muscle, and 4 mL into the external urethral sphincter with a follow-up of 12 wk post-injection. Outcome Measures: Treatment success, Incontinence-Specific Quality-of-Life Instrument (I-QoL), maximum detrusor pressure at first DO and DESD ($P_{\text{detmaxDO-DESD}}$), volume at first DO and DESD ($V_{\text{DO-DESD}}$), maximum urethral closure pressure (MUCP), duration of first DO and DESD, voiding volume, urinary incontinence, and complete dryness.	1. Compared to baseline I-QoL scores significantly increased from 32.06 to 62.45 at 12 wk follow-up ($p<0.05$). Overall participants reported satisfaction with the treatment, reporting less autonomic dysreflexia, decreased UI, less symptomatic UTI and more complete dryness. 2. Significant decreases were seen in $P_{\text{detmax DO-DESD}}$ ($p<0.05$), MUCP ($p<0.05$), and duration of first DO and DESD ($p<0.05$) post-injection at 12 wk. 3. Voiding volume consistently increased from 2 wk to 12 wk post-injection ($p<0.05$), as did the occurrence of complete dryness ($p<0.05$). Urinary infections significantly decreased with injection from 2 wk to 12 wk ($p<0.05$).
Yang et al. 2015 China Pre-Post N=15	Population: DESD; Mean age: 40.5 yr; Gender: males=15; ASIA classification: A=7, B=4, C=3, D=1; Mean time post-injury: 10.13 mo.	1. P_{IP} ($p<0.01$), urethral pressure profilometry ($p<0.01$), PVR ($p<0.01$) all significantly decreased with treatment from

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
	<p>Treatment: All participants received a 100 U onabotulinumtoxinA (OnaBTX) injection into the external urethral sphincter.</p> <p>Outcome Measures: Maximum detrusor pressure (P_{det}), detrusor leak point pressure (P_{lp}), maximum pressure on urethral pressure profilometry, post-void residual volume (PVR), and maximum flow rate (Q_{max}).</p>	baseline to post-injection. Q_{max} significantly increased ($p=0.01$), while P_{det} was not significantly impacted by treatment.
Kuo 2013 Taiwan Pre-Post N=55	<p>Population: Injury etiology: SCI=47, MS=6, myelitis=2; All participants had detrusor sphincter dyssynergia: urinary incontinence (n=13), difficult urination (n=12), mixed urinary incontinence and difficult urination (n=30).</p> <p>Intervention: Participants treated with urethral sphincter injection of 100U of BTX-A (n=33) or detrusor injection of 200U of BTX-A (n=22).</p> <p>Outcome Measures: Urodynamic parameters (cystometric bladder capacity (ml), voiding pressure (cmH₂O), maximum flow rate (ml/s), postvoid residual (PVR, ml), Quality of life (QoL) via UDI-6 and IIIQ-7; satisfaction of treatment.</p>	<ol style="list-style-type: none"> 1. Urodynamic parameters showed significant improvements in both groups; in the urethral BTX-A group, voiding pressure and PVR decreased, but bladder capacity remain unchanged whereas in the detrusor BTX-A group, bladder capacity and PVR increased, while voiding pressure and maximum flow rate decreased and detrusor overactivity disappeared in 50% of the participants. 2. Satisfaction post-treatment was perceived in 60.6% of the urethral BTX-A group and 77.3% of the detrusor BTX-A group. 3. For the urethral BTX-A group QoL, there was significant improvements in IIIQ-7 scores, but no significant change in UDI-6 scores whereas for the detrusor BTX-A group both IIIQ-7 and UDI-6 scores showed significant improvement. 4. The changes of IIIQ-7 and UDI-6 in the detrusor BTX-A group were significantly greater than those in the urethral BTX-A group. 5. Major causes of dissatisfaction with treatment were increased incontinence grade (n=16, 48.5%) and increased urgency (n=5, 15.2%) for the urethral group and increased PVR (n=11, 50%), and difficulty urinating (n=11, 50%) for the detrusor group.
Chen et al. 2010 Taiwan Pre-Post N=18	<p>Population: Mean age: 36.7 yr; males=18, females=0; Level of injury: C=13, T=5; Severity of Injury: AIS A=9, B=5, C=3, D=1.</p>	<ol style="list-style-type: none"> 1. No significant change was seen in detrusor pressure and detrusor leak point pressure post injection.

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
	<p>Intervention: Participants were injected with 100U of onaBTx through the perineum into the external urethral sphincter.</p> <p>Outcome Measures: Detrusor pressure, detrusor leak point pressure, pure pressure, intramuscular electromyography (iEMG), static pure pressure were taken at baseline and 4 weeks post injection. Post-void Residual (PVR) was measured at baseline, 1 mo, 2, mo, 4 mo and 6 mo post injection.</p>	<ol style="list-style-type: none"> 1 mo post injection, significant reduction was seen in: <ul style="list-style-type: none"> • Pure pressure, $p=0.023$ • iEMG, $p=0.008$ • Static pure pressure, $p=0.012$ Significant reducing in PVR was seen up to 6 mo post injection, $p<0.05$.
Tsai et al. 2009 Taiwan Pre-Post N=18	<p>Population: Mean age: 33.8 yr; Level of injury: C=8, T=10; Severity of injury: AIS A=14, B=1, C=3</p> <p>Intervention: Individuals with SCI and detrusor sphincter dyssynergia, voiding difficulty, and inadequate response to oral medications were injected with 100 units of BTX-A transperineally into the external urethral sphincter with electromyography and fluoroscopic guidance.</p> <p>Outcome Measures: Post-Void Residual (PVR), leak point pressure, maximal intravesical pressure, urethral pressure.</p>	<ol style="list-style-type: none"> Post BTX-A injections, significant improvement and clinically successful results were seen in postvoid residual volume (100%), leak point pressure (down to <40 cm H₂O in 72%), maximal intravesical pressure (down to <40 cm H₂O in 72%) and urethral pressure (94%) ($p<0.05$). BTX-A injection also resulted in improvement in the quality of life index, $p<0.01$.
Kuo 2008 Taiwan Pre-post N=33	<p>Population: Mean age: 41 yr; Gender: males=22, females=11; Level of Injury: C=9, T=12, L=5, MS=5, Transverse myelitis=2.</p> <p>Intervention: Prospective investigation of satisfaction and Quality of Life (QoL) after urethral injection of 100 U BTX-A in individuals with chronic suprasacral SCI & Detrusor sphincter dysneriga.</p> <p>Outcome Measures: Urodynamic study, Post void residual incontinence grade (PVR) (0 – 3), difficulty urinating (0 – 3), QoL. Successful outcome=moderate or very satisfied whereas not or mildly satisfied=failure of treatment, Incontinence Impact Questionnaire (IIQ-7).</p>	<ol style="list-style-type: none"> Significant decrease in voiding detrusor pressure was seen 45.7 ± 22.7 vs. 30.7 ± 15.5 cm H₂O ($p=0.016$) Significant increase in max flow rate ($p=0.047$) and decrease in PVR ($p=0.025$) was seen. A decrease was seen in difficulty urinating (78.8%), PVR (69.7%), UTI frequency (67%), autonomic dysreflexia (50%). Significant improvement in QoL index of IIQ-7 was seen at 3 mo compared to baseline ($p=0.001$) but no such improvement was seen in UDI-6 (urogenital Distress inventory).
Phelan et al. 2001 USA Pre-Post N=21	<p>Population: Age range 34-74 yr; Gender: males=8, females=13.</p> <p>Intervention: Botulinum A toxin (80-100 units) injected via cytoscopic collagen</p>	<p>No statistics provided.</p> <ol style="list-style-type: none"> 19/21 subjects voiding without catheterization after injection. 14 reported significant subjective improvement in voiding patterns.

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
	needle/cytoscope into the external sphincter at 3, 6, 9 and 12 o'clock. Outcome Measures: Able to void without catheterization.	3. Postoperative PVR by 71%.
Soler et al. 2016 France Case Series N=99	Population: DSD; Mean age: 38.4 yr; Gender: males=99; Level of injury: tetraplegia=72, paraplegia=27; Mean time post-injury: 99.1 mo. Treatment: Participants were injected with 100 U of onabotulinumtoxinA (OnaBTX) into the urethra. Data was collected at baseline and at 1 mo post-injection. Outcome Measures: Treatment success, post-void residual (PVR) volume and %, occurrence of dysuria, retention, voiding mode and autonomic dysreflexia (AD) signs.	<ol style="list-style-type: none"> 1. For the 48 participants whose injections were effective, the effectiveness lasted for a mean time of 6.5 mo. 2. PVR volume ($p<0.01$), PVR% ($p<0.01$), and dysuria ($p<0.01$) significantly decreased with treatment from baseline to 1 mo post-injection. 3. Retention was present in 19 participants initially, post-treatment, 4 had excellent retention, 9 improved, and 6 remained unchanged. Overall treatment improved retention ($p<0.01$). 4. At baseline, voiding mode was distributed across participants as 51 spontaneous, 29 spontaneous + CIC, 12 CIC only, and 4 indwelling catheter. Post-treatment, 68 participants used spontaneous voiding, 22 spontaneous voiding + CIC, 9 CIC only, and 0 participants used an indwelling catheter. 5. All participants initially had signs of AD. With treatment 49 cases disappeared, 20 improved and 13 were unchanged ($p<0.01$).

Discussion

Detrusor external sphincter dyssynergia and associated high bladder pressures, vesicoureteral reflux, and frequent UTIs are associated with poor long-term outcomes in persons with SCI. These individuals may develop upper tract deterioration and/or suffer incontinence and poor QoL. Injection of botulinum toxin into the external urethra reduces bladder pressures, improves the incidence of UTI, and in some individuals, normalizes bladder emptying (Tsai et al. 2009; Kuo 2008). The impact of increased incontinence after sphincter injection, along with improved urodynamic parameters were studied by Kuo (2008; 2013). While this author cautions that QoL can decrease due to increased incontinence experienced by some individuals, careful individual selection and combinatorial approaches may allow some to benefit from the clearly evident improvement in urodynamic parameters and UTI incidence. Tsai et al. (2009) showed statistically significant improvement in QoL post-injection but did not reveal data on incontinence. Huang et al. (2016) also

showed significantly improved QoL as well as data demonstrating complete dryness in all participants at 2 weeks sustained at 8 and 16 weeks.

Kuo (2013) found that combined detrusor and additional low-dose urethral sphincter BTX-A injections in individuals with incomplete SCI and detrusor sphincter dyssynergia, was effective in producing less urinary incontinence and preservation of spontaneous voiding. As well, participants with detrusor sphincter dyssynergia treated only with detrusor BTX-A injections (i.e., 200 U) improved QoL ratings to a greater extent than participants treated with only urethral injections (i.e. 100 U). Yang et al. (2016) performed transrectal ultrasound-guided catheter transurethral injections (100U) into the external urethral sphincter to treat DESD and achieved a success rate of 75.2%. In a case series of 99 individuals who received urethral injections of botulinum toxin to treat DSD, good outcomes were observed in 89% of participants; were the presence of detrusor contractions and normal bladder neck activity were strong predictors of good outcomes (Soler et al. 2016).

The improvements found in post-voiding residual volumes demonstrated by Kuo (2008, 2013) and Tsai et al. (2009) were initially demonstrated by DeSeze et al. (2002); who conducted a double blind RCT in which lidocaine as a control injection (n=8) was compared to botulinum toxin A (BTxA) as active treatment (n=5). DeSeze et al. (2002) found BTxA improved post void residual volume in individuals with SCI to a greater extent than lidocaine. One month following the injection of BTxA into the external sphincter, post-void residual volume decreased significantly from 159.4 mL to 105.0 mL and participants who previously presented with autonomic dysreflexia no longer exhibited symptoms.

In the clinical setting, a test dose of BTX-A combined with integrated electromyography is the optimal method for evaluation of dose and efficacy. Chen et al. (2010) demonstrated that a single low dose (100 U) of BTX-A, applied into the external urethral sphincter cystoscopically, could be monitored 4 weeks post-injection for objective measures of efficacy. Severe urethral sphincter spasticity as documented through integrated electromyography served as an indication for repeat injections or higher doses. Additional studies demonstrated a decrease in symptoms of autonomic hyperreflexia in at least 60% of participants (Tsai et al. 2009, Kuo 2008, Dykstra et al. 1988; Dykstra & Sidi 1990; Petit et al. 1998; Schurch et al.1996). Almost all participants showed post-injection sphincter denervation on electromyography resulting in temporary relief of these symptoms for approximately 2-3 months; after which additional subsequent BTxA injections were needed to maintain results (Dykstra et al. 1988; Dykstra & Sidi 1990).

Schurch et al. (1996) compared the effectiveness of transurethral versus transperineal botulinum toxin A injections in a prospective controlled study. The study found that transurethral botulinum toxin injections were more effective in reducing urethral pressure than transperineal injections. However, other symptoms were improved with either injection method. Tsai et al. (2009) described a method of transperineal sphincter injections using fluoroscopic guidance and electromyography that dramatically improved bladder emptying, with most individuals returning to voiding.

Participants were able to avoid frequent ICs with three being able to discontinue indwelling catheterization altogether.

Schurch et al. (1996) also revealed the additive effects of recurrent BTx injections resulting from the prolonged inhibition of acetylcholine release. After 3 monthly injections, the therapeutic effects of BTx lasted as long as 9 months compared to only 2-3 months with 1 injection. Women, as a result of anatomical differences, often have greater difficulty performing self-catheterization than do men. Therefore the “normalization” of voiding as a result of botulinum toxin injections into the sphincter may play an even greater role in the urologic management of females with SCI. Phelan et al. (2001) were the first to demonstrate the successful use of botulinum toxin A in women. Their study of 13 females showed that all but one was able to spontaneously void following botulinum A injection. More study of the long term outcomes of “spontaneous voiding” after sphincter injection in women is required.

Chen et al. (2010) evaluated the effects of a single transrectal ultrasound-guided transperineal injection of 100 U onabTx to the external urethral sphincter to treat DESD. As the prostate gland represented a key landmark in the transrectal ultrasound-guided injection, the study was limited to male subjects. Video-urodynamic results obtained at an average of 33.3 days postinjection showed significant reduction in dynamic urethral pressure, integrated electromyography, and static urethral pressure. The onabTx injection did not produce a significant decrease in maximal detrusor pressure. This was the first study to demonstrate the effect of transrectal ultrasound -guided transperineal onabTx injection into the external urethral sphincter and the potential for achieving outcomes similar to transurethral injection.

While not specifically mentioned in the above studies, a group of individuals likely to benefit from injections of BTX-A into the sphincter are men who have persistently elevated bladder volumes while using condom drainage. Reasons why individuals with SCI chose condom drainage include a reluctance to perform self catheterization or alternatively there is persistent incontinence on IC regimes despite adequate trials of anticholinergic medication. These individuals could theoretically benefit from improved drainage, as residual urine is a common cause of UTI, and accompanying elevated bladder pressures place the upper genitourinary tracts at risk. Whether or not such individuals actually resume “voiding” to allow for the discontinuation of condom drainage altogether has not been addressed.

Botulinum toxin therapy is advantageous as it allows one to avoid major surgical procedures and their associated risks. Botulinum toxin injections decrease the resistance to urine outflow by relaxing the external sphincter. This in turn decreases post-void residuals in 70% of individuals, with acceptable voiding pressures (Tsai et al. 2009). Symptoms such as autonomic dysreflexia and UTI incidence also appear to be reduced. Sphincter denervation, however, is transient and repeated injections are required to maintain therapeutic results. Post-injection urodynamic studies should be conducted to document that resultant voiding pressures fall in the acceptable range. For individuals with SCI with neurogenic bladder that do not experience unacceptable incontinence, botulinum toxin injections into the external sphincter

can improve bladder emptying. Further study is required to determine whether or not recurrent sphincter injections and related improvements in voiding pressures and UTI incidence result in better long term upper tract outcomes. Furthermore, to ensure widespread clinical uptake studies are needed to identify the individuals who are best suited to maximize the benefits of sphincter injections while avoiding unacceptable incontinence.

Conclusion

There is level 1 evidence (from one RCT and several controlled and uncontrolled trials; DeSeze et al. 2002) that botulinum toxin injected into the external urinary sphincter may be effective in improving outcomes associated with bladder emptying in persons with neurogenic bladder due to SCI.

There is level 4 evidence (from one case series; Soler et al 2016) that the presence of detrusor contractions and normal bladder neck activity may be strong predictors of good outcomes for urethral injections of botulinum toxin to treat DSD.

Botulinum toxin injected into the sphincter is effective in assisting with bladder emptying for persons with neurogenic bladder due to SCI.

The presence of detrusor contractions and normal bladder neck activity may be strong predictors of good outcomes for DSD treated with BTX.

4.3.3. Other Pharmaceutical Treatments for Bladder Emptying

Beyond the typical alpha adrenergic and botulinum toxin approaches to improving bladder emptying, other pharmaceutical interventions have been explored. While these approaches still are few in number, this section describes primarily the use of 4-Aminopyridine (Grijalva et al. 2010) and isosorbide dinitrate (Reitz et al. 2004). 4-Aminopyridine prepared in various commercial formulations for the treatment of MS-related walking difficulties is also known as fampridine [ampyra, fampyra]. Most SCI specific studies involving 4-Aminopyridine assess bladder sensation and/ or control with respect to outcomes relevant to bladder management; often conducting more global assessments of function following treatment. This section reports only on bladder specific outcomes.

Table 10 Other Pharmaceutical Treatments for Bladder Emptying

Author Year Country Score Research Design Total Sample Size	Methods	Outcome
Grijalva et al. 2010 Mexico Phase 1: RCT; N=14	Population: AIS A; Mean age=29 years; male=10, female=4; Level of	1. 3 individuals were able to walk without assistance and 1

Author Year Country Score Research Design Total Sample Size	Methods	Outcome
Phase 2: Pre-Post PEDro=9 N=12	injury: C=7, T=7; Time since injury=6.21 years Intervention: 30 mg of 4-aminopyridine per day Outcome Measures: Scores of the ASIA motor and sensory scales, the SCIM, sphincter control and somatosensory evoked potentials	individual changed to an incomplete injury. 2. In terms of bladder sensation and control, 5 individuals reported an improvement while 4 out of 9 male individuals had psychogenic erection. 3. 7 individuals showed improvement in somatosensory evoked potentials. 4. 1 individual suffered epileptic seizures and another had persistent anxiety and insomnia.
Reitz et al. 2004 Switzerland Pre-Post N=12	Population: Mean age: 32 yr (range 29-36 yr); Gender: males=12, females=0. Intervention: Following a bladder emptying by clean intermittent catheterization (n=6) and suprapubic tapping (n=6), individuals were sublingually administered 10 mg of isosorbide dinitrate. Outcome Measures: Maximal bladder pressure, external urethral sphincter pressure, reflex volume, and residual volume.	1. External urethral sphincter pressure at both rest and dyssynergic contraction reduced significantly after nitric oxide treatment ($p<0.05$; $p<0.05$); however, bladder pressures at rest and during contraction as well as reflex volume remain unchanged. 2. In the individuals who used suprapubic tapping for bladder emptying the mean post triggering residual volume was significantly reduced ($p<0.05$).

Discussion

4-Aminopyridine is a potassium channel blocker, prolonging action potentials and increasing neurotransmitter release at the neuromuscular junction. Only one study to date, Grijalva et al. (2010), has explicitly commented on bladder function following administration of fampridine. During the open-label portion of the study where dosage levels of fampridine peaked, 3 of 12 participants regained both sensation and control of the bladder sphincter, and 1 of 12 regained sensation only. The paucity of literature in this area does not yet warrant fampridine as a primary treatment of bladder management in SCI.

Isosorbide dinitrate is a drug typically used to prevent angina attacks. However, it has been studied for the use of improving bladder function among 12 males post SCI (Reitz et al. 2004). In this single pre-post study, it was found that isosorbide dinitrate reduced external urethral sphincter pressure along with dyssynergic contraction; however, bladder pressures remained unchanged.

Conclusion

There is level 4 evidence (from one pre-post study; Reitz et al. 2004) that isosorbide dinitrate may be effective in reducing eternal urethral pressure and dyssynergic contraction.

There is level 4 evidence (from one pre-post study; Griljava et al. 2010) that 4-aminopyridine, at sufficient dosage, may be effective in restoring sensation and/or control of the bladder sphincter.

Isosorbide dinitrate may improve control of the bladder post SCI; although, more evidence is needed to support this as a treatment option

4-Aminopyridine at sufficient dosage may return sensation and control of the bladder sphincter following SCI; more evidence is needed to support this as a treatment option.

4.4 Enhancing Bladder Emptying Non-Pharmacologically

4.4.1 Comparing Methods of Conservative Bladder Emptying

Bladder emptying must be conducted under low pressure conditions in order to prevent upper urinary tract complications such as reflux, infections and even renal failure. The choice of SCI-related bladder management method depends on the type of bladder dysfunction (e.g., incomplete emptying, incontinence, dyssynergia) and other secondary aspects of the SCI such as the individual's functional capabilities, health, resources and other concomitant conditions. Urodynamic assessment is likely to be necessary in most individuals to fully understand the dysfunction in specific structures in the lower urinary tract. Thereafter, the chosen method of bladder management must result in continence, be acceptable to the individual with neurogenic bladder, and facilitate the greatest independence. During rehabilitation and after spinal shock has subsided, people with SCI are initiated with the most conservative treatment options first (Wyndaele 2008). Individuals are then taught how to manage the chosen method and are advised as to complications and alternatives. The section below reviews several papers that address the outcome of groups of individuals treated with the spectrum of conservative bladder management methods.

Conservative methods for bladder management includes behavioural therapy (triggered reflex voiding, bladder expression through Crede and/or Valsalva maneuver, and toileting assistance; catheters (intermittent or indwelling, condom (males only) or other external applicances); pharmacotherapy; and finally electro stimulation (electrical neuromodulation, electrical stimulation of the pelvic floor or intravesically). If residual bladder function permits, spontaneously “triggered” or expression voiding without the need for an external drainage system may be an option, although there are a variety of complications that can result from high bladder pressures with these approaches (Wyndaele et al. 2001). Suprapubic catheterization (SPC) is occasionally chosen in the subacute period given that

disturbance to the urethra can be avoided. However, the complication rate remains high for this invasive technique and thus it should be chosen only when conservative methods are unsuccessful and it must be accompanied by comprehensive education for daily care.

Urodynamic studies provide information on lower urinary tract health, storage and emptying pressure, reflux status, and are essential to the choice of bladder management method(s) individualized for each individual. Having access to urodynamic data can also assist later decision making if changes to management methods are required. Green (2004), Drake et al. (2005), and Yavuser et al. (2000), address these issues, listing some of the common complications as reason for change of management methods: frequent UTI's, upper tract deterioration, increased post void residual urine volume, bladder or kidney stones, functional decline and individual request. The section below presents data on studies which attempt to clarify the type and incidence of complications associated with the above methods of bladder management. For the most part, these approaches are considered in advance of more invasive options involving bladder augmentation surgery or stimulator implantation (covered in later sections).

Table 11 Comparison Studies of Conservative Bladder Emptying

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
Gu et al. 2015 China RCT PEDro=7 N=107	<p>Population: Urinary retention; Mean age: 35.7 yr; Gender: males=80, females=27; ASIA classification: B=37, C=53, D=17.</p> <p>Intervention: Individuals were randomized to Clean intermittent catheterization (CIC) (group 1) (n=35), Electroacupuncture combined with CIC (group 2) (n=38), or Sham acupuncture combined with CIC (group 3).</p> <p>Outcome Measures: Residual urine volume, voided volume, bladder balance, frequency of CIC.</p>	<ol style="list-style-type: none"> 1. At 1 mo follow-up, group 2 had a significantly higher number of bladder balance participants compared to group 1 ($p=0.019$) or group 3 ($p=0.019$). 2. At 1 mo follow-up, group 2 participants had significantly lower frequency of CIC compared to group 1 ($p<0.001$) or group 3 ($p<0.001$), and group 3 was also significantly lower than group 1 ($p<0.01$). 3. In terms of residual urine volume at 1 mo follow-up, group 2 was significantly lower than group 3 ($p<0.001$) and group 3 was significantly lower than group 1 ($p=0.018$). 4. At 1 mo follow-up, group 2 had a significantly higher voided volume compared to group 1 ($p<0.001$) and group 3 ($p<0.001$), with no significant differences between groups 1 and 3. 5. At 3 mo follow-up, significant differences were found between groups in terms of residual urine volume ($p<0.001$), with groups

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
		<p>ordered as 1, 3, and 2 in terms of decreasing volume.</p> <p>6. At 3 mo follow-up, significant differences were found between groups in terms of voided volume ($p<0.001$), with groups ordered as 1, 3, and 2 in terms of increasing volume.</p>
<p>Giannantoni et al. 1998 Italy Case Control N=78</p>	<p>Population: SCI: Age: 35 yr; Gender: males=57, females=21; Severity of injury: AIS: A/B=68, C/D=10; Mean time post-injury=89 mo.</p> <p>Intervention: Group 1: Individuals using clean intermittent catheterisation (IC). Group 2: Individuals using other methods of emptying (31 using Abdominal straining, tapping, or Crede manoeuvre, 5 indwelling catheter, 7 spontaneous voiding)</p> <p>Outcome Measures: Urodynamic studies (UDS) (all anticholinergics were held); renal function (BUN, creatinine, creatinine clearance), ultrasound, intravenous pyelogram (IVP) and/or voiding cystourethrogram (VCUG).</p>	<ol style="list-style-type: none"> Both groups had similar clinical and UDS characteristics, and length of time treated with a foley catheter (67.9 versus 75 mo) There were significantly more abnormalities on US or Cystourethrography in Group 2 (22 versus 36 individuals) $p=0.03$ Upper urinary tract damage (hydronephrosis, renal stones, reflux) occurred more commonly in group 2 ($n=13$) vs. group 1 ($n=4$) $p=0.03$. Clean IC was believed to be the only explanation for the improved outcome in group 1
<p>Drake et al. 2005 UK/USA Pre-Post N=222</p>	<p>Population: Mean age: 57.4 yr; Gender: male=171; females=51. Mean time post-injury=33 yr.</p> <p>Intervention: Individuals were divided according to their bladder management method: balanced reflex voiding; intermittent catheterization; indwelling urethral or suprapubic catheter; normal micturition.</p> <p>Outcome Measures: Risk of urinary tract infection (UTI), other complications. Individuals were prospectively followed for 6 yr.</p>	<ol style="list-style-type: none"> Complications including renal failure were significantly related to both age and yr post injury. No significant difference in risk of a urinary tract infection* was seen for the different bladder management methods (IDUC, $p=-0.17$; IC, $p=0.45$; straining, $p=0.87$; normal voiding, $p=0.30$. *UTI incidence=1 or more UTIs in yr prior to assessment. 28.8% changed bladder management method during the study period, particularly those in balanced reflex voiding group. Urodynamic studies were not done routinely
<p>Bartel et al. 2014 Switzerland Case Series N=2825</p>	<p>Population: Bladder stone group ($n=93$): Mean age: 50 yr; Gender: males=69, females=24; Level of injury: cervical=34, thoracic=49, lumbar=9, sacral=1; Severity of injury: complete=75, incomplete=18; ASIA classification: A=53, B=22, C=13, D=5; Injury etiology: trauma=74,</p>	<ol style="list-style-type: none"> Of the 2825 SCI individuals, 93 had bladder stones (2.8%). In terms of bladder management methods, bladder stones were observed in 11% of suprapubic catheter, 6.6% of transurethral catheter, 2% of intermittent catheterization, and 1.1% of reflex micturition.

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
	<p>multiple sclerosis=10, other=9; Mean time post-injury: 9.5 yr.</p> <p>Intervention: Charts were reviewed for spinal cord injury individuals who had a bladder stone.</p> <p>Outcome Measures: Bladder management method, period to stone development, bladder stone recurrence rate.</p>	<p>3. In terms of period to stone development, the mean for suprapubic catheter was 59 mo, transurethral catheter was 31 mo, intermittent catheterization was 116 mo, and reflex micturition was 211 mo.</p> <p>4. The bladder stone recurrence rate was 28% for suprapubic catheter, 40% for transurethral catheter, 22% for intermittent catheterization, and 0% for reflex micturition.</p>
<p>Afsar et al. 2013 Turkey Case Series N=164</p>	<p>Population: Mean age: 40.7 yr (range 23-65 yr); Gender: males=102, females=62; Level of injury: Tetraplegia=43, Paraplegia=87, Conus-Cauda Equina Syndrome=34; Time post-injury: 51.5 d (range 5-292 d).</p> <p>Intervention: Retrospective review of bladder management and emptying methods.</p> <p>Outcome Measures: Bladder management method, urinary tract infection (UTI) prevalence, functional independence measure (FIM) scores.</p>	<p>1. Bladder emptying method at discharge was: indwelling catheter (n=16, 9.8%), clean intermittent catheterization (n=104, 63.4%), reflex voiding (n=25, 15.2%), and normal voiding (n=19, 11.6%). While at follow up emptying method was: indwelling catheter (n=21, 13.1%), clean intermittent catheterization (n=60, 37.5%), reflex voiding (n=57, 35.6%), and normal voiding (n=22, 13.8%).</p> <p>2. 42% of individuals using clean intermittent catheterization changed their bladder emptying method. Also rate of reverting to urethral indwelling catheter usage was 21.4%.</p> <p>3. The number of UTIs was highest in individuals using indwelling catheters.</p>
<p>Cohbara et al. 2013 Japan Case Series N=234</p>	<p>Population: Mean age: 57.2±14 yr (range=13-87, median=61); Gender: males=195, females=39; Level of injury: Cervical; Etiology of injury: Traumatic=204, Non-traumatic=30. Severity of Injury: ASIA B=23 (9.8%), C=90 (38.5%), D=120 (51.7%); Time post-injury: 1-10 mo.</p> <p>Intervention: Chart review.</p> <p>Outcome Measures: Urinary management, spontaneous voiding, urinary sensation, detrusor overactivity.</p>	<p>1. Between admission and discharge, the number of individuals using:</p> <ul style="list-style-type: none"> • urethral catheterization declined (48.3% vs. 9.4%, respectively) • suprapubic cystostomy with indwelling catheters increased (0.9% vs. 10.7%, respectively) • nursing care clean IC (5.5% vs. 2.6%, respectively) • self-IC increased (0.9% vs. 15.8%, respectively) • spontaneously voiding increased (42.7% vs. 57.2%, respectively) <p>2. There was no difference in urinary management between the sexes.</p>

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
		<p>3. At discharge, the spontaneous voiding rates of individuals with ASIA B,C and D classification were 13.0, 37.8 and 80.2% resp. ($p<0.001$)</p> <p>Of the 113 individuals who had urethral catheterization at admission, 35 were spontaneously voiding at discharge.</p>
<p>El-Masri et al. 2012 United Kingdom Case Series N=119</p>	<p>Population: Mean age: 29 ± 12 yr (range=16-63); Gender: male=99, female=20 Level of injury: paraplegic=60, tetraplegic=50; Neurological level: ASIA A=63, B=8, C=14, D=34.</p> <p>Intervention: N/A – Data analysis of bladder management and urinary complications divided into Phase 1: Preadmission to MCSI, Phase 2: During first hospitalization at MCSI, and Phase 3: Post discharge resp. Review of results from routine clinical assessment, urine analyses, ultrasound scans or intra venous urograms (IVU) that were completed every 1 or 2 yr (cystoscopies also performed in individuals with suprapubic or indwelling catheters).</p> <p>Outcome Measures: Bladder management (i.e. indwelling urethral catheterization (IndUC), assisted clean intermittent catheterization (A-IC), clean intermittent self-IC (S-IC), reflex voiding (RV) resp.), Urinary complications, Length of stay.</p>	<p>Phase 1</p> <ol style="list-style-type: none"> 1. All individuals (119) were initially managed with IndUC; 81 had the method of urine drainage documented immediately before admission of which 56 (69%) had IndUC, 22 (27%) had A-IC, and 3 (4%) used RV and/or bladder expression resp. 2. 2 male individuals that were admitted 15 and 38 d post injury resp. were suspected of having UTI. <p>Phase 2</p> <ol style="list-style-type: none"> 3. Soon after admission, bladder management was changed from IndUC to A-IC. 4. Of the 119 individuals, 45 (38%) had complications: UTI (31), UTI plus reflux or hydronephrosis ($n=7$), and other ($n=7$). 5. There was no significant difference in complications by ASIA scores, length of stay or level of injury. <p>Phase 3</p> <ol style="list-style-type: none"> 6. Of the 119 individuals, 73 (61%) developed complications, most commonly UTI. 7. All ASIA D ($n=24$) subjects did not require intervention for urinary drainage; only 3 had a mild UTI. 8. 60% of those individuals using RV with or without bladder expression developed complications. 9. Of the 10 individuals who continued to use IndUC post-discharge, 6 had tetraplegia versus 4 with paraplegia. 10. No significant difference in complications by level of injury

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
		<p>but there was by severity of injury ($p<0.01$).</p>
<p>Böthig et al. 2012 Germany Case Series N=56</p>	<p>Population: Mean age: 45 yr (range=17-78 yr); Gender: male=40, female=16; Level of injury: C0=11, C1=0, C2=29, C3=14, C4=2; Neurological level: ASIA A=46, B=4, C=6. All individuals had long-term-ventilation and bladder drainage was obtained using either suprapubic catheter (SPC) (male=28, female=10, mean age: 49.9 yr), intermittent catheter (IC) performed by home caregivers (male=8, female=4, mean age: 31.8 yr), or other methods such as transurethral catheter (2), reflex voiding by suprapubic tapping (2) or and IC per umbilical stoma (2) resp.</p> <p>Intervention: NA – Data analysis of a Quality of Life (QoL) questionnaire (ICIQ-SF) and urological morbidity of 3 groups: Suprapubic Catheter (SPC), Intermittent Catheter (IC) and Other resp.</p> <p>Outcome Measures: Bladder management, Urological morbidity, Quality of Life (QoL).</p>	<ol style="list-style-type: none"> 1. Only the data from SPC and IC individuals were used for analysis (N=50). 2. The difference in mean age between the SPC group and IC group was statistically significant. ($p=0.0035$) 3. There was no difference between the gender and method of bladder management ($p=0.718$). 4. During the follow-up period, 7 of the 50 individuals changed from IC to SPC due to urethral complications. 5. Of the SPC group, 10/38 had 15 urological interventions, while the other 28 had no complications or procedures. 6. Of the IC group (now=12+7), 11 individuals had a total of 19 readmissions, while only 8 had no complications or procedures. 7. The leading cause of readmission in the SPC versus IC groups was bladder stones versus urethral trauma resp. 8. Individuals with IC experienced significantly more urological complications than with SPC. ($p<0.05$) 9. 47/56 (84%) individuals completed the QoL questionnaire of which 43 were included for analysis (SPC=32, IC=11). 10. QoL scores for the SPC versus IC group were 3.06 versus 4.27 resp. which was not statistically

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
		significant (p=0.368) (ref. 0=best/16=worst)
Hansen et al. 2007 Denmark Case Series N=236	<p>Population: Mean age: 50.5 yr; Gender: males=193, females=43; Mean follow-up time=24.1 yr; Level of injury: paraplegic=126, tetraplegic=110; Severity of injury: complete=102, incomplete=134.</p> <p>Intervention: Retrospective analysis of renal calculi development associated with various factors including bladder management method (normal emptying, suprapubic tapping/crede, intermittent catheter (IC), indwelling catheter); individual questionnaire about kidney stones.</p> <p>Outcome Measures: Prevalence of calculi, risk of calculi.</p>	<ol style="list-style-type: none"> 1. At least 1 episode of renal calculi was seen in 47 individuals and at least 1 episode of bladder calculi was seen in 33 of individuals. 2. The first 6 mo after injury had the highest risk for getting renal and bladder calculus. 3. No significant difference was seen between the type of bladder emptying method and the prevalence of calculi (trend was towards more stones in those with indwelling catheters).
Green 2004 USA Case Series N=479	<p>Population: SCI: Mean age: 27 yr; Gender: males=383, females=96; Individuals admitted over a 10 yr period were chosen. 10 yr follow up data available for 426 individuals, 15 yr follow-up data available for 412 individuals.</p> <p>Intervention: SCI individuals' medical records were retrospectively reviewed to determine changes in bladder management techniques. Questionnaires were also sent.</p> <p>Outcome Measures: Bladder management techniques.</p>	<ol style="list-style-type: none"> 1. Of the individuals discharged with an intermittent catheterization program (ICP), 398 remained on the program at 1 yr follow-up. 2. At 5 yr follow up, 80% of individuals were catheter free (50% used an ICP). 3. At 15 yr follow up, of the 166 individuals, 42 changed to chronic indwelling catheters, while 111 were catheter-free state or used ICP.
Ord et al. 2003 England Case Series N=457	<p>Population: SCI with >6 mo on any 1 form of management: Mean age: 29-40 yr for various groups; Gender: males=402, females=55; Level of injury: T3 – T9; Severity of injury: complete, incomplete; Follow-up time=48-107 mo.</p> <p>Intervention: Assessment of various bladder management methods (i.e., sphincterotomy, condom, intermittent catheter (IC),</p>	<ol style="list-style-type: none"> 1. Both forms of indwelling catheterization had an increased risk of getting bladder stones and requiring hospitalization for bladder stones over IC and condom drainage with or without sphincterotomy. 2. Relative to IC, hazard ratio was 10.5 for suprapubic catheters and 12.8 for indwelling urethral catheters.

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
	indwelling urethral catheter, suprapubic catheter+combinations of each). Outcome measures: Bladder stone formation rate.	3. Incidence density ratio (like odds ratio) was 40.7 for developing bladder stones for indwelling catheters relative to IC. Condom incidence density ratio was 7.5 relative to IC. 4. % Annual risk for stone formation: Condom & Sphincterotomy 0%; IC 0.2%; Expression voiding with or without condom 0.5%; Indwelling catheter 4% (first stone), 16% (subsequent stone).
Groah et al. 2002 USA Case Series N=21	Population: SCI with bladder cancer: Mean age: 48 yr; mean time post-injury=20 yr. Intervention: SCI bladder cancer individuals' data was analyzed to determine risk factors for bladder cancer. Outcome Measures: Bladder management methods, prevalence of bladder cancer, risk for bladder cancer, mortality rate due to bladder cancer.	1. Bladder management methods included: <ul style="list-style-type: none"> • Indwelling catheters (IDC), 15 individuals. • Non indwelling catheters (NIDC) spon. Void, condom, IC: 3 individuals. • Both indwelling and nonindwelling catheters (Multi) duration of IDC use 20 yr, 3 individuals. 2. Development of bladder calculi was significantly higher in individuals using IDC than NIDC ($p<0.001$) 10 versus 2 individuals but bore no relationship to incidence of CA. 3. SCI individuals were 15.2x (95% CI, 9.2-23.3) more likely to develop bladder cancer than the general population. IDC 4.9x more likely to develop bladder cancer than NIDC 4. Bladder management method ($p<0.02$) and age at SCI ($p<0.01$) significantly predicted bladder cancer. 5. SCI individuals using IDC have a risk factor of 77 per 100,000 person yr of bladder cancer, starting at 12 yr post injury. 6. Of the 13 individuals that died, 12 were due to bladder cancer. Of these 12 individuals, 10 used IDC methods while 2 used Multi method. 7. No mortality rate was found in the NIDC group.
Weld & Dmochowski 2000 USA	Population: SCI: Mean age: 33.9-41.0 yr; Gender: males=313, females=3; Level of injury: suprasacral=269,	1. Frequency of those managed by IC, voiding spontaneously, suprapubic and urethral

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
Case Series N=316	sacral=47; Severity of injury: complete=45, incomplete=271; Mean follow-up=17.8-19.3 yr for various groups. Intervention: Assessment of various bladder management methods (i.e., intermittent catheterization (IC), voiding spontaneously, indwelling urethral catheter, suprapubic catheter). Outcome Measures: Urological complication rate (epididymitis, pyelonephritis, upper tract stone, bladder stone, urethral strictures, periurethral abscess, vesicoureteral reflux, abnormal upper tracts).	catheterization was 92, 74, 36 and 114 subjects respectively. 2. Complication rates for the above groups were 27.2%, 32.4%, 44.4% and 53.5% respectively. 3. Urethral catheter users had the highest rates for epididymitis, pyelonephritis, upper tract stone, bladder stone, urethral strictures and periurethral abscess. 4. Suprapubic catheter users had the highest rates for vesicoureteral reflux and abnormal upper tracts.
Yavuzer et al. 2000 Turkey Case Series N=50	Population: SCI: Mean age: 38 yr; Gender: males=36, females=14; Level of injury: paraplegia=43, tetraplegia=7; Severity of injury: AIS: A-D; Time post- injury=124 d; Rehabilitation LOS=130 d; Follow-up time=24 mo. Intervention: Follow-up of those with various bladder management methods. Outcome Measures: Bladder management method, compliance.	1. At admission 43 individuals used indwelling catheter and by discharge from rehabilitation, intermittent catheter (IC) was used by 37. 2. At 2 yr follow-up, of 38 people using IC, 20 had reverted back to indwelling catheter by 24 mo, 16 continued with IC. 3. Tetraplegics had lower compliance with IC than paraplegics ($p<0.05$) - majority of tetraplegics (80%) reverted to indwelling catheter versus only 40% of paraplegics. 4. More females (60% versus 50%) reverted to indwelling catheters but this was not significant. 5. More with complete injuries reverted to indwelling catheters (68% versus 31%, $p<0.01$). 6. Main reasons for changing method=dependence on care givers, severe spasticity, incontinence and inconvenience (females).
Gallien et al. 1998 France Case Series N=182	Population: Mean age: 41.45 yr; Gender: males=129, females=53; Severity of injury: complete=69, incomplete=113; Mean time post-injury=8 yr. Intervention: Bladder management method relative to urinary tract infection (UTI) and other complications was retrospectively reviewed and a questionnaire was sent to all	1. Prevalence of complications was related to: <ul style="list-style-type: none"> Type of bladder management at discharge: 129 individuals using clean IC, 137 using percussion and all individuals using indwelling catheters had at least one urologic complication.

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
	<p>individuals and attending physicians.</p> <p>Outcome Measures: Method of bladder management; complication: lithiasis, urinary infections, orchiepidymitis, urethral trauma, vesicorenal reflux, renal failure.</p>	<ul style="list-style-type: none"> Gender, with males having a higher probability than females ($p<0.0001$). <ol style="list-style-type: none"> Urinary infections were significantly higher in: <ul style="list-style-type: none"> Individuals with complete lesions ($p=0.0001$). Use of a protection or a urine collector ($p=0.0022$). Urinary infections were not significantly related to: <ul style="list-style-type: none"> Time since injury. Method of bladder management (those on indwelling catheters were not part of UTI analysis). Intermittent catheterization was the main method of bladder management.

Note: AIS=ASIA Impairment Scale; IVP=Intravesicle Pressure; UTI=Urinary Tract Infection; VCUG=Voiding Cystourethrogram

Summarized Level 5 Evidence Studies:

The following level 5 evidence studies have been reviewed, and the overarching findings from the studies are highlighted in this section. As noted at the start of this chapter, these types of studies are not included in the discussion or in the conclusions. Krebs et al. (2015) found a significantly higher rate of urethral strictures in men using IC (25%; $p=0.001$) than in men using other bladder evacuation methods (14%) with a third of strictures requiring surgical intervention. One observational study by Shavelle et al. (2015) found increased mortality for males needing catheterization. Martins et al. (2013) reported 71% of individuals used clean intermittent catheterization, 18.4% ($n=7$) used condom catheters, 7.8% ($n=3$) used suprapubic drainage, and 2.6% ($n=1$) used tapping. 65.7% of individuals tested positive for asymptomatic bacteriuria where E.coli was the most prevalent (60%). Antibiotic resistance rates from bacteria were 73.3% to Ampicillin, 60% to Sulfamethoxazole-Trimethoprim, and 33.3% to Norfloxacin.

Discussion

A retrospective analysis of 234 individuals with incomplete cervical cord injuries (Gohbara et al. 2013) found that during initial rehabilitation, individuals were managed by urethral catheterization, suprapubic cystostomy, self or assisted administration of clean IC, clean IC with occasional spontaneous voiding, or spontaneous voiding alone. The severity of paralysis (e.g., AIS score) and urinary sensation (presence/absence of desire to urinate) were found to be predictive parameters for improvement in voiding function over the course of rehabilitation. The majority of individuals' bladder function improved during rehabilitation and

those individuals who were admitted with catheterization and discharged with spontaneous voiding, did so on average by 85.2 days (range 16-142). An interesting finding in this Japanese study is the high rate of AIS D (80.2%) individuals compared to published rates from other international SCI populations (46-59% in Europe, Hogel et al. 2012; 29-32% in the USA, DeVivo 2007, 28% in Canada, Pickett et al. 2006).

In keeping with offering conservative management options first, El-Masri et al. (2012) found that supervised sequential management methods beginning with a brief period of indwelling urethral catheterization followed in IC and/or reflex voiding over the longer term of regular surveillance (8-21 years) and timely intervention, kept complication rates to 62% (compared to 93% reported by Weld & Dmochowski 2000). Of the 62% of complications, only 22.6% were related to the upper urinary tract.

Another non-pharmacological approach to augment bladder management is electroacupuncture (EA) in combination with CIC. An RCT carried out by Gu et al (2015) provided data in support of reduced residual urine volume and CIC frequency while increasing voided volume when EA was combined with CIC compared to CIC alone ($p < 0.001$). (Gu et al 2015).

Several authors have examined the frequency of a variety of urological and renal complications associated with various forms of chronic bladder management (Ord et al. 2003; Weld & Dmochowski, 2000; Hackler 1982). These authors have all employed retrospective chart reviews to examine complication rates associated with long-term follow-up data. In general, these authors concur that the greatest numbers of complications occur with long-term use of indwelling suprapubic and urethral catheters. In particular, of these investigations, Weld and Dmochowski (2000) employed a large sample ($N=357$) and examined the greatest range of complications. These authors noted that long-term urethral catheterization was associated with the largest overall number of complications, with long-term SPC ranked next. Depending on the specific complication, one of these two methods was associated with the highest incidence. Urethral catheter users had the highest rates for epididymitis, pyelonephritis, upper tract stones, bladder stones, urethral strictures and periurethral abscess. Krebs et al. (2015), in an observational review of 1,044 individual charts, concluded that the occurrence rate of urethral strictures is significantly higher in men using IC (25%; $p < 0.001$) than in men using other bladder evacuation methods (14%) with a third of strictures requiring surgical intervention. Suprapubic catheter users had the highest rates for vesicoureteral reflux and abnormal upper tracts. It should be noted that these authors did not account for changing bladder management methods, preferring to simplify the analysis by classifying the results by the most predominate bladder management method. An observational trial inclusive of 8,206 cases found the need for catheterization was associated with increased mortality, and slightly higher (not statistically different) for indwelling catheter use, that is postulated to be linked to increased risk of infection or being more severely disabled. (Shavelle et al. 2015).

Ord et al. (2003) examined a relatively large dataset ($n=467$) and examined all the combinations of changing methods. These authors limited their analysis to the

effect of various bladder management techniques on the risk of bladder stone formation. Similar to Weld and Dmochowski (2000), these authors also found a slightly greater incidence of bladder stones for indwelling urethral catheters compared to SPC. Each of these methods, resulted in a greater incidence of bladder stones than IC. Ord et al. (2003) reported hazard ratios relative to IC of 10.5 for SPC and 12.8 for indwelling urethral catheters. In contrast, Hackler (1982) reported comparisons between long-term complication rates among those with condom (Texas), urethral (Foley) and SPC and found markedly higher rates for those managed with SPC even though the follow-up period for these individuals was only 5 years as compared to 20 years for those managed with the other 2 methods. However, these findings reflected a much smaller series of individuals (N=31) and the comparisons were made from individuals from different time periods reflecting different “generations” of care. In a large-scale retrospective analysis (Bartel et al 2014, n=2825) SPC, transurethral catheter, IC and reflex micturition were associated with 11/6.6/2/1.1% bladder stone observance, 59/31/116/211 mean months for bladder stone development, and 28/40/22/0% bladder stone recurrence, respectively.

It should be noted that even though the data favour IC or triggered spontaneous voiding, it is not always possible to use these methods. Lack of independence for catheterization can limit the use of IC in women and those with tetraplegia (Yavuzer et al. 2000). While every effort is made to start individuals on IC programs, some individuals change to other methods over time. Drake et al. (2005) reported 28.8% of individuals change their bladder management method, while Yavuzer et al. (2000) found that up to 60% of individuals changed from intermittent to indwelling catheter use. Green et al. (2004) found that only 25% changed to indwelling catheters over 15 years. The primary reasons indicated for changing methods were a greater dependence on care-givers than originally thought, presence of severe spasticity, incontinence and inconvenience with IC (females only). Thus, assisting individuals in choosing the most optimal method of bladder management is important. If less optimal methods of management are used post-injury, appropriate or increased surveillance must continue, given the described complication rates.

In select groups of individuals such as those with tetraplegia and who are respirator-dependent, use of SPC (compared to IC or indwelling catheterization alone or combined with stoma or tapping) resulted in lower urological complications and better QoL, as long as close urological surveillance occurs at least annually (Bothig et al. 2012; n=56). SPC resulted in fewer instances ($p<0.05$) of ureteric reflux, bladder/kidney stones, or bleeding for high-tetraplegic individuals with long term ventilation. SPC was increasingly used with increasing age, regardless of gender.

Conclusions

There is level 1b evidence (from one RCT; Gu et al 2015) that electroacupuncture in combination with CIC results in reduced residual volume and CIC frequency while increasing voided volume.

There is level 4 evidence (from one case series study; El Masri et al. 2012) that severity of injury and urinary sensation could be predictive parameters of future voiding function.

There is level 4 evidence (from one case series study; Gohbara et al. 2013) that supervised, sequential conservative bladder management options result in favourable urological complication rates.

There is level 4 evidence (from two case series studies; Ord et al. 2003; Weld & Dmochowski 2000) that indwelling urethral catheterization is associated with a higher rate of acute urological complications than intermittent catheterization.

There is level 4 evidence (from one case series study; Weld & Dmochowski 2000) that prolonged indwelling catheterization, whether suprapubic or urethral, may result in a higher long-term rate of urological and renal complications than intermittent catheterization, condom catheterization or triggered spontaneous voiding.

There is level 4 evidence (from two case series studies; Ord et al. 2003; Weld & Dmochowski 2000) that intermittent catheterization, whether performed acutely or chronically, has the lowest complication rate.

There is level 4 evidence (from two case series studies; Yavuser et al. 2000; Green 2004) that those who use intermittent catheterization at discharge from rehabilitation may have difficulty continuing, especially those with tetraplegia and complete injuries. Females also have more difficulty than males in maintaining compliance with IC procedures.

There is level 4 evidence (from one case series; Bothig et al. 2012) supporting significantly fewer urological complications and higher quality of life for high-tetraplegic respirator-dependent individuals who use suprapubic catheters (versus intermittent catheterization) for bladder management.

There is level 4 evidence (from 1 case series; Bartel et al 2014, n=2825) that supra pubic catheter use is most highly associated with bladder stone occurrence while transurethral catheters are most highly associated bladder stone recurrence.

Electroacupuncture in combination with CIC results in reduced residual volume and CIC frequency while increasing voided volume.

Supervised sequential conservative bladder management may result in favourable urological complication rates.

Severity of injury and urinary sensation could be predictive parameters for future voiding function.

Intermittent catheterization, whether performed acutely or chronically, may have the lowest complication rate.

Indwelling catheterization, whether suprapubic or urethral or whether conducted acutely or chronically, may result in a higher long-term rate of urological and renal complications than other management methods.

Persons with tetraplegia and complete injuries, and to a lesser degree in females, may have difficulty in maintaining compliance with intermittent catheterization procedures following discharge from rehabilitation.

Bladder management via suprapubic catheterization may be the better option for individuals that are high tetraplegics and respirator-dependent.

Suprapubic catheter use may be more associated with bladder stone occurrence while transurethral catheters may be more associated with bladder stone recurrence.

It is possible that males using IC are more likely to develop urethral strictures of which some might need surgical intervention.

There may be an association with males needing catheterization having a higher mortality rate.

4.4.2 Intermittent Catheterization

Intermittent catheterization is the preferred method of bladder management, with a reduced incidence of renal impairment, reflux, stone disease, bladder cancer and possibly UTI compared to other methods of bladder management (Groah et al. 2002; Weld & Dmochowski 2000; Ord et al. 2003). The first section (3.4.2.1) outlines those studies focusing on specific aspects of IC including timing of catheterization, effectiveness, long-term follow-up, and QoL. The second section (3.4.2.2) outlines studies examining catheter types.

4.4.2.1 Specific Aspects of using Intermittent Catheterization

Table 12 Specific Aspects of using Intermittent Catheterization

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
Polliack et al. 2005 Israel RCT PEDro=6 N=24	<p>Population: Study group: Mean age: 42.7 yr; Gender: males=9, females=4; Level of injury: paraplegic=5, tetraplegia=8; Control group: Mean age: 53.46 yr; Gender: males=6, females=5; Level of injury: paraplegic=6, tetraplegic=5. Injury severity: AIS A-D.</p> <p>Intervention: Individuals were randomized to 1) volume-dependent intermittent catheterization (IC) as measured by a portable ultrasound device (PUD) or 2) time dependent IC; F/U period 12-30 d.</p> <p>Outcome Measures: Frequency of catheterization, time to perform, total cost, complications.</p>	<ol style="list-style-type: none"> 1. Compared to the control group, the study group had 6 fewer catheterizations/day (44% decrease), required 20 minutes less time to perform volume measurements and catheterizations (49% decrease), and experienced 46% less cost ($p<0.001$).
Oh et al. 2006 Korea Prospective Controlled Trial N=282	<p>Population: SCI individuals =132: Mean age: 41.8 yr (range 18-80 yr); Gender male=81, female=51; Injury level: cervical=36, noncervical=96; Severity of injury: paraplegic=24, tetraplegic=108; Duration of catheterization use: 24.2 mo. Controls=150: Mean age: 41.8 yr; Gender: male=90, women=60.</p> <p>Intervention: Health related quality of life (HRQoL) questionnaire to determine psychological and social status of individuals.</p> <p>Outcome Measures: HRQoL measured by the Medical Outcomes Study 36-Item Short-Form General Health Survey (SF-36).</p>	<ol style="list-style-type: none"> 1. SF-36 scores did not reveal significant differences between the men and women in the individual group. 2. SF-36 scores of individuals were significantly lower compared to controls (physical functioning: $p<0.001$; role-emotional functioning: $p=0.002$; vitality: $p<0.064$; mental health: $p<0.001$; social functioning: $p<0.001$; bodily pain: $p=0.025$; general health: $p=0.013$).
Kriz and Relichova 2014 Czech Republic Cohort N=41	<p>Population: Mean age: 33.3 yr; Gender: males=39, females=2; Level of injury: C4=8, C5=11, C6=15, C7=7.</p> <p>Intervention: Individuals were separated into four cohorts based on level of injury and all received training to perform self-catheterization.</p> <p>Outcome Measures: Urinary diversion method used, reason for not using intermittent catheterization (IC).</p>	<ol style="list-style-type: none"> 1. Of the 8 participants in the C4 group, 7 had an indwelling suprapubic catheter and 1 had an indwelling transurethral catheter. Wrist extensor muscle strength varied between grade 0 and 1 in all subjects, except for one participant with grade 3. 2. Of the 11 participants in the C5 group, 4 had independent IC, 2 had assisted IC, and 5 had an indwelling suprapubic catheter. Reasons for continuing to use an indwelling catheter included failure to develop a functional grip, repetitive severe autonomic dysreflexia, prompt

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
		<p>reflex erection, and reduced wrist extensor muscle strength.</p> <ol style="list-style-type: none"> Of the 15 participants in the C6 group, 10 had independent IC, 2 had assisted IC, and 3 had an indwelling suprapubic catheter. Reasons for continuing to use an indwelling catheter included failure to achieve a functional grip, repeated bladder surgery, and cognitive impairment. Of the 7 participants in the C7 group, 6 had independent IC, 0 had assisted IC, and 1 had an indwelling suprapubic catheter. The reason for continuing to use an indwelling catheter was severe abductor spasticity.
<p>Perrouin-Verbe et al. 1995 France Case Control N=188</p>	<p>Population: <i>Group 1 (clean intermittent catheterization, IC):</i> Mean age: 38 yr; Gender: males=113, females=46; Level of injury: thoracic=67, conus medullaris syndrome=20, cauda equina syndrome=22; Severity of injury: tetraplegia=50, <i>Group 2 (Individuals who discontinued clean IC after 2 yr=8):</i> Mean age: 38 yr; Gender: males=8; Level of injury: C=1, T=4, TL=1, LS=2; Severity of injury: Frankel grade: A=6, D=2; <i>Group 3 (Individuals performing clean IC for over 5 yr, N=21):</i> Mean age: 37.3 yr; Gender: males=21; Level of injury: C=2, T=10, TL=6, LS=3; Severity of injury: Frankel grade: A=17, B=1, C=2, D=1; Duration of clean IC=9.5 yr.</p> <p>Intervention: Data of SCI individuals using clean IC was retrospectively reviewed.</p> <p>Outcome Measures: Infection rate (urinary tract and genital), incontinence, duration of clean IC use, complications, procreation, individual satisfaction (visual analogue scale).</p>	<p>Group 1:</p> <ol style="list-style-type: none"> 95 individuals had asymptomatic cytobacteriological infection; 45 had symptomatic lower urinary tract infection. Males had a significantly higher rate of infection than females ($p<0.05$); epididymitis (n=16), stricture (n=8). Deterioration of the upper urinary tract was seen in 3 individuals and was correlated with high intravesical pressure. <p>Group 2:</p> <ol style="list-style-type: none"> Even with use of anticholinergic drugs, 5 individuals were incontinent. Mean time before discontinuance of catheterisation was 5.25 yr. Reasons for discontinuance included persistent incontinence (n=5), upper urinary tract deterioration (n=1), catheterisation difficulty (n=4), urethral stricture (n=1). <p>Group 3:</p> <ol style="list-style-type: none"> Group comprised of 10 with detrusor areflexia; 11 with DESD (7 used anticholinergic drugs) Symptomatic infections less than once every two yr in most individuals but 2-4/yr in 4 individuals.

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
		<ol style="list-style-type: none"> Catheterization was difficult (n=11) or impossible (n=5) for some. Rate of urethral stricture was 19% and epididymitis was 28.5%; these rates increased with the number of yr of clean IC use.
<p>Wilde et al. 2016 United States Pre-Post N_{initial}=29; N_{final}=23</p>	<p>Population: Mean age: 43.52 yr; Gender: males=15, females=14; Level of injury: cervical=7, thoracic=17, cervical/thoracic=1, lumbar/sacral=2, thoracic/lumbar=1, unknown=1; Severity of injury: complete=13, incomplete=13; Mean time post-injury: 16 yr; Injury etiology: spinal cord injury=26, other spinal cord disease=3.</p> <p>Intervention: Web-based intermittent catheter (IC) self-management intervention, intended to teach awareness, self-monitoring, improve adherence to IC frequency, and to balance fluid intake with activity. This program included web-based information, an online educational booklet, an interactive urinary diary, three nurse phone consultations, and peer-led discussion forums.</p> <p>Outcome Measures: Frequency and intervals of IC, average urine output estimate, material used to contract catheter, adverse events, acceptance and usability of intervention, website usage, Stanford Chronic Disease Self-Management Program (CDSMP), self-management questions, Intermittent Self-Catheter Questionnaire (ISC-Q), Psychological Well Being Scale.</p>	<ol style="list-style-type: none"> At 3 mo follow-up, no significant improvements were observed for ISC-Q, Psychological Well-being Scale, and CDSMP. There was a significant increase in the self-management scale (p=0.032). Mean typical catheterizing output increased from 323.4 to 355 ml. All pages of the educational booklet were viewed but every participant did not look at the whole booklet. The most viewed sections pertained to optimal fluid intake, best IC intervals, and recognizing symptoms of urinary tract infection. Over half of the total time spent on the website was devoted to urinary diary use. A majority of participants agreed or strongly agreed that the intake and output diary, journal, educational materials, and nurse calls were useful. However, responses to the forum were mixed. Scores for the usability of the web-based information were high and most people enjoyed working with the study nurse. At 3 mo follow-up, many participants reported changes in the intervals with more catheterizing every 2-3 h. However, the majority performed the procedure every 4-6 h and 4-6 times/d at both baseline and follow-up. Frequency of urinary tract infection and pain did not change significantly.
<p>Pannek & Kullik 2009b Germany</p>	<p>Population: Mean age: 39.5 ±14 yr; Gender: male=31, female=10; level of injury: C=9, T=23, L=9; Level of injury:</p>	<ol style="list-style-type: none"> Bladder management was successful in 14 individuals. Of the 27 individuals with treatment

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
Post-test N=41	Paraplegia=28, Tetraplegia=13; mean time post-injury=4 yr Intervention: Bladder management via intermittent self-catheterization, anticholinergic therapy, BTX-A Outcome Measures: the Qualiveen questionnaire, urodynamics, treatment success	failure, 16 reported decreasing efficacy of BTX-A injections and 11 reported significant detrusor over activity despite anticholinergic therapy in both groups. 2. Qualiveen scale ratings concerning individual's fears and feelings were greater for individuals with suboptimal bladder function; all individuals listed as having treatment failure were incontinent. 3. Depression has an impact on QoL, but only continence was directly related to QoL. Level of injury was not significant to influence QoL.
Subramanian et al. 2016 United Kingdom Case Series N=5	Population: Mean age: 41.6 yr; Gender: males; Level of injury: paraplegia=2, tetraplegia=3. Intervention: Transurethral catheter. Outcome Measures: To describe individuals with an incorrect placement of a Foley catheter leading to inflation of Foley balloon in urethra.	1. Five cases of intra-urethral Foley catheter balloon inflation due to unskilled catheterisation were described. 2. Symptoms manifested include bypassing and unsatisfactory drainage, kidney pain, urethral bleeding, increased spasms and sweating, urine infection, erosion of urethra, breakdown of skin in perineum, and urinary fistula. 3. Risk factors include lack of sensation in urethra, trauma to urethra during previous catheterisations, spasm of pelvic floor muscles or urethral sphincter, altered anatomy due to past surgery, and habit of using spinal cord injury individuals for clinical skill practice by student nurses and trainee doctors.
Ku et al. 2006 Korea Case Series N=140	Population: Gender: males=100, females=40; Severity of injury: complete=34, incomplete=106; Time post-injury= 17 yr. Intervention: Review of urological medical records from January 1987 to December 2003 on individuals with SCI. Methods of bladder management included spontaneous voiding, clean intermittent catheterization (IC), suprapubic or indwelling catheters.	1. Overall, 39 individuals had epididymo-orchitis. 2. Epididymo-orchitis was more common for individuals on IC than with indwelling urethral catheterization (p=0.03). 3. Rate of urethral stricture: 0% urethral catheterization, 4.3% voiding spontaneously, 18.2% IC, and 2.8% suprapubic catheter.

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
	Outcome Measures: Individuals with epididymo-orchitis, variables associated with risk.	<ol style="list-style-type: none"> 4. Individuals on IC had a 7 fold higher risk (odds ratio, 6.96; 95% CI, 1.26-38.53, p=0.026). 5. IC was an independent risk factor for epididymo-orchitis.
Ord et al. 2003 England Case Series N=457	<p>Population: SCI with >6 mo on any 1 form of management: Mean age: 29-40 yr for various groups; Gender: males=402, females=55; Level of injury: T3 – T9; Severity of injury: complete, incomplete; Follow-up time=48-107 mo.</p> <p>Intervention: Assessment of various bladder management methods (i.e., sphincterotomy, condom, intermittent catheter (IC), indwelling urethral catheter, suprapubic catheter+ combinations of each).</p> <p>Outcome measures: Bladder stone formation rate.</p>	<ol style="list-style-type: none"> 1. Both forms of indwelling catheterization had an increased risk of getting bladder stones and requiring hospitalization for bladder stones over IC and condom drainage with or without sphincterectomy. 2. Relative to IC, hazard ratio was 10.5 for suprapubic catheters and 12.8 for indwelling urethral catheters. 3. Incidence density ratio (like odds ratio) was 40.7 for developing bladder stones for indwelling catheters relative to IC. Condom incidence density ratio was 7.5 relative to IC. 4. % Annual risk for stone formation: Condom & Sphincterotomy 0%; IC 0.2%; Expression voiding with or without condom 0.5%; Indwelling catheter 4% (first stone), 16% (subsequent stone).
Weld & Dmochowski 2000 USA Case Series N=316	<p>Population: SCI: Mean age: 33.9-41.0 yr; Gender: males=313, females=3; Level of injury: suprasacral=269, sacral=47; Severity of injury: complete=45, incomplete=271; Mean follow-up=17.8-19.3 yr for various groups.</p> <p>Intervention: Assessment of various bladder management methods (i.e., intermittent catheterization (IC), voiding spontaneously, indwelling urethral catheter, suprapubic catheter).</p> <p>Outcome Measures: Urological complication rate (epididymitis, pyelonephritis, upper tract stone, bladder stone, urethral strictures, periurethral abscess, vesicoureteral reflux, abnormal upper tracts).</p>	<ol style="list-style-type: none"> 1. Frequency of those managed by IC, voiding spontaneously, suprapubic and urethral catheterization was 92, 74, 36 and 114 subjects respectively. 2. Complication rates for the above groups were 27.2%, 32.4%, 44.4% and 53.5% respectively. 3. Urethral catheter users had the highest rates for epididymitis, pyelonephritis, upper tract stone, bladder stone, urethral strictures and periurethral abscess. 4. Suprapubic catheter users had the highest rates for vesicoureteral reflux and abnormal upper tracts.
Jensen et al. 1995 Norway Case Series N=12	Population: Age Range 17-72 yr; Gender: males=11, females=1; Severity of injury: complete, incomplete; Time post-injury: 3-7 mo.	<ol style="list-style-type: none"> 1. 7 individuals had 50-100mL residual urine; 2 individuals had >100mL residuals. 2. 9 individuals had >1 UTI during hospital stay.

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
	Intervention: Three ultrasonographic measurements of residual urine after Intermittent catheterization Outcome Measures: Residual urine volume; urinary tract infections (UTI).	3. No correlation between residual urine volume and UTI incidence ($r=0.19$ (mean), $p=0.52$; $r=0.16$ (max), $p=0.63$).
Nanninga et al. 1982 USA Case Series N=85	Population: Gender: males=71, females=14, Level of injury: paraplegia=56, tetraplegia=29; Severity of injury: complete=64, incomplete=21 Intervention: Individuals on intermittent catheterization followed for 11 mo (range 6-72). Outcome Measures: Excretory urogram and cystogram at 6 mo intervals. Urine culture. Serum urea and creatinine	1. 12 developed reflux, 16 developed ureterectasis or hydroureteronephrosis. 11 of these 28 had elevated creatinine. 2. 64 had at least 1 urinary tract infection (UTI), 1 had bladder calculi. 3. Treatment in 15: Increased frequency of catheterization. Avoiding short duration high fluid intakes. 3 had sphincterotomy. 10 were converted to indwelling catheterization.

Summarized Level 5 Evidence Studies:

Woodbury et al. (2008) reported mean frequency of UTIs for IC users was 2.6 ± 2.6 in the last 12 months. Among IC users, females had a significantly greater number of UTIs than males ($p=0.003$). Sex, number of catheterizations, age, and severity of injury were each correlated with infection rate. Time lost from social activities due to UTIs lead to poorer QoL than the actual number of UTIs or days lost from work. Akkoc et al. (2013) observed no difference between bladder management groups in general health perception, personal relationships, and sleep/energy domain scores. There was a significant difference among urinary incontinence groups only in symptom severity scores, for individuals with urinary incontinence several times/d, and those with urinary incontinence several times a week were found to be significantly higher than of individuals without urinary incontinence ($P<0.001$ and $P=0.018$).

Discussion

Intermittent catheterization is the mode of bladder management generally associated with the fewest long-term complications (Groah et al. 2002; Weld & Dmochowski 2000; Ord et al. 2003). However, there are some complications that occur with higher frequency in individuals who intermittently catheterize. For example, increased urethral complications (19% incidence) may lead to urosepsis and epididymorchitis (28.5% incidence), and strictures (Kredbs et al 2015) and may result in increased morbidity and reduced fertility (Ku et al. 2006), and mortality (Shavelle et al. 2015). Despite IC-related higher rates of complications, there is good consensus among the larger retrospective studies available that IC programs are still

preferred for the protection of the upper urinary tract through regular emptying with low bladder pressures (Giannantoni et al. 2001). Episodes of pyelonephritis and UTI are also reduced when bladder emptying is conducted consistently and completely in the absence of indwelling catheters (Groah et al. 2002; Weld & Dmochowski 2000; Ord et al. 2003; Giannantoni et al. 2001; Woodbury et al. 2008).

Perrouin-Verbe et al. (1995) showed that individuals most likely to continue with IC would be those who are able to independently catheterize and those who have an acceptable level of continence. SCI lesion level is shown to be predictive for independent IC with lower level cervical lesions having higher success when compared to higher level cervical lesions. (Kriz and Relichova 2014). For example, of 7 C7 participants, 6 (86%) were able to independently participate and the 7th resorted to an indwelling suprapubic catheter as a result of severe abductor spasticity. In contrast, of 8 C4 participants, none used IC given minimal wrist extensor muscle strength. Sixty-seven percent and 36% of C6 and C5 participants, respectively, were able to independently catheterize. Pannek & Kullik (2009b) showed that individuals who employ self-IC and have optimal bladder function, perceived QoL is higher than those with suboptimal function. Akkoc et al. (2013) compared individuals using various bladder management methods; those with normal spontaneous micturition had the highest QoL whereas those using an attendant to perform IC had the lower QoL. The authors reported, however, that there was no difference in personal relationships, general health perception, and sleep/fatigue among groups. These findings are in contrast to those by Oh et al. (2006) who found significant differences in many variables measured by the SF-36 between individuals with SCI and able-bodied controls. It is essential to consider an individual's activities of daily living, psychological factors (and other concurrent comorbidities) and potential caregiving needs when IC is being introduced early after SCI. If intra-urethral catheterizations must be considered, unskilled catheterization are associated with complications resulting from lack of sensation in the urethra, urethral sphincter spasm, and false passage due to previous urethral trauma. (Subramanian et al. 2016)

A very low incidence of bladder stones (Bartel et al. 2014) and hydronephrosis were reported in Perrouin-Verbe et al. (1995; 2%), consistent with previously discussed studies. However, Nanninga et al. (1982) reported upper tract changes in 33% of individuals. While this range is large, it is possible that management of individuals in 1982 involved less stringent control of high bladder pressures which is the cause of upper tract disease in many cases (Nanninga et al. 1982). Nanninga noted that high bladder pressures may occur even in individuals who remain continent or nearly continent between catheterizations, and that the problem can at least be partially avoided by increasing the frequency of catheterization. An IC self-management pre-post study using web-based tools and, nursing phone consultations and peer-led discussions showed a modest improvement in IC frequency and fluid intake, without a change in UTIs, pain and catheter related self-efficacy and quality of life. (Wilde et al. 2016).

Other options for individuals with persistently elevated pressures already on IC programs are detrusor OnaBTx injections and/or anticholinergic medications. It is important to note that regular follow-up of these individuals including tests of

bladder physiology and upper tract function is recommended to monitor for changes and for increasing incidence of complications with time (Perrouin-Verb et al. 1995; Nanninga et al. 1982).

Finally, in a small RCT, Polliak et al. (2005) used a portable ultrasound device to measure bladder volumes among a group of individuals post SCI. Compared to those who used time-dependent IC, those using volume-dependent IC had significantly fewer catheterizations which resulted in a significant reduction in cost ($p < 0.001$).

Conclusions

There is level 1b evidence (from one RCT; Polliack et al. 2005) that using a portable ultrasound device reduces the frequency and cost of intermittent catheterizations.

Level 2 evidence (from 1 cohort study; Kriz and Relichova 2014) reflects the higher likelihood of IC independence based on the individual's neurological level of lesion, with lower cervical lesions (e.g. C7) being more favourable than higher cervical lesions (e.g. C4).

There is level 4 evidence (from many non-randomized controls) that urethral complications and epididymoorchitis occurs more frequently in those using IC programs for bladder emptying, but the advantages of improved upper tract outcome over those with indwelling catheters outweigh these disadvantages.

There is level 4 evidence (from 1 pre-post study; Wilde et al. 2016) showing that an IC self-management educational program may lead to modest improvement in IC self-management.

Portable ultrasound device can improve the scheduling of intermittent catheterizations.

Lower cervical lesion levels are likely predictive of more IC independence.

Urethral complications and epididymoorchitis occur more frequently in those using intermittent catheterization programs.

IC self-management educational programs may be modestly helpful.

4.4.2.2 Comparison of Intermittent Catheterization Catheter Types

Table 13 Comparison of Intermittent Catheterization Catheter Types

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
Birmingham et al. 2013 UK Systematic Review AMSTAR=8 N=8 studies	<p>Population: <u>Vapnek et al. 2003 (n=62)</u>: Mean age: 40 yr; Gender: males=62, females=0. <u>Cardenas et al. 2009 (n=56)</u>: Mean age=41 yr; Gender: males=29, females=27. <u>De Ridder et al. 2005 (n=123)</u>: Mean age: 37 yr; Gender: males=123, females=0. <u>Sutherland et al. 1996 (n=33)</u>: Mean age: 12 yr; Gender: males=33, females=0. <u>Pachler et al. 1999 (n=43)</u>: Mean age: 71 yr; Gender: males=43, females=0. <u>Giannantoni et al. 2001 (n=18)</u>: Mean age: 38 yr; Gender: males=16, females=2. <u>King et al. 1992 (n=46)</u>: Mean age: 29 yr; Gender: males=40, females=6. <u>Duffy et al. 1995 (n=80)</u>: Mean age: 72 yr; Gender: males=80, females=0.</p> <p>Treatment: A cost effective analysis using a probabilistic Markov model to compare lifetime costs and quality adjusted life years (QALYs) for gel reservoir catheters and clean non-coated self-catheters. Relevant articles were retrieved through a literature search from Medline, Embase, Cochrane, and Cinahl from 2002 to April 2011.</p> <p>Outcome Measures: Symptomatic urinary tract infection (UTI), cost effectiveness.</p>	<ol style="list-style-type: none"> 1. Individuals using gel reservoir and hydrophilic catheters were significantly less likely to report one or more UTIs compared with sterile non-coated catheters (p=0.04). 2. When measured as monthly UTIs (p=0.84) or UTIs per yr (p=0.60), there was no significant difference between hydrophilic and sterile non-coated catheters. 3. There was little difference in the incidence of one or more UTIs for people using clean versus sterile non-coated catheters (p=0.86). 4. Gel reservoir catheters are not cost-effective compared to clean non-coated self-catheters.
Chartier-Kastler et al. 2013 France RCT crossover PEDro=8 N=103	<p>Population: SCI: Mean age: 53.8 yr (range 22.6-87.5 yr); Etiology of injury: traumatic SCI=53, spinal tumor=4, spina bifida=3, MS=19, other=39; Time post-injury: 13.3 yr (range 0.9-47 yr); Severity of injury: complete paraplegia=33, incomplete paraplegia=38, complete tetraplegia=3, and incomplete tetraplegia=9, unsure=33.</p> <p>Intervention: Effectiveness of a compact catheter versus a standard catheter evaluated in a 2 wk crossover trial.</p> <p>Outcome Measures: Intermittent self-catheterization questionnaire (quality of life); Visual Analogue Scale (VAS)</p>	<ol style="list-style-type: none"> 1. Intermittent catheterization questionnaire score increased significantly with compact catheter use (p<0.001). There was a mean difference of 17±1.8 points between the compact and standard intermittent catheters. 2. The compact catheter was preferred over a standard catheter by 67/106 (63%) individuals (p=0.007). 3. Mean VAS satisfaction score was significantly different in favour of the compact catheter (p=0.037).
Costa et al. 2013 United States RCT crossover PEDro=7	<p>Population: Male SCI individuals: Mean Age: 38.4 yr; Reason for intermittent catheterization: SCI (n=79), Other (n=2)</p>	<ol style="list-style-type: none"> 1. Subjects preferred the control catheter (91.4%) to the test catheter (8.6%).

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
N=81	<p>Intervention: Subjects were randomized into groups for use of Apogee hydrophilic catheters in one of two lengths: 1) 30 cm-test size, or 2) 40 cm-control size. Subjects then crossed over to other arm.</p> <p>Outcome Measures: Ease of use, and catheter preference.</p>	2. Preference for the control catheter was due to complete bladder emptying (70%), satisfactory length (74%), ease of draining into a receptacle (58%) with portable urine being the most utilized (37%), followed by toilet (35%).
Denys et al. 2012 France RCT crossover PEDro=7 N=97	<p>Population: SCI: Median age: 46 yr (range 19-64 yr); Median duration of intermittent catheterization: 11 yr (range 0.33-52 yr); Injury etiology: SCI=57.7%, multiple sclerosis=25.8%, spina bifida=4.1%, other=12.4%.</p> <p>Intervention: Subjects were randomized into two groups to use either 1) a "no-touch" VaPro hydrophilic catheter, or 2) a standard convention catheter, for intermittent catheterization over 15 days. Subjects were then crossed to the other arm.</p> <p>Outcome Measures: Questionnaire evaluating individuals' experiences before the start of the trial and after each 15 d period of catheter use.</p>	<ol style="list-style-type: none"> 1. More than 50% of individuals would recommend the VaPro Catheter. 2. More than 75% of individuals felt confident and more secure with the new catheter. 3. More men than women preferred the VaPro catheter (p=0.030).
Chartier-Kastler et al. 2011 France RCT crossover PEDro=8 N=36	<p>Population: Male SCI individuals: Median age: 43.2 yr (range 20-70 yr); Median time using catheters: 39 mo. (range 1-219 mo); Median number of catheters used per day: 6. (range 4-10 d); Etiology of injury: traumatic=24, non-traumatic=12; severity of injury: complete tetraplegia=3, incomplete tetraplegia=6, complete paraplegia=4, incomplete paraplegia=22, unknown=1; AIS score: A=7,19.4%, B=5,13.9%, C=8, 22.2%, D=16, 45.5%.</p> <p>Intervention: Participants were randomized to either a standard coated catheter or a single-use compact coated catheter and switched at crossover.</p> <p>Outcome Measures: Visual Analogue Scale (VAS) for discomfort, ease of use, discretion, degree of pain, stinging or resistance.</p>	<ol style="list-style-type: none"> 1. The compact catheter did not have more discomfort than the standard-length catheter, however there were significant differences between participants from different countries in comfort levels (p=0.0315). 2. Significant difference in favour of the compact catheter for discretion, carrying and disposal (p<0.0001). 3. The standard catheter had significantly higher mean degrees of resistance than the compact catheter (p=0.0273). 4. No difference was observed between the catheters with pain and stinging (p=0.6831)
Domurath et al. 2011 Germany RCT crossover PEDro=8	<p>Population: Male SCI individuals: Mean age: 40 yr (range 21-66 yr); AIS: A =20, B=9, C=3, and D=5; Mean duration of intermittent</p>	1. The two catheters did not differ in bladder emptying performance, and the test catheter was no less

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
N=37	catheterization: 88.76 mo (range 2-264 mo). Intervention: Evaluate the performance of SpeediCath Compact catheter (30-cm) versus control catheter in a crossover trial. Outcome Measures: Residual Urine (RU) Volume; subject evaluation of their experience, sensation, disposal, bleeding and discomfort with the test and control catheters, final catheter preference.	inferior by RU volume to the control catheter.
Sarica et al. 2010 Turkey RCT PEDro=5 N=25	Population: Mean age: 37.04 yr; Males=18+yr, injury<6 mo, Severity of Injury: ASIA scale-A=8, B=6, C=7, D=4; Level of injury: paraplegia=21, tetraplegia=4 Intervention: Subjects were randomized into one of three groups for the use of 1) hydrophilic catheters, 2) gel-lubricated standard catheters, or 3) standard polyvinyl chloride catheters (PVC) for intermittent catheterization (IC). Outcome Measures: Incidence of urinary tract infections (UTIs), presence of microhematuria, adverse events	<ol style="list-style-type: none"> 1. No significant differences in the frequency of UTI among types of catheter were reported ($p<0.05$). 2. The gel lubricated and the hydrophilic catheter received higher individual satisfaction vs. PVC ($p<0.05$). 3. The gel lubricated catheter found to be superior to hydrophilic and PVC catheters in terms of urethral microtrauma, pyuria and satisfaction. 4. Cost of intermittent catheterization was higher compared to PVC catheters/d.
Biering-Sorensen et al. 2007 Denmark RCT crossover PEDro=6 N=24	Population: Female SCI individuals: Mean age: 44 yr (range 19-64 yr); Severity of injury: paraplegia=20, tetraplegia=4; Mean duration of intermittent catheterization (IC) use: 8.3 yr (range 4 mo to 23 yr); Mean number of catheterizations per day: 5.5 (range 2-9). Intervention: Participants were randomized to one of two catheters 1) SpeediCath Compact or 2) reference catheter. Subjects then switched to the other arm. Outcome Measures: Residual urine (RU) volume, length and handling of the SpeediCath Compact catheter.	<ol style="list-style-type: none"> 1. There was no difference between the catheters in RU volume. 2. 23/24 (95.83%) found handling the SpeediCath compact catheter easy and their satisfaction was either satisfactory or very satisfactory.
De Ridder et al. 2005 Spain RCT PEDro=5 N=123	Population: SCI individuals using hydrophilic versus peripheral venous catheter (PVC): Mean Age: 37 yr; Gender: males=123, females=0; Severity of injury: AIS: A-D. Intervention: SpeediCath® hydrophilic catheter versus conventional uncoated PVC	<ol style="list-style-type: none"> 1. Lower incidence of UTIs in those using SpeediCath hydrophilic versus PVC ($p=0.02$). 2. No difference in number of bleeding episodes or occurrence of hematuria, leukocyturia and bacteriuria between groups. No significant difference in satisfaction.

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
	catheter for intermittent catheterization (IC) over 12 mo. Outcome Measures: Occurrence of symptomatic urinary tract infection (UTIs), hematuria, strictures, convenience of use/satisfaction with catheter at 6 and 12 mo.	3. 54% dropout rate (slightly more so in hydrophilic group) partially due to the fact that many subjects no longer needed to catheterize when bladder function was regained within the 1 yr period.
Giannantoni et al. 2001 Italy RCT PEDro=9 N=18	Population: SCI: Mean Age: 38.2 yr; Level of injury: C5-Cauda Equina; Severity of injury: AIS: A-D; Time post- injury=18-60 d. Intervention: Subjects were randomized into two groups to use either 1) Instacath® non-hydrophilic pre-lubricated catheter or 2) conventional uncoated Nelaton polyvinyl chloride catheters (PVC) for intermittent catheterization (IC). Subjects then crossed over to the other arm. Outcome Measures: Symptomatic UTI and asymptomatic bacteriuria, incidence of urethral complications (bleeding and urethral cell counts), visual analog scale of individual satisfaction.	1. Lower incidence of UTIs ($p=0.03$) and asymptomatic bacteriuria ($p=0.0244$) of those using pre-lubricated catheters versus PVC. 2. Fewer epithelial cells found on pre-lubricated catheter versus conventional ($p=0.01$), reported to be indicative of a 2-fold reduction of microtrauma. 3. 2 people had urethral bleeding with conventional catheter, 0 with pre-lubricated. 4. Pre-lubricated catheters had significantly higher satisfaction scores for 4 of 5 items on the scale. 5. 3 subjects requiring assistance with the conventional catheter became independent with the pre-lubricated catheter (order effect unreported) 6. No subject had impaired renal function of upper and lower tract abnormalities with either catheter.
Waller et al. 1997 Sweden RCT PEDro=7 N=14	Population: SCI treated at SCI Unit: Mean age: 30 yr; Level of injury: paraplegia=5, tetraplegia=8; Severity of injury: complete=8, incomplete=6; Time post-injury=5 d-5 mo. Intervention: Individuals were randomized to 1) Lo-Fric® hydrophilic catheters or 2) EasiCath® hydrophilic catheters for intermittent catheterization (IC) for 10 days; individuals then crossed-over to the other arm. Outcome Measures: Friction force on removal, number of times catheter "stuck", urinary tract infection (UTIs), osmolality.	1. Lo-Fric® catheter had significantly reduced friction (55%) as compared to Easicath® ($p<0.001$). 2. Nurses reported fewer times catheters had "stickings" with Lo-Fric® catheter as compared to Easicath® (3 versus 42). 3. There was no significant difference in the incidence of UTIs with either catheter (2 versus 3). 4. Mean catheterization time was similar for both catheters. 5. Lo-Fric® catheter had >10x higher osmolality as compared to Easicath®. 6. Lower friction, higher osmolality may reduce adhesion and urethral damage.

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
Bjerkklund Johansen et al. 2007 Sweden Pre-Post N=378	<p>Population: Mean age: 43.5 yr; Gender: male=283, 75%, female=95, 25%; Injury etiology: SCI=65.6%, spina bifida=2.3%, MS=9.6%, other=22.5%; Mean duration of intermittent catheter (IC) use: 4.6 yr; frequency of IC use: 3/day=13.6%, 5/day=14%, 6/day=15.6%, 7/day=19.3%.</p> <p>Intervention: Administration of a novel hydrophilic catheter device (LoFric Primo®) for a 2-wk trial.</p> <p>Outcome Measures: Visual Analogue Scale scores (insertion, withdrawal, handling, time spent, perception of clean intermittent catheterisation)</p>	<ol style="list-style-type: none"> 55.2% of individuals were happy and wished to continue using the novel catheter; of these, 74% of individuals previously used standard polyvinyl chloride catheters (PVC) and 26% of those were using pre-lubricated PVC (p=0.04). VAS results indicated individuals in general found the novel product more troublesome with handling and general satisfaction (p=0.0001). However, for insertion, withdrawal, time spent, and general perception of IC no statistically significant difference was discovered. As well, abilities to comply with activities of daily life was not decreased by the novel catheter (p=0.0001).
Kovindha et al. 2004 Austria Pre-Post N=28	<p>Population: Mean age: 38.5 yr; Gender: males=28, females=0; Level of injury: paraplegia=23, tetraplegia=4, neurogenic bladder=1; Severity of injury: AIS: A or B=20, C or D=8; Mean duration of clean intermittent catheterization (IC) use=4.8 yr. Mean duration of use of each catheter 35 mo.</p> <p>Intervention: Reusable silicone catheters.</p> <p>Outcome Measures: Urinary management, urethral abnormality, catheter stiffness, complications.</p>	<ol style="list-style-type: none"> Urinary management method was not significantly related to UTI. Increased frequency of clean IC was significantly related to decreased urethral abnormality (p<0.05). Reused catheters had increased stiffness of 20%. Complications included urethral bleeding (n=3), urethra pus (n=5), epididymitis (n=5), passing stones (n=4), foul smelly urine (n=18), fever and cloudy urine (n=10); 6/10 individuals had 2-3 episodes/yr Ultrasound found mild hydronephrosis (n=2), mild pelvocalyceal dilation (n=1), focal thinning of parenchyma (n=1), and multiple bladder calculi (n=1).
Wyndaele et al. 2000 Belgium Pre-Post N=39	<p>Population: Male SCI individuals: Mean age: 45 yr (range 19-74 yr); Etiology of bladder dysfunction: SCI=21, neurological disease=12, other=6; Mean neurological bladder dysfunction duration: 7.8 yr (range 1-23).</p> <p>Intervention: Subjects who normally used conventional catheters for intermittent</p>	<ol style="list-style-type: none"> Time needed for clean IC was not different with both techniques. Difficult introduction or difficult retreat of the catheter were not different in frequency. Impossibility to introduce the catheter was less frequent. Urethritis and urethral bleeding were less frequent than during the use of conventional

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
	catheterization (IC) changed to hydrophilic low-friction Uroath-Gel catheter. Outcome Measures: Time to catheterize, satisfaction, urodynamic parameters.	catheters. Satisfaction was better with the low friction catheters. 3. Negative satisfaction was mainly related to the availability and the use of water to lubricate the catheter, difficulty of manipulation and fear for cost.
Spinu et al. 2012 Romania Case Series N=50	Population: Neurogenic bladder dysfunction individuals=50: Hydrophilic catheter use=35; Mean age: 43.85 yr (range 19-63 yr); Gender: male=31, female=4. Non-hydrophilic catheter use=15: Mean age: 45.46 yr (range 22-62 yr); Gender: male=13, female=2. Intervention: Evaluation of individuals using either hydrophilic or non-hydrophilic catheters for intermittent catheterization (IC). Outcome measures: Inflammatory response; bleeding episodes, urinary tract infection (UTI) activations, satisfaction level.	1. Compared to those using non-hydrophilic catheters, those using hydrophilic catheters presented with a significantly lower number of inflammatory episodes at scrotal level ($p=0.0001$), a significantly lower number of post/intra/inter catheterization bleeding episodes ($p=0.0001$), and expressed a significantly higher satisfaction level ($p<0.0001$).
Waller et al. 1995 Sweden Case Series N=30	Population: SCI: Median age: 37 yr (range 24-61 yr); median clean intermittent catheterization use: 7 yr (range 5-9 yr); Gender: male=26, female=4. Intervention: Retrospective chart review of individuals using disposable hydrophilic low friction catheters for intermittent catheterization (IC). Outcome Measures: Urodynamic parameters	1. No hydronephrosis, pyelonephritis or renal scarring in any of the individuals. 2. Among 3 individuals who had decreased their IC regimen, signs of upper tract dilation developed but the excretory urogram returned to normal after correction of the regimen. 3. Of 30 individuals, 12 (40%) maintained sterile urine; 4 of the remaining 18 with bacteriuria had episodes of urinary sepsis and chronic infections. 4. Two individuals had epididymitis. 5. In one individual, two dilation attempts had failed, but the individual could perform IC regimen. 6. One individual with Crohn's disease had advanced urethral changes in the acute phase but could perform IC with a small catheter. 7. One individual has had recurrent modifications of the urethral wall but no development of a false passage.

Discussion

The traditional catheter used for IC has long been the polyvinyl catheter (PVC) in varying lengths and gauges individualized for each individual. However, recent advances in catheter material, lubricant, and length have led to the development of several new catheter types. Hydrophilic catheters are made of a water-adherent polymer that, when lubricated with water, creates an extremely slippery surface effective for smooth insertion. Frictionless insertion reduces incidence of UTIs, bleeding, and other urinary complications. Other methods to reduce friction include gel-lubricated or pre-coated non-hydrophilic catheters. In total, there have been ten RCTs, and several small non-RCTs, investigating varying types and properties of catheters used for IC.

Several studies and one systematic review (Bermingham et al. 2013) have aimed to determine whether there is a superior catheter type for IC. In a small RCT, Sarica et al. (2010) found that gel-lubricated non-hydrophilic catheters were superior to hydrophilic and PVC catheters in terms of reduced urethral microtrauma and pyuria, and increased individual satisfaction, despite higher cost. However, there was no significant difference rate of UTIs between groups. Giannantoni et al. (2001) also examined pre-lubricated non-hydrophilic catheters versus conventional PVC catheters and demonstrated a reduction in the incidence of UTIs and the presence of asymptomatic bacteriuria. Of note, there were three subjects initially requiring assistance with a conventional catheter transitioning to independence with a pre-lubricated catheter. However, the order of catheter use by type was not reported. In terms of general satisfaction, subjects rated the pre-lubricated catheter significantly higher than the conventional catheter with respect to comfort, ease of insertion, extraction, and handling. De Ridder et al. (2005) compared hydrophilic catheters to non-coated PVC catheters and found reduced incidence of UTIs in favour of the hydrophilic catheter. Although this multi-centre investigation employed a RCT design (N=123), results should be cautiously interpreted given a 54% drop-out rate.

An additional investigation examined the effect of osmolality on two different hydrophilic catheters. Waller et al. (1997) demonstrated reduced friction with the high-osmolality catheter versus the other, a finding corroborated by nursing reports of fewer catheter “stickings”. These differences did not translate into clinically significant results for differences in the incidence of UTIs with either hydrophilic catheter type.

To reduce risk of infection, a new “no touch” ValPro® catheter has been developed and being trialled for use. Denys et al. (2012) performed a crossover RCT whereby individuals trialled the ValPro® catheter and a standard catheter. The authors reported that the majority of individuals were confident and secure with catheter (>75%) and would recommend it (>50%). It is important to note that bacteremia analyses were not conducted.

To improve QoL and user satisfaction, discrete compact size catheters continue to be developed. Chartier-Kastler et al. (2011) examined the effectiveness of compact catheters compared to standard catheters in a small crossover RCT. The authors reported that individuals were more satisfied with the compact versus standard

catheters as the former were more discrete when carrying and disposing; further, the standard catheter had greater resistance on insertion. The findings were echoed in a recent, large crossover RCT by Chartier-Kasler et al. (2013) and a small crossover RCT by Biering-Sorensen et al. (2007) where greater satisfaction was reported with use of the compact versus standard catheters.

While catheter length generally reflects the anatomy of the user, some compact catheters are shorter in length (30 cm) than standard catheters (40 cm). A comparison of the two catheters in terms of residual IC urine volume has demonstrated no significant difference in two crossover RCTs (Domurath et al. 2011; Biering-Sorensen et al. 2007). While a third crossover RCT by Costa et al. (2013) found that subjects reported greater satisfaction with standard catheters versus compact catheters for bladder emptying, only descriptive statistics were reported.

A study by Kovindha et al. (2004), provides data on reusable silicone catheters (average of 3 years of usage). The frequency of UTIs reported for the reusable catheter was comparable to that reported for standard disposable catheters (3-7 days of usage), but inferior to frequencies reported for pre-lubricated catheters. Kovindha et al. (2004) stated that the long-term silicone catheter is an economical option for those in developing countries. In developing countries, the high cost of the single use, pre-lubricated catheters is prohibitive outside of exceptional situations.

It should be noted that some assistive devices that may enhance compliance with intermittent catheterization for those with impaired hand function do exist but are likely not in widespread use. For example, Adler and Kirshblum (2003) reported a series of 9 individuals with C5-C7 SCI, originally unable to perform intermittent catheterization, that were subsequently satisfied and successful with a device to help performance of intermittent catheterization.

Conclusion

There is level 1b evidence (from one RCT; Giannantoni et al. 2001) that, compared to conventional poly vinyl chloride catheters, pre-lubricated non-hydrophilic catheters are associated with fewer UTIs and reduced urethral bleeding.

There is level 2 evidence (from one RCT; De Ridder et al. 2005) that, compared to conventional poly vinyl catheters, hydrophilic catheters may be associated with fewer UTIs, but not necessarily urethral bleeding.

There is level 2 evidence (from one RCT; Sarica et al. 2010) that, compared to hydrophilic or conventional poly vinyl catheters, pre-lubricated non-hydrophilic catheters are associated with reduced pyuria and greater individual satisfaction.

There is level 1b evidence (from two RCTs; Giannantoni et al. 2001; Sarica et al. 2010) that, compared to hydrophilic or conventional poly vinyl catheters, pre-lubricated non-hydrophilic catheters are associated with reduced urethral microtrauma.

There is level 1b evidence (from one crossover RCT; Denys et al. 2012) that compared to standard catheters, no-touch catheters may promote greater confidence and security to individuals performing intermittent catheterization post SCI.

There is level 1a evidence (from three crossover RCTs; Chartier-Kastler et al. 2011, 2013; Biering-Sorensen et al. 2007) that, compared to standard catheters, compact catheters may be more discrete for carrying and disposing and therefore provide greater satisfaction to individuals performing intermittent catheterizations post SCI.

There is level 1b evidence (from two cross-over RCTs; Domurath et al. 2011; Biering-Sorensen et al. 2007) that compact catheters (30 cm) and standard catheters (40 cm) provide comparable bladder performance with equitable residual urine volume.

Although both pre-lubricated and hydrophilic catheters have been associated with reduced incidence of UTIs as compared to conventional PVC catheters, less urethral microtrauma with their use may only be seen with pre-lubricated catheters.

Compact catheters are more discrete than standard catheters for carrying and disposal but offer comparable performance in bladder emptying and residual urine volumes.

4.4.3 Triggering-Type or Expression Voiding Methods of Bladder Management

Individuals with SCI undergoing individual rehabilitation are sometimes taught various maneuvers in order to initiate or attempt spontaneous voiding, termed “expression voiding” as well as to provide a “trigger” to initiate voiding (Wyndaele et al. 2001). Only one study examining these methods met the criteria for inclusion in the present review.

Table 14 Triggering-Type or Expression Voiding Methods

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
Elmelund et al. 2018 Denmark RCT PEDro=3 N _{Initial} =36 N _{Final} =26	Population: Pelvic floor muscle training (PFMT): Mean age=47yr; Gender: males=0, females=13; Etiology: SCI=11; Myelomeningocele=2. Time since injury=13yr; Inclusion criteria: Women with incomplete spinal cord injury and urinary incontinence.	1. Participants in the PFMT group showed significant decreases in OUP-squeezing, OUP-resting, and a significant increase in IE when comparing baseline to post-intervention (at 12 weeks) (p<0.05). There were no significant differences in participant-reported mean bladder capacity, max bladder

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
	<p>Pelvic floor muscle training combined with intravaginal electrical stimulation (PFMT+IVES): Mean age=59yr; Gender: males=0, females=13; Etiology: SCI=12; Myelomeningocele=1; Time since injury=10yr; Inclusion criteria: Women with incomplete spinal cord injury and urinary incontinence.</p> <p>Intervention: Participants in the PFMT groups were instructed to perform 30 near-maximal contractions of 5-10-s followed by 10 s of pause. Participants in the PFMT+IVES were to perform the same exercises but with the addition of vaginal electrical stimulation during the exercises using an electrical stimulation device. Two stimulation programs were used; intermittent stimulation (40 Hz, 250 microsecond pulse width applied for 7.5-10 min during exercises with 5-10 s of stimulation followed by 10-s breaks), and continuous stimulation (10 Hz, 250 microsecond pulse width applied for 10-20 min). Outcome measures were assessed at baseline, post-intervention (week 12), and follow-up (week 24). Both groups performed the intervention on a daily basis for 12 wk.</p> <p>Outcome Measures: Reflectometry: opening urethral pressure-squeezing (OUP-squeezing); OPU-resting; Self-reported outcomes: daily episodes of urinary incontinence (UI); mean bladder capacity; max bladder capacity; daily voiding episodes (VE).</p>	<p>capacity, and VE when comparing baseline to post-intervention ($p>0.05$).</p> <ol style="list-style-type: none"> Participants in the PFMT+IVES showed no significant differences for any of the variables indicated when comparing baseline to post-intervention ($p>0.05$). PFMT was only more effective for OUP-resting when comparing baseline to post-intervention ($p=0.018$). When comparing baseline to follow up (24 weeks), PFMT showed significant increases in UI and max bladder capacity ($p<0.05$). PFMT+IVES showed no significant differences in outcomes when comparing 24 wk follow-up to baseline ($p>0.05$). There was no significant difference in the effectiveness of both interventions for all outcomes when comparing baseline to the 24 wk follow-up ($p>0.05$).
Shendy et al. 2015 Egypt RCT PEDro=6 N=30	<p>Population: Transcutaneous electrical nerve stimulation (TENS group): Mean age=28.1 yr; Pelvic floor biofeedback (PFBFB group): Mean age=28.3 yr.</p> <p>Intervention: Individuals with precipitancy overactive bladder</p>	<ol style="list-style-type: none"> After treatment, bladder volume at first desire to void ($p=0.001$), maximum cystometric capacity ($p=0.001$), detrusor pressure at maximum flow rate ($p=0.002$), and maximum flow rate ($p=0.001$) significantly increased

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
	<p>and erectile dysfunction were randomized to 1) TENS, which involved two surface electrodes placed directly over the skin of S2 for 30 min at 50 Hz (n=15) or 2) PFBFB, which involved contraction of the pelvic floor muscles in the fowler lying position while watching the electromyography biofeedback activities (n=15). Both groups performed pelvic floor exercises, 90 contractions per day after training session.</p> <p>Outcome Measures: Bladder volume at first desire to void, maximum bladder capacity, maximum flow rate, detrusor pressure at maximum flow rate, right side amplitude per time (A/T), left side A/T, right side upper centile amplitude (UCA), left side UCA, International Index of Erectile Function Questionnaire (IIEF-5).</p>	<p>in TENS group but only the maximum flow rate ($p=0.042$) significantly increased in the PFBFB group. There were no significant differences between groups, except for the detrusor pressure at maximum flow rate being significantly higher in the TENS group both before ($p=0.008$) and after ($p=0.001$) treatment.</p> <ol style="list-style-type: none"> 2. Post-treatment, the TENS group had significantly higher right side A/T ($p=0.001$), left side A/T ($p=0.001$), right side UCA ($p=0.029$), left side UCE ($p=0.041$), and IIEF-5 ($p=0.013$) compared to PFBFB group. 3. In terms of right side A/T, left side A/T, right side UCA, left side UCA, and IIEF-5, the PFBFB group did not have any significant increases post-treatment while TENS had significant increases post-treatment ($p=0.001$).
<p>Xia et al. 2014 China RCT PEDro=6 N=42</p>	<p>Population: Neurogenic bladder; Treatment group: Mean age: 37.2 yr, Gender: males=13, females=8; Time post-injury: 2.4 mo; Control group: Mean age: 37.5 yr; Gender: males=14, females=7; Mean time post-injury: 2.6 mo.</p> <p>Intervention: Individuals were randomized to 1) Treatment group (n=21): Acupuncture treatment, consisting of 10 stimulations over 2 weeks or 2) Control group (n=21): Bladder training, including interval water drinking, timed voiding, and intermittent catheterization.</p> <p>Outcome Measures: Bladder capacity, residual urine volume, bladder pressure, rectal pressure, detrusor pressure, bladder compliance, International Prostate Symptom Score (IPSS), and efficacy rate.</p>	<ol style="list-style-type: none"> 1. Compared with control group, the treatment group had significantly increased bladder capacity and compliance, and significantly reduced residual urine volume, bladder pressure, rectal pressure, and detrusor pressure ($p<0.05$). 2. IPSS values for both groups were significantly lower post-treatment ($p<0.05$), with treatment group scores significantly lower than control group score ($p<0.05$). 3. The total efficacy rate in the treatment group was significantly higher than the control group ($p=0.043$).

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
Greenstein et al. 1992 USA Case Series N=5	<p>Population: SCI: Age: 29-58 yr; Gender: males=5, females=0; Level of injury: paraplegia, upper motor neuron bladder=3, lower motor neuron bladder=2; Severity of injury: complete=1, incomplete=4; Time post-injury=2.5-34 yr.</p> <p>Intervention: Voiding by Valsalva (n=4) or Crede maneuver (n=1)</p> <p>Outcome Measures: Urodynamics: bladder pressure at end of filling and during voiding, external sphincter activity, renal function/anatomy, and urinary tract infections (UTIs).</p>	<ol style="list-style-type: none"> 1. The Valsalva procedure enabled bladder emptying in 4 and the Crede procedure in 1 people. 2. Max. intravesical pressure during voiding ranged from 95–160cm H₂O 3. 2 of 5 people developed significant vesicoureteral reflux. 1 also had impaired renal function and hydronephrosis which resolved when switched to IC 4. 3 had symptomatic UTIs and 1 had an asymptomatic UTI.

Note: IC=Intermittent Catheters; UTI=Urinary Tract Infection

Discussion

Elmund et al. (2018) conducted an RCT to examine the effect of pelvic floor muscle training (PFMC) alone, compared to a combination therapy with intravaginal electrical stimulation (IVES) on urinary incontinence in women post-SCI. After the 24-week study period, the results showed no difference between groups on the International Consultation on Incontinence Questionnaire urinary incontinence short form (ICIQ-UI-SF) or episodes of urinary incontinence. The PFMT group had a significant change from baseline on the ICIQ-UI-SF and daily episode of urinary incontinence at 12-weeks but was not sustained over the complete study period.

Greenstein et al. (1992) documented the use of Valsalva (n=4) and Crede (n=1) maneuvers to initiate spontaneous voiding in a small case series of five males with paraplegia (upper motor neuron bladder=3, lower motor neuron bladder=2). Greenstein et al. (1992) note that “Valsalva is defined as increased abdominal pressure using the diaphragm and/or abdominal musculature. The Crede maneuver is suprapubic manual pressure applied over the bladder” (p. 254).

Bladder training with transcutaneous electrical nerve stimulation (TENS) compared to pelvic floor biofeedback (PFBFB) revealed significant improvements in bladder volume at first desire to void ($p=0.001$), maximum cystometric capacity ($p=0.001$), detrusor pressure at maximum flow rate ($p=0.02$), and maximum flow rate ($p=0.001$). Only maximum flow rate improved significantly ($p=0.042$) with PFBFB. (Shendy et al. 2015). Another option in bladder training involved electroacupuncture (EA) assisted behavioural training to initiate urination that resulted in increased bladder volume and compliance and decreased residual urine volume, bladder/rectal/detrusor pressures when compared to pre-treatment and controls (all measures $p<0.05$ for post-treatment and controls). Furthermore, the International Prostate Symptom

Score (IPSS) significantly improved in the EA group compared to the control group (behavioural training only) and over and above the significant improvement post behavioural training of the controls (p,0.05). (Xia et al. 2014)

Greenstein et al. (1992) intended to examine the potential for long-term complications in those who employed these techniques over an extended period of time. High intravesical pressure was documented during voiding. The authors suggested that long-term monitoring for these individuals is advisable and intermittent catheterization should replace these methods in the event of urological complications. Triggered voiding and use of the Crede maneuver to initiate “voiding” should only be considered in individuals with normal upper tracts, provided that urodynamic studies demonstrate low pressure storage and “voiding”, and that there is a low incidence of UTI.

Conclusion

There is level 1b evidence (from 1 RCT; Elmend et al. 2018) that pelvic floor muscle training (PFMT) combined with intravaginal electrical stimulation is no more effective than PFMT alone for urinary incontinence.

There is level 1b evidence (from 1 RCT; Shendy et al. 2015) supports the use of TENS biofeedback bladder training to improve bladder function.

There is level 1b evidence (from 1 RCT; Xia et al. 2014) is the basis for electroacupuncture assistive bladder training to improve bladder function.

There is level 4 evidence (from one case series study; Greenstein et al. 1992) that triggering mechanisms such as the Valsalva or Crede maneuvers may assist some individuals with neurogenic bladder in emptying their bladders without catheterization; however, high intra-vesical voiding pressures can occur which can lead to renal complications.

TENS biofeedback and electroacupuncture assisted bladder training improve bladder function.

Valsalva or Crede maneuver may assist some individuals to void spontaneously but produce high intra-vesical pressure, increasing the risk for long-term complications.

4.4.4 Indwelling Catheterization (Urethral or Suprapubic)

Urethral catheterization may be the bladder management method of choice for a variety of reasons including the following: ease of management, inadequate hand function for Intermediate catheterizations, severe spasticity, low bladder capacity with high detrusor pressures and/or persistent incontinence especially in women, and pressure ulcers (Yavuzer et al. 2000). Suprapubic catheterization, first described in SCI by Cook and Smith (1976), is the preferred choice for those individuals who require an indwelling catheter but have severe urethral disease. Weld and

Dmochowski (2000) presented data showing a lower overall complication rate from SPC use than from urethral catheter use (44.4% vs. 53% respectively). Since indwelling catheterization is sometimes unavoidable, becoming familiar with the various potential complications and appropriate monitoring is important for clinical and self-management of neurogenic bladder.

Based on a series of case review studies (most described earlier in Section 13.4.3.1) comparing various bladder management methods, long-term use of indwelling catheters is associated with generally higher rates of complications (Wyndaele et al. 1985; Gallien et al. 1998; Weld & Dmochowski, 2000) in contrast to other methods (especially intermediate catheterizations). For example, Ord et al. (2003) noted a significantly greater chance of having bladder stones with long-term SPC or urethral indwelling catheter use as indicated by hazard ratios of 10.5 and 12.8 relative to intermittent catheterization respectively. Indwelling catheterization has also been linked to significantly higher rates of bladder cancer development (Groah et al. 2002; Kaufman et al. 1977) and upper tract deterioration (Weld & Dmochowski 2000) as compared to those who use long-term intermittent catheterization.

Table 15 Indwelling Catheterization

Author Year Country Score Research Design Total Sample Size	Methods	Outcome
McGee et al. 2017 USA Pre-Post N=17	<p>Population: Mean age=49.71±14.29yr; Gender: males=13; female=4; Etiology: SCI=17; Time since injury=12.76±9.13yr.</p> <p>Intervention: A custom silicone 12-Fr Foley-stimulating catheter with stainless steel electrode contacts was inserted into individuals' urethra such that the balloon lay in the bladder neck to allow for the electrodes to target the proximal and distal urethra. Multiple electrodes were present along the length of the electrode to allow for stimulation to be customized to each individual. Battery-powered electrical stimulators delivered charge-balanced, asymmetric biphasic current pulses with a pulse width of 0.2 ms for a duration of 20 seconds. Blocks of 16 randomized combinations of single-site or 2-site co-stimulation (proximal and distal) were presented at different frequencies (2,10,20, and 40 Hz), as well as different amplitudes (2x threshold (T) and 4T) under isovolumetric conditions. Outcome</p>	<ol style="list-style-type: none"> 1. There was a significant effect of stimulation frequency on stimulation-evoked mean Pdet when stimulation was applied to both the proximal and distal urethra ($p<0.001$). 2. There were combinations of proximal and distal intraurethral stimulation that produced significantly different effects on mean Pdet (e.g. stimulating proximal region at 10 hz produced inhibitory effects, whereas stimulating the distal region at 10 Hz produced excitatory effects) ($p<0.001$). 3. Changing one of the frequencies during co-stimulation resulted in significant effects to mean Pdet ($p<0.05$). 4. Specific patterns of co-stimulation were more effective than others (e.g. 2 Hz proximal-2 Hz distal and 30 Hz proximal-40 Hz distal were more effective and 10Hz distal was least effective).

Author Year Country Score Research Design Total Sample Size	Methods	Outcome
	<p>measures were assessed at baseline and during stimulation.</p> <p>Outcome Measures: mean detrusor pressures (Pdet); pelvic floor electromyographic activity (EMG).</p>	<p>5. There was a significant difference in normalized EMG activity between periods with stimulation on compared to periods with stimulation off</p> <p>6. A significant interaction between normalized EMG, stimulation frequency, and stimulation-on periods indicated that changes in rectified and integrated EMG activity were dependent upon stimulation frequency ($p<0.01$).</p>
<p>Locke et al. 1985 USA Pre-Post N=25</p>	<p>Population: SCI individuals with indwelling catheters: Length of indwelling catheterization=17.6 yr.</p> <p>Intervention: SCI individuals with indwelling catheters were evaluated for presence of bladder malignancy.</p> <p>Outcome Measures: Urinalysis, urine culture, cytology, serum urea, creatinine, white cell count, hematocrit. Excretory urography results, cystoscopy results.</p>	<p>1. Cystoscopy results indicated suspicious lesions in 4 individuals and squamous cell carcinoma in 2.</p> <p>2. Excretory urography results indicated:</p> <ul style="list-style-type: none"> • Bladder calculi in 7 individuals. • Renal calculi in 5 individuals. • Normal in 9 individuals. • 1 individual had a surgically absent kidney. <p>3. Bacteriuria universally present.</p>
<p>El Masri et al. 2014 United Kingdom Case Series N=262</p>	<p>Population: Level of injury: cervical=168, thoracic-lumbar=94; Severity of injury: complete=153, incomplete=109; Injury etiology: traumatic spinal cord injury.</p> <p>Intervention: The positive findings from cystourethroscopic surveillance were reviewed for individuals using a suprapubic catheter or urethral catheter, comparing symptomatic vs. asymptomatic groups.</p> <p>Outcome Measures: Number of procedures, indications for cystourethroscopy.</p>	<p>1. Of the 262 included individuals, there were 419 cystoscopies performed.</p> <p>2. In the symptomatic group, 78 procedures had a suprapubic catheter and 67 had a urethral catheter. In the asymptomatic group, 186 procedures had a suprapubic catheter and 88 had a urethral catheter.</p> <p>3. In the symptomatic group using suprapubic catheters, the indications for cystourethroscopy were recurrent blockage (35%), urinary tract infection (UTI) (20%), previous history of metaplasia (19%), radiological finding of calculi (17%), and autonomic dysreflexia + UTI (9%). In the symptomatic group using urethral catheters, the indications for cystourethroscopy were UTI (35%), insertion of suprapubic catheter (31%), recurrent blockage (13%), radiological</p>

Author Year Country Score Research Design Total Sample Size	Methods	Outcome
		finding of calculi (9%), autonomic dysreflexia + UTI (9%), and previous history of metaplasia (3%).
Katsumi et al. 2010 USA Case Series N=179	<p>Population: SCI individuals: <i>Urethral Catheter (UC; n=133)</i>: Mean Age: 63.1 yr; Gender: males=132, females=47; Level of injury: C=60, T=63, L=5, MS=5; Time post-injury: 35.5 yr; <i>Suprapubic Catheter (SPC; n=46)</i>: Mean age: 59.9 yr; Gender: males=46, females=0; Level of injury: C=30, T=12, L=3, MS=1; Time post-injury: 31.2 yr.</p> <p>Intervention: Retrospective chart review of individuals using either UC or SPC.</p> <p>Outcome Measures: Urinary tract infection (UTI), presence of bladder stones, renal calculi, urethral complications, scrotal abscesses, epididymitis, gross hematuria and cancer.</p>	<ol style="list-style-type: none"> 1. There was no significant difference in frequency of UTIs or other bladder complications among individuals using various catheter types. 2. There were catheter specific complications specific to each group that could not be compared. These complications included erosion in the UC group and urethral leakage from the SPC group. 3. Average serum creatinine for the UC and SPC groups respectively was 0.74 mg and 0.67 mg per 100 mL.
Sugimura et al. 2008 New Zealand Case Series N=149	<p>Population: Gender: males=124, females=25; Level of injury: paraplegia=68, tetraplegia=96.</p> <p>Intervention: SCI individuals managed with SPC were retrospectively reviewed for complications.</p> <p>Outcome Measures: UTIs and other complications assessed over a mean follow-up period of 68 mo (range=3-179 mo).</p>	<ol style="list-style-type: none"> 1. 73 individuals experienced no complications 2. 43 experienced UTIs. 3. The most common lower tract complication was bladder stones (33 individuals). 4. Renal complication was seen in 20 out of 149 individuals. 5. Only 9 individuals experienced renal scarring. 6. 11 individuals experienced urethral incontinence
MacDiarmid et al. 1995 USA Case Series N=44	<p>Population: Traumatic SCI with indwelling suprapubic catheter for >1 yr: Mean age: 36 yr; Gender: males=31, females=13; Level of injury: paraplegia, tetraplegia; Follow-up time=69 mo; Duration of catheterization=58 mo.</p> <p>Intervention: Assessment of urological/renal complication rate associated with suprapubic cystostomy drainage. (35 individuals had videourodynamic studies)</p> <p>Outcome Measures: Incidence of urological and renal complications.</p>	<ol style="list-style-type: none"> 1. Percentages reported for various complications: 0% renal deterioration, 0% vesicoureteral reflux, 0% clinical bladder carcinoma, 11% incontinence, 100% asymptomatic bacteriuria, UTIs: 43% uncomplicated and 9% complicated, 5% hematuria, 7% renal calculi, 41% bladder calculi, 36% blocked cystostomy tubes; 3 individuals developed abscesses.
Peatfield et al. 1983 England Case Series N=41	<p>Population: SCI: Level of injury: paraplegia=15, tetraplegia=25.</p> <p>Intervention: Long-term follow-up (>8 yr) of those managed originally</p>	<ol style="list-style-type: none"> 1. 15/41 had died, 2 due to renal causes; 10 yr survival rate 68%, 15 yr 63%.

Author Year Country Score Research Design Total Sample Size	Methods	Outcome
	by suprapubic catheter as reported in 1976. Outcome Measures: Mortality, renal function.	2. 22 of 23 surviving, evaluable individuals had normal blood urea levels. 3. IVP Results: 15 Normal, 3 bilateral pelvic/ureter dilation, 2 kidney stones, 3 non-functioning kidneys.
Hackler 1982 USA Case Series N=31	Population: SCI: Level of injury: all above T11; Time since injury=>5 yr. Intervention: Assessment of urological/renal complication rate associated with suprapubic cystostomy drainage of ≥5 yr versus condom or Foley catheter drainage. Outcome Measures: Intravenous urography (IVU) and cystourethrogram (CUG) evaluated at ≥5 yr post-injury.	1. Renal complication rate is greater after 8 yr of suprapubic cystostomy (SPC) than for those with 20 yr use of condom or to a lesser extent Foley catheter drainage. 2. Percentages reported for various complications: Normal - 39% with suprapubic versus 51% Foley and 66% condom; Caliectasis (calculi) - 50% with SPC versus 24% Foley and 23% condom; Hydronephrosis - 10% with SPC versus 19% Foley and 10% condom. 3. 6 individuals were on anticholinergic medications. 4/6 maintained normal urinary tracts.
Kaufman et al. 1977 USA Case Series N=62	Population: SCI; 4 groups: Group 1 (n=25): permanent bladder catheters >10 yr, Group 2 (n=24): permanent catheters <10 yr, Group 3 (n=11): short-term (post injury only) catheter drainage, Group 4 (n=2): bladder diversions. Intervention: Urinalysis and urine cultures, Cystoscopy and bladder biopsies on all individuals. Urethral biopsies in 29 individuals Outcome Measures: Incidence of squamous metaplasia of bladder or urethra, and bladder cancer.	1. Mean time with indwelling catheter: group 1=18.8 yr, group 2=3.9 yr, group 3=<1 yr, group 4=2 yr and 24 yr. 2. Few individuals had suprapubic catheters 3. Squamous cell carcinoma found in 6 individuals, but 5 individuals were in group 1 and had had catheters in place for mean of 21 yr. 4. Only 1 individual had tumor visible endoscopically 5. Squamous metaplasia present in 20 individuals in group 1, 10 in group 2, 2 in group 3, and 1 of 2 individuals in group 4 (24 yr use of indwelling catheter) 6. Cytology was negative in all individuals (with and without cancer) 7. Presence of cystitis, urinary tract infection, renal impairment, pain, did not correlate with cancer incidence.

Author Year Country Score Research Design Total Sample Size	Methods	Outcome
		8. Gross and microscopic hematuria did correlate with bladder cancer.

Summarized Level 5 Evidence Studies:

Sheriff 1998 Primary indications for insertion included failed intermittent catheterization (IC) due to poor hand function, persistent incontinence, recurrent urinary tract infections (UTIs) or bulbar strictures. In individuals using suprapubic catheter for >2 yr - no apparent decline in renal function.

10% complication rate, including 2.7% incidence of small bowel injury. Overall complaint rate was reported at 30%. Most common was recurrent catheter block in 28 individuals, persistent urinary leakage in 13 and a recurrent symptomatic UTI in 6. 75 individuals had bladder calculi requiring intervention. Bladder capacity remained stable, detrusor pressure significantly decreased, and previously trabeculated bladder became smooth. Satisfaction survey indicated that for a variety of questions (e.g. impact on life, pleasure with the switch, would you do it again, etc.) 70-90% of those responding answered favourably.

Discussion

McGee et al. (2017) measured the urodynamic effects of electrical co-stimulation of two sites in the urethra in individuals post-SCI. The study authors found that pudendal nerve afferents are a promising target to restore lost bladder control, as stimulation with different frequencies may be used to treat urinary incontinence and increase continent volumes or to generate stimulation-evoked bladder contractions for on-demand voiding. Co-stimulation of multiple afferent reflex pathways was found to enhance activation of spinal circuits and improve bladder emptying in SCI when stimulation of a single pathway is not sufficient. Electromyographic activity indicated that multiple reflex pathways were recruited through stimulation that contributed to bladder activation. The size of reflex bladder contractions evoked by stimulation was dependent on stimulation location or reflex activated and stimulation frequency.

Although intermittent catheterization is the first choice for neurogenic bladder management, some individuals with subacute SCI are managed with indwelling catheters due to prolonged high urine output states, frequent medical illnesses or surgical complications, or severe incontinence. Suprapubic catheterization is occasionally considered during this early period if urethral damage has occurred as a result of prolonged urethral catheter use. Later, in chronic situations, SPC may also be favored by individuals with SCI who are obese, or have severe lower extremity spasticity, inadequate hand function, persistent incontinence, urethral stricture or erosion, or because of perceived increased ability to engage in sexual relations (Weld & Dmochowski, 2000; Peatfield et al. 1983). Prostatitis and orchiepidymitis occur less

frequently in those with SPC but upper tract deterioration remains a concern (Gallien et al. 1998; Weld & Dmochowski 2000; Sugimura et al. 2008).

Hackler (1982) has suggested that upper tract deterioration may be reduced with concomitant use of anticholinergic medication. MacDiarmid et al. (1995) hypothesized that clinical factors may also reduce the complication rate. They attributed the low incidence of complications during the year-long data collection period to strict adherence to a catheter protocol with regular follow-up and close surveillance utilizing a dedicated medical and nursing team and informed primary care practitioners. Sugimura et al. (2008) also noted that upper tract complication rates resulting from SPC may be lower than earlier studies suggested and reported a 13.4% renal complication rate associated with a mean follow-up period of 68 months. Furthermore, Sherriff et al. (1998) conducted a satisfaction survey regarding SPC use which indicated 70-90% satisfaction based on questions such as impact on life, pleasure with the switch, and “would you do it again”, etc.

Several of the studies described above on SPC contain a relatively short follow-up period (<10 years). The specific concerns regarding indwelling catheter use centre on the potential for urological complications with long-term use. Many individuals are injured as young adults and may live for greater than 50 years and therefore the target for safety monitoring regarding bladder management choice should emulate SCI life expectancy. According to the prospective study by Kaufman et al. (1977), the risk of bladder cancer with indwelling urethral catheters increase significantly with duration of use. Interestingly, his data suggest that routine screening with bladder biopsy may be indicated in addition to cystoscopy for those at highest risk of bladder cancer. Research since this time suggests, however, that there is no good evidence for screening cystoscopy in this population; the requirements of a test to be a good screening tool have not met (Yang et al. 1999). Kaufman et al. (1977) did not include a significant number of SPC users, but Groah et al. (2002) did include both types of indwelling catheter users, and clearly showed a higher incidence of bladder cancer in such individuals compared to those not managing their bladders with indwelling catheters. El Masri et al. (2014) also noted that 10% of the asymptomatic SPC and IUC users showed squamous metaplastic changes. Stone disease, upper tract deterioration, reflux, and chronic infection remain additional long-term concerns in those who resort to indwelling catheter use, with a slightly lower overall incidence reported in those with suprapubic versus urethral catheters (Weld & Dmochowski 2000).

A recent study by Katsumi et al. (2010) has shown that regardless of indwelling catheterization method, there were no significant differences in frequency of UTIs or other comparable bladder complications. While each method was correlated with unique complications, one type of catheterization was not superior over the other (Katsumi et al. 2010). Although El Masri et al. (2014) agrees that both types of indwelling catheters result in similar complications, recurrent catheter blockage was predominant in those using SPC and symptomatic UTIs for indwelling urethral catheters (IUC). Of note, Tasoglu et al. (2015) described 3 cases of indwelling Foley catheter related iatrogenic hypospadias resulting from decreased self-care and attention in individuals with psychiatric co-morbidities. In these cases, CIC would be

the preferred form of bladder management in order to avoid this unfortunate complication.

Conclusion

There is level 4 evidence (from one pre-post study; McGee et al. 2017) that co-stimulation of multiple afferent reflex pathways was found to enhance activation of spinal circuits and improve bladder emptying in SCI when stimulation of a single pathway is not sufficient.

There is level 4 evidence (from four cases series studies, one observational study, and one pre-post study) that despite an associated significant incidence of urological and renal complications, acute and chronic indwelling catheterization may be a reasonable choice for bladder management for people with poor hand function, lack of caregiver assistance, severe lower limb spasticity, urethral disease, and persistent incontinence with intermittent catheterization.

There is level 4 evidence (from one cohort and one case series study; Groah et al. 2002; El Masri et al. 2014) that those with indwelling catheters are at higher risk for bladder cancer compared to those with non-indwelling catheter management programs.

There is level 4 evidence (from 1 case series; El Masri et al. 2014) that recurrent catheter blockage is associated predominantly with SPC use and symptomatic UTIs with IUC use.

With diligent care and ongoing medical follow-up, indwelling urethral and suprapubic catheterization may be an effective and satisfactory bladder management choice for some people, though there is insufficient evidence to report lifelong safety of such a regime.

Compared to non-indwelling methods, indwelling catheter users are at higher risk of bladder cancer, especially in the second decade of use, though risk also increases during the first decade of use.

4.4.5 Condom Catheterization

A viable option for bladder management in males is condom catheterization. As noted above, condom catheterization is associated with relatively fewer complications than indwelling methods but more complications than intermittent catheterization (Ord et al. 2003; Hackler 1982). However, complications may still arise, as described by Newman and Price (1985). Of greatest concern is incomplete drainage, which may lead to persistently high bladder pressures, recurrent UTI and the likelihood of renal complications including glomerular filtration rate deterioration described below. Sometimes this situation necessitates adjuvant daily or twice daily catheterization, medications, or sphincterotomy. Medications to

improve drainage, such as alpha blockers can improve emptying by reducing outlet resistance, and sometimes by reducing pressures. Newman and Price (1985) raise practical issues such as cleanliness and proper use of appliances. Application difficulties with condom catheterization are likely problematic in the event of impaired hand function. Slippage of the condom can result in leaks. Perakash et al. (1992) describe the use of penile implants, in part to circumvent this issue with condom application.

Table 16 Condom Catheterization

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
Newman & Price 1985 USA Pre-Post N=60	<p>Population: SCI individuals with external catheters: Gender: males=60; Level of injury: paraplegia=25, tetraplegia=35; Severity of injury: complete=47, incomplete=13. 17 had sphincterotomies, either before or after switching to condom drainage</p> <p>Intervention: Individuals went through a renal function evaluation which included: roentgenographic studies, and glomerular filtration rates. Urine cultures, antibody coated bacteria determinations were done. Individuals were interviewed about their bladder emptying habits. Mean time external catheter was used was 48 mo.</p> <p>Outcome Measures: Urine infections, (a positive culture was defined as any organisms growing), mean time of external catheter use, renal and bladder abnormalities, glomerular filtration rate.</p>	<ol style="list-style-type: none"> 32 individuals had positive urine cultures. Tetraplegic individuals were more likely to have positive cultures than paraplegics (61% versus 44%). Complete lesions individuals were more likely than incomplete lesions individuals to have positive urine cultures (60% versus 31%). 27 of 34 individuals that were previously free of morphologic abnormalities developed changes including positive urine cultures, reflux (4), bladder diverticula (14) and trabeculation (26), urethral dilatation. 5 of 26 individuals who initially had morphologic defects became free of abnormalities. No change in glomerular filtration rate was seen in 46 individuals, while 2 improved and 12 deteriorated.
Perakash et al. 1992 USA Case Series N=79	<p>Population: SCI: Mean age: 41.9 yr; Level of injury: paraplegia=37, tetraplegia=38; cauda equina=4; Severity of injury: complete=61, incomplete=18; Mean time post-injury=8.24 yr.</p> <p>Intervention: Follow-up of individuals implanted with a penile implant allowing improved condom placement or sexual penetration.</p> <p>Outcome Measures: Failures, complications, Quality of Life Satisfaction survey.</p>	<ol style="list-style-type: none"> Penile implants in place for a mean of 7.08 yr. Overall failure rate was 8% with an infection complication rate of <2%. Prior to implant, 61 people lost condoms and had accidents with urine leakage >2/week, while only 15 reported condom loss 1-2/week after the implant. Prior to implant, 14 people had indwelling catheters, while none had indwelling catheters after.

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
		5. 54 individuals expressed satisfaction with sexual intercourse. 7. All felt it was easier to keep themselves clean and dry.

Discussion

Bladder management through condom drainage is often chosen to overcome persistent incontinence that may occur with other methods of bladder management. However, periodic monitoring for bladder “residuals” and complete emptying may be necessary, as emphasized by Newman and Price (1985) following a review of 60 SCI individuals with external catheters. Elevated residuals should raise the suspicion of possible excessive bladder pressure resulting from incomplete emptying from a spastic sphincter or areflexic bladder. This is a situation that can easily be assessed by urodynamic studies. Though Newman and Price (1985) indicated a high prevalence of bladder trabeculation, and implied that this occurred secondary to high pressure, no corroborating urodynamic data was provided. Sphincterotomy is a surgical procedure that eliminates outlet resistance and one that almost 30% of the study group in Newman and Price (1985) had undergone. Another problem commonly described with condom drainage is infection. It is difficult to make conclusions in this area based on the rather generalized description of a positive culture (“any organism growing”) as presented by Newman and Price (1985).

Some individuals prefer condom drainage for convenience, as there is usually no need or reduced need to catheterize, compared to regimes that involve sole use of clean IC. However, this convenience can be offset by accidental leaks, and skin problems at the site of condom attachment. Perikash et al. (1992) conducted a retrospective analysis of 79 male individuals with penile implants in place over a mean time of 7.1 years. A primary reason for obtaining a penile implant in these individuals, among others, was to provide a stable penile shaft to hold a condom for external urinary drainage. In addition, penile implantation allowed some to switch to a more effective and safer bladder management method (i.e. 18% no longer required an indwelling catheter). All individuals reported improved continence as reflected in the general observation that it was easier to keep themselves clean and dry.

Conclusions

There is level 4 evidence (from one Newman & Price 1985) that condom drainage may be associated with urinary tract infection and upper tract deterioration.

There is level 4 evidence (from one case series; Perikash et al. 1992) that penile implants may allow easier use of condom catheters, thereby reducing incontinence and improving sexual function.

Individuals using condom drainage should be monitored for complete emptying and for low pressure drainage to reduce UTI and upper tract deterioration; sphincterotomy may eventually be required.

Penile implants may allow easier use of condom catheters and reduce incontinence.

4.4.6 Continent Catheterizable Stoma and Incontinent Urinary Diversion

People with tetraplegia, especially females, often have difficulty performing clean intermittent catheterization. In addition, females are more troubled by persistent incontinence. The surgical methods described in this section can result in the ability to self-catheterize, allowing the individual to benefit from intermittent rather than indwelling bladder catheterization, the latter being associated with a higher rate of complications. The mitrofanoff channel involves the use of an autologous tubular structure, usually the appendix, as a cutaneous catheterizable stoma. Implantation in the bladder via a submucosal tunnel provides continence to the conduit (Zommick et al. 2003; Sylora et al. 1997). The stoma can be hidden in the umbilicus. While performed often in children, the procedure has less commonly been performed in adults. Long term followup is reportedly good up to 60 months (Zommick et al. 2003 [n=7]; Hakenberg et al, 2001 [n=4]), but has not been reported with respect to the potential for malignancies. Karsenty et al. (2008) describes a similar procedure, performed in 13 individuals with incontinence and inability to self-catheterize.

Ileal conduit diversion, another surgical approach more commonly performed in females, is also often considered for reasons of lack of manual dexterity or ease of care and convenience (Pazooki et al. 2006; Chartier-Kastler et al. 2002). This technique aims to establish low-pressure urinary drainage by diverting urine prior to entering the bladder and connecting the ureters to an external urinary collection system via a catheter passed through the ileal lumen. This procedure is sometimes conducted along with removal of the bladder as well (Chartier-Kastler et al. 2002; Kato et al. 2002). Peterson et al. (2012) observed that during the period from 1998 to 2005 in the USA, urinary diversion was used more frequently by older individuals (>41 years, reliant on Medicare) than bladder augmentation as the treatment choice. But due to missing data (e.g., level of injury, failed previous bladder augmentation, renal function status, etc.), the reasons behind treatment choices are not completely understood.

Table 17 Continent Catheterizable Stoma and Incontinent Urinary Diversion

Author Year Country Score Research Design Total Sample Size	Methods	Outcome
Continent Catheterizable Stoma		

Author Year Country Score Research Design Total Sample Size	Methods	Outcome
Karsenty et al. 2008 France Pre-Post N=13	<p>Population: Mean age: 42 yr; Gender: males=2, females=11; Level of injury: cervical=5, thoracic=5, sacral=1. cauda equina=1 other=1; All were unable to self catheterize. Mean time post-injury=12.2 yr; Mean follow-up=44 mo.</p> <p>Intervention: Individuals underwent a novel procedure involving a cutaneous continent diversion composed of an abdominal continent stoma combined with enterocystoplasty which was used to facilitate self-catheterization.</p> <p>Outcome Measures: Complications, continence, catheterization difficulties, functional bladder capacity and serum creatinine.</p>	<ol style="list-style-type: none"> 1. Complications included postoperative infections (5 urinary, 2 pulmonary) and 1 pelvic abscess and 1 small bowel occlusion both requiring surgery 2. In all individuals, the catheterizable stoma was continent, but 3 females had stress leakage through native urethra, 2 requiring secondary bladder neck closure. 3. All individuals could self catheterize. 4. An increase from 180ml to 540ml was seen in functional bladder capacity from pre to post surgery. 5. No change in serum creatinine was seen post surgery.
Sylora et al. 1997 USA Pre-Post N=7	<p>Population: Age Range 19 to 44 yr; Gender: males=4, females=3; Level of injury: tetraplegia=7. All individuals had adequate bladder capacity and were on anticholinergics</p> <p>Intervention: Individuals underwent Mitrofanoff umbilical appendicovesicostomy with appendix or ileum. F/U 5–20 mo.</p> <p>Outcome Measures: Bladder capacity, continence, complications.</p>	<ol style="list-style-type: none"> 1. No significant changes were seen in bladder capacity. 2. All individuals were continent. 3. Complications included transient stress urinary incontinence which resolved spontaneously (n=1) and stomal revision (n=1).
Hakenberg et al. 2001 Germany Case Series N=5	<p>Population: Mean age: 31 yr; Gender: males=1, females=4; Level of injury: tetraplegia=5; Mean time post-injury=22 mo. F/U 21–40 mo. All individuals on anticholinergics both pre and post surgery.</p> <p>Intervention: Individuals underwent appendicovesicostomy and a cutaneous stoma was placed in the lower right abdominal quadrant.</p> <p>Outcome Measures: Independent clean intermittent catheterization (IC), stomal stenosis, urinary tract infections, satisfaction.</p>	<ol style="list-style-type: none"> 1. All individuals were able to independently perform clean IC and were continent. 2. Stomal stenosis did not occur. 3. 2 individuals experienced urinary tract infections once, and 1 individual had repeated occurrences. 4. 3 out of 5 individuals were highly satisfied with the results. 5. Post-op bladder compliance 20–44 mm H₂O.
Incontinent Urinary Diversion		
Perrouin-Verbe et al. 2016 France Pre-Post	<p>Population: Median age: 35 yr; Gender: males=7, females=22; Level of injury: cervical=17, thoracic=10,</p>	<ol style="list-style-type: none"> 1. During the first mo post-surgery, there were three minor complications, two major complications and no deaths.

Author Year Country Score Research Design Total Sample Size	Methods	Outcome
N=29	<p>lumbar=2; Median time post-injury: 9 yr.</p> <p>Intervention: Individuals unable to perform intermittent self-catheterization through the native urethra received continent cutaneous urinary diversion with a concomitant supratrigonal and augmentation enterocystoplasty.</p> <p>Outcome Measures: Postoperative complications, duration of hospitalization, long-term complications, urethral continence, antimuscarinics, onabotulinum toxin A, detrusor overactivity, low bladder compliance, maximal cystometric capacity, maximal detrusor pressure, creatinine clearance, upper urinary tract dilation, quality of life.</p>	<ol style="list-style-type: none"> The overall complication rate was 44.8% and the total reoperation rate was 24.1%. Compared to before surgery, the number of participants with urethral incontinence ($p=0.013$), using antimuscarinics, using onabotulinum toxin A, with detrusor overactivity ($p=0.0006$), with low bladder compliance ($p=0.05$), and upper urinary tract dilation significantly decreased. There was a significant increase for the median maximal cystometric capacity ($p=0.021$), a significant decrease for maximal detrusor pressure ($p=0.05$), and no significant difference in creatinine clearance. Urethral continence was achieved in 96% of participants and quality of life was improved in 90%.
Craven & Etchells 1998 Australia Pre-Post N=27	<p>Population: SCI individuals with ileostomy, colostomy, or urostomy.</p> <p>Intervention: No intervention – chart review</p> <p>Outcome Measures: Questionnaire for physical, psychological, quality of life (QoL) and lifestyle effects after surgery.</p>	<ol style="list-style-type: none"> 11 individuals underwent urostomy (Indications: chronic UTI in all, 1 recurrent calculi, 3 hydronephrosis) Three individuals required cyctectomy, while a fourth was advised to get one Although 27 charts reviewed only 18 individuals located to complete the questionnaire: <ul style="list-style-type: none"> Bowel and bladder management greatly improved in most cases, resulting in improved QoL for these individuals. Positive psychological effects. Long-term impact on renal health not assessed.
Peterson et al. 2012 USA Case Series N=3051	<p>Population: Ileal loop urinary diversion=1919, Bladder augmentation=1132; Mean age: 40 yr.</p> <p>Intervention: Review of individuals' information undergoing either ileal loop urinary diversion or bladder augmentation.</p> <p>Outcome Measures: Sociodemographic characteristics and care settings.</p>	<ol style="list-style-type: none"> Individuals who had ileal loop diversions were older than those who received bladder augmentation (mean age of 46 versus 34 yr $p<0.001$). Ileal loop diversion individuals were most likely to have Medicare as the primary payer, whereas private insurance was used most among bladder augmentation ($p<0.001$).

Author Year Country Score Research Design Total Sample Size	Methods	Outcome
		<ol style="list-style-type: none"> Individuals were more likely to get bladder augmentation at teaching institutions than those at non-teaching institutions (42% versus 23%; $p<0.001$). Ileal loop diversions required longer LOS and used more healthcare resources than bladder augmentation. More likely to be discharged to home healthcare (37.0% versus 23.6%; $p<0.001$).
Colli & Lloyd 2011 USA Case Series N=35	<p>Population: Mean age: 44.7yr (range=25-78yr); Gender: male=11, female=24; mean LOS=4.1 d; Etiology of injury: SCI=77, MS=5, Cerebrovascular accident=3; Abdominal BNC=31; Transvaginal bladder neck closure=4; Mean follow up=27 mo</p> <p>Intervention: Bladder neck closure (BNC)</p> <p>Outcome Measures: Renal functions measure, complication rate.</p>	<ol style="list-style-type: none"> Indications for BNC included: severe urethral erosion (80%), decutis ulcer (40%), urethrocutaneous fistula (11%), and severe incontinence (9%). Most individuals reported multiple indications for surgery. Overall, the complications rate was 16.7%.
Zommick et al. 2003 USA Case Series N=21	<p>Population: Age Range 17-51 yr; Gender: males=12, females=9; Level of injury=Cervical Spine.</p> <p>Intervention: Review of charts, and individuals contacted by independent reviewer to determine satisfaction and quality of life (QoL) after lower urinary tract reconstruction.</p> <p>Outcome Measures: Visual Analogue Scale measuring satisfaction, nonvalidated QoL questionnaires.</p>	<ol style="list-style-type: none"> 68% reported improved QoL after bladder reconstruction. Satisfaction was high in most individuals (8 ≥ out of 10), with lower ratings relating to complications that arose.
Chartier-Kastler et al. 2002 France Case Series N=33	<p>Population: MS (N=4), CP (N=3), Myelitis (N=3), Other (N=2), SCI (N=21); Mean Age=40.6 years; Gender: males=14, females=19; Level of injury: cervical=32, thoracic=25, C1-T10=14, T11-L1=6, below L2=1; Severity of injury: complete, incomplete; Mean follow-up=48 months.</p> <p>Intervention: Follow-up evaluation of those having cutaneous ileal conduit (ileo-ureterostomy) diversion.</p> <p>Outcome Measures: IVU, serum creatinine, cystoscopy, urine</p>	<ol style="list-style-type: none"> No statistical comparisons reported Initial surgery was successful. All individuals became continent after initially being incontinent prior to surgery. Of 17 with pre-op hydronephrosis, 10 showed a decrease or disappearance. 12 individuals developed one or more complications during follow-up. 4 early complications and 13 late complications. Most prevalent long-term complications were pyocystitis

Author Year Country Score Research Design Total Sample Size	Methods	Outcome
	cultures and pre/post incidence of UTIs, visual analog individual satisfaction. Collected at follow-up as indicated above.	(4-3 requiring cystectomy), pyelonephritis (4) and urethral leak (2). 6. Satisfaction survey indicated none regretted surgery (9.1±2.8 out of 10).
Kato et al. 2002 Japan Case Series N=16	Population: SCI: Mean Age=46years; Gender: males=13, females=3; Level of injury: tetraplegia; Mean follow-up time=8.7years. Intervention: Follow-up evaluation of those having ileal conduit formation. Outcome Measures: Review of charts (deaths, complications, subjective statements of satisfaction, serum creatinine where completed)	1. No statistical comparisons reported 2. Serum creatinine remained stable 3. 3 subjects died (constrictive ileus, unknown, septicemia associated with UTIs) during the follow-up period. 4. 5/16 individuals had calculus formation in the upper urinary tract; 3 had severe UTI's as a result 5. 8 subjects of 13 in whom a bladder was initially preserved sustained a pyocyst. 6. 5 experienced calculus formation in the upper urinary tract, 3 of these having severe UTIs as a result. 7. Most individuals were more satisfied with procedure than previous management method upon survey a few months after operation (no long-term follow-up on this issue).

Discussion

Continent Catheterizable Stoma

Despite small sample sizes, the results of the above studies are very promising. High levels of continence, independence, and the ability to manage the bladder with IC are reported in all three studies. The stability of serum creatinine has implications for upper tract function (Karsenty et al. 2008). Hakenberg et al. (2001) reported safe urodynamic bladder storage pressures (20-44 mm H₂O) in individuals that underwent appendicovesicostomy with cutaneous stoma. Participants in this study and the study by Sylora et al. (1997) were kept on anticholinergic medication, a consideration that ensures low pressure storage in those with persistent hyperreflexia and dyssynergia and contributes to ongoing continence. Complications occurred most concerning of which were those requiring surgical procedures (i.e., pelvic abscess, bowel occlusion, stomal revision for stenosis). Larger sample sizes would be necessary to determine true incidence. Length of follow-up ranged from 20 to 44 months, which does not provide sufficient long-term safety

and effectiveness data. However, given the importance of the clinical achievements (i.e., independent use of intermittent catheterization and continence), further study with larger sample sizes is warranted.

Incontinent Urinary Diversion

Ileal conduit diversion is another surgical procedure noted with some frequency in the literature. Chartier-Kastler et al. (2002) and Kato et al. (2002) have reported separate case series (N=33 and N=16 respectively) examining this approach. Chartier-Kastler et al. (2002) reported that all individuals became continent after initially being incontinent prior to surgery. Kato et al. (2002) reported that most individuals were more satisfied with the procedure than their previous management method upon survey a few months after the operation. Both authors also reported several long-term complications (e.g. pyocystitis, suprapubic collection with genital secretions, chronic urethral leakage, and acute pyelonephritis). However, it is uncertain if these high complication rates would be comparable in the event individuals had continued with their previous form of bladder management, as often surgical procedures are performed only if other more conservative methods are unsuccessful. Controlled trials (e.g. case control) would be beneficial to address this issue.

Colli and Lloyd (2011) evaluated a series of cases (n=35) involving bladder neck closure (BNC) which was paired with permanent SPC diversion as opposed to other forms of urinary diversion, such as ileovesicotomy or continent catheterizable stoma. Their results suggest that BNC in conjunction with SPC diversion offers urethral continence with a reasonable complication rate (17%). Additional advantages conferred by this technique include a straightforward operative approach without violation of the peritoneum, no need for enteric reconstruction, and possible reduction of bowel complications. Specific disadvantages were noted such as a reduced likelihood of success in very low bladder capacity individuals.

Continent cutaneous urinary diversion (CCUD) augmented with enterocystoplasty is an option for individuals who are unable to per intermittent self-catheterization (ISC) through the urethra. Perrouin-Verbe et al. (2016) reported primary complications, of CCUD with augmentation enterocystoplasty, related to the catheter tube and to bladder enlargement and recommended annual monitoring despite urethral continence (96%) and QoL (90%) improvement.

Conclusions

There is level 4 evidence (from one case series and one pre-post study; Hakenberg et al. 2001; Sylora et al. 1997) that most individuals who receive catheterizable stomas become newly continent and can self-catheterize. It appears possible that this surgical intervention could protect upper tract function. Larger studies are needed to better evaluate true incidence of complications, and long-term bladder and renal outcome.

There is level 4 evidence (from two case series studies; Chartier-Kastler et al. 2002; Kato et al. 2002) that most individuals undergoing cutaneous ileal conduit (ileo-ureterostomy) diversion became newly continent and were more satisfied than with their previous bladder management method. Long-term follow-up demonstrated the presence of a high incidence of urological or renal complications.

There is level 4 evidence (from one pre-post study; Perrouin-Verbe et al 2016) that continent cutaneous urinary diversion (CCUD) with augmentation enterocystoplasty results in increased urethral continence and QoL despite complications of the catheter tube and bladder enlargement that would benefit from annual monitoring.

Catheterizable abdominal stomas may increase the likelihood of achieving continence and independence in self-catherization and may result in a bladder management program that offers more optimal upper tract protection.

Cutaneous ileal conduit diversion may increase the likelihood of achieving continence but may also be associated with a high incidence of various long-term complications.

Continent cutaneous urinary diversion (CCUD) with augmentation enterocystoplasty may improve urethral continence and QoL.

4.4.7 Electrical Stimulation for Bladder Emptying and Enhancing Volumes

Although electrostimulation to enhance bladder volume and induce voiding has been studied since the 1950s it was not until the development of the Brindley anterior sacral nerve root stimulator, and subsequent implantation of the first device in a human in 1978 that widespread clinical applications have been available (Egon et al. 1998; Brindley et al. 1982). Others have noted the important role of Tanagho and Schmidt (1982) in developing this approach – also termed sacral neuromodulation – by conducting a series of experiments to elucidate the neuroanatomical basis of electrical stimulation in enhancing bladder function (Hassouna et al. 2003). Although there are several configurations, Creasey et al. (2001) described the system employed in most investigations (i.e., the Finetech-Brindley system) as consisting of an implanted internal stimulator-receiver which is controlled and powered via telemetered radio transmission by an external controller-transmitter. Cables and electrodes are also implanted which are held in contact with sacral nerves (i.e., often S2-S4). This system allows programmable stimulation patterns and permits control of both bowel and bladder function. Often dorsal sacral rhizotomy is performed at the same time as stimulator implantation (Vastenholt et al. 2003; Creasey et al. 2001; Egon et al. 1998; Martens et al. 2011).

Various investigators have examined other forms of stimulation including direct bladder stimulation (Madersbacher et al. 1982; Radziszewski et al. 2009, 2013) or stimulators intended for other purposes such as enhancing muscle functions for improving movement, spasticity or muscle strength (Katz et al. 1991; Wheeler et al. 1986). In addition, multi-functional stimulators may be configured to provide similar

stimulation patterns to similar targets as the bladder-specific stimulators. A systematic review of dorsal genital nerve stimulation in a variety of individuals with detrusor overactivity (Farag et al. 2012) confirms its utility in improving bladder capacity and incontinence. As noted previously (Section 3.2.1 Electrical Stimulation to Enhance Bladder Volumes), the present section describes studies that assess outcomes associated with both bladder emptying and bladder storage as appropriately configured stimulation may result in improvements in both of these functions.

Table 18 Stimulation Methods to Trigger Bladder Emptying and Enhance Bladder Volume

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
Systematic Reviews		
Ren et al. 2016 United Kingdom Review of published articles from Jan1975- Jan2014 AMSTAR=6 N=20	<p>Method: Conduct a literature review on electrical nerve stimulation to promote micturition.</p> <p>Databases: PubMed</p> <p>Level of evidence: Unknown</p> <p>Questions/measures/hypothesis: No specific hypotheses were tested by the authors</p>	<ol style="list-style-type: none"> 1. Four methods of electrical nerve stimulation were reviewed, sacral anterior root stimulation and sacral deafferentation, modification of the Finetech-Brindley stimulator, pudendal nerve stimulation (PN), and sacral neuromodulation (SNM). 2. The Finetech-Brindley stimulator is discussed, as well as subsequent iterations of the device. From 1976-1992, 500 individuals were implanted with the device and after a mean follow-up of 4 years, 411 individuals still used their stimulators for micturition. 3. Further iterations of the device include the SARS/SDAF version which of the 440 SCI individuals who received the device, 95% still used it for micturition and 83% maintained continence at follow-up. 4. PN involves the contact of an electrode catheter with the PN trunk. This technique has not been deemed very successful as it could only produce low bladder contractions, which did not result in effective voiding. 5. SNM has had significant positive effects on individuals, such that 69% of individuals significantly improved and 5 no longer needed CISC, there were no major complications and 66% of

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
		individuals were still responsive after 55 mo follow-up.
Interventional Studies		
Fergany et al. 2017 Egypt RCT PEDro=6 N=80	<p>Population: Pulsed electromagnetic field therapy (PEMFT): Mean age=39.45±9.30yr; Gender: males=24, females=16; Etiology: SCI=40; Inclusion criteria: presence of neurogenic overactive bladder. Transcutaneous electrical nerve stimulation (TENS): Mean age=40.85±8.37yr; Gender: males=26, females=14; Etiology: SCI=40; Inclusion criteria: presence of neurogenic overactive bladder.</p> <p>Intervention: Participants in the PEMFT group received sacral PEMFT consisting of 5 Hz with a 15% intensity output for 5s/min. Participants in the TENS group received sacral TENS consisting of 10 Hz with a generated pulse of 700 s. Both groups had 20 min/session, 3x/wk, for 20 sessions. Outcome measures were assessed at baseline and post-intervention.</p> <p>Outcome Measures: urinary flow rate (Qmax); max. cystometric capacity (MCC); volume at first uninhibited detrusor activity (dV).</p>	<ol style="list-style-type: none"> Both groups showed significant increases in MCC (p=0.001), dV (p=0.001), and Qmax (p=0.001). Post-intervention values were significantly greater in PEMFT for MCC (p=0.001), dV (p=0.002), and Qmax (p=0.021).
Jo et al. 2016 Korea RCT PEDro=6 N=10	<p>Population: Neurogenic detrusor overactivity; Mean age: 41.2 yr; Gender: males=7, females=3; ASIA classification: A/B.</p> <p>Intervention: Individuals were randomized to receive percutaneous bipolar radiofrequency neurotomy on both the S2 and S3 nerves (n=5) or conventional medical treatment (n=5). Two-year follow-up of Kim et al. 2015.</p> <p>Outcome Measures: Frequency of incontinence, volume of incontinence, International Consultation on Incontinence Questionnaire (ICIQ), urinary incontinence quality of life scale (I-QOL), maximum cystometric capacity, maximum detrusor pressure during filling, volume at maximal detrusor pressure during</p>	<ol style="list-style-type: none"> With measurements at baseline, 6 mo, 12 mo, and 24 mo follow-up, daily mean volume of incontinence showed a significant group effect (p<0.05) but no time effect. ICIQ showed a significant time (p=0.000), group (p=0.049), and time by group interaction effect (p=0.000). Frequency of incontinence showed only a significant time effect (p=0.003) and a significant time by group interaction (p=0.001). I-QOL showed only a significant time effect (p=0.025) and a significant time by group interaction (p=0.001). Reflex detrusor volume at first contraction (p=0.009), maximum detrusor pressure during filling (p=0.028), volume at maximal detrusor pressure

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	filling, reflex detrusor volume at first contraction.	during filling ($p=0.009$) and maximum cystometric capacity ($p=0.028$) all showed significant intergroup differences in terms of improvement from baseline to 24 mo follow-up.
Chen et al. 2015 China RCT PEDro=6 $N_{\text{initial}}=100$; $N_{\text{final}}=98$	<p>Population: Neurogenic detrusor overactivity; Mean age: 33.2 yr; Gender: males=91, females=6; Level of injury: cervical=28, thoracic=47, lumbar=23; Severity of injury: complete=75, incomplete=23; Mean time post-injury: 3.4 yr.</p> <p>Intervention: Individuals were randomized to receive 1) percutaneous tibial nerve stimulation (PTNS group), consisting of surface electrodes placed at the ankle over the course of the tibia nerve for 30 min, 2 times per week, for 4 weeks or 2) solifenacin succinate (SS group), with 5 mg once a day for 4 weeks.</p> <p>Outcome Measures: Clean intermittent catheterization (CIC) frequency, fluid intake, volume per catheterization, total leakage volume per day, Incontinence Quality of Life (I-QOL), adverse events.</p>	<ol style="list-style-type: none"> 1. No significant differences were observed post-treatment and between groups in terms of CIC frequency and fluid intake. 2. Compared to baseline, the volume per catheterization significantly increased ($p<0.05$), the total leakage volume per day decreased ($p<0.05$), and the I-QOL significantly improved ($p<0.05$) for both groups at 2 wk and 4 wk follow-up. However, no significant differences were observed between 2 wk and 4 wk follow-up within groups, or between groups. 3. No adverse events were reported in PTNS group, compared to 5 participants in SS group reporting dry mouth (2 resulting in study discontinuation).
Kim et al. 2015 Korea RCT PEDro=6 $N=10$	<p>Population: Neurogenic detrusor overactivity; Mean age: 41.2 yr; Gender: males=7, females=3; Level of injury: cervical=5, thoracic=5; ASIA classification: A=7, B=3.</p> <p>Intervention: Individuals were randomized to receive percutaneous bipolar continuous radiofrequency ablation of S2/S3 nerves ($n=5$) or conventional medical treatment ($n=5$).</p> <p>Outcome Measures: Frequency of incontinence, volume of incontinence, International Consultation on Incontinence Questionnaire (ICIQ), urinary incontinence quality of life scale (I-QOL), maximum cystometric capacity (MCC), maximum detrusor pressure during filling (MDP), volume at maximal detrusor pressure during filling (volume at MDP), reflex detrusor volume at first contraction (RDV).</p>	<ol style="list-style-type: none"> 1. With measurements at baseline, 1 mo, and 3 mo follow-up, daily mean volume of incontinence showed a significant time effect (0.043) and group effect (0.012), but not a significant time by group interaction. ICIQ showed a significant time effect ($p=0.005$) and time by group interaction ($p=0.020$), but not a significant group effect. Frequency of incontinence showed a significant time effect (0.004) and time by group effect ($p=0.003$), but not a significant group effect. I-QOL showed a significant time effect (0.024) and time by group interaction ($p=0.007$), but not a significant group effect. 2. RDV ($p=0.029$) and volume at MDP ($p=0.029$) showed significant intergroup differences in terms of

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		improvement from baseline to 3 mo follow-up, while MDP and MCC showed no significant differences.
Shendy et al. 2015 Egypt RCT PEDro=6 N=30	<p>Population: Transcutaneous electrical nerve stimulation (TENS group): Mean age=28.1 yr; Pelvic floor biofeedback (PFBFB group): Mean age=28.3 yr.</p> <p>Intervention: Individuals with precipitancy overactive bladder and erectile dysfunction were randomized to 1) TENS, which involved two surface electrodes placed directly over the skin of S2 for 30 min at 50 Hz (n=15) or 2) PFBFB, which involved contraction of the pelvic floor muscles in the fowler lying position while watching the electromyography biofeedback activities (n=15). Both groups performed pelvic floor exercises, 90 contractions per day after training session.</p> <p>Outcome Measures: Bladder volume at first desire to void, maximum bladder capacity, maximum flow rate, detrusor pressure at maximum flow rate, right side amplitude per time (A/T), left side A/T, right side upper centile amplitude (UCA), left side UCA, International Index of Erectile Function Questionnaire (IIEF-5).</p>	<ol style="list-style-type: none"> 1. After treatment, bladder volume at first desire to void ($p=0.001$), maximum cystometric capacity ($p=0.001$), detrusor pressure at maximum flow rate ($p=0.002$), and maximum flow rate ($p=0.001$) significantly increased in TENS group but only the maximum flow rate ($p=0.042$) significantly increased in the PFBFB group. There were no significant differences between groups, except for the detrusor pressure at maximum flow rate being significantly higher in the TENS group both before ($p=0.008$) and after ($p=0.001$) treatment. 2. Post-treatment, the TENS group had significantly higher right side A/T ($p=0.001$), left side A/T ($p=0.001$), right side UCA ($p=0.029$), left side UCE ($p=0.041$), and IIEF-5 ($p=0.013$) compared to PFBFB group. 3. In terms of right side A/T, left side A/T, right side UCA, left side UCA, and IIEF-5, PFBFB group did not have any significant increases post-treatment while TENS had significant increases post-treatment ($p=0.001$).
Radziszewski et al. 2013 Poland *Follow-up study to Radziszewski et al. 2009 Pre-post N=28	<p>Population: Age range 16-68 yr; Gender: males=22, females=6; Time post-injury: 2-26 mo.</p> <p>Intervention: Transcutaneous electrical stimulation (ES) of the urinary bladder as a treatment for micturition disorders in individuals after SCI.</p> <p>Outcome Measures: Bladder capacity, post-void residual urine, opening pressure, intravesical pressure, and maximum flow.</p>	<ol style="list-style-type: none"> 1. Transcutaneous ES of the urinary bladder produced a significant increase in bladder capacity ($p=0.001$). 2. Post-void residual urine in the urinary bladder decreased by a mean of 81.9 ml ($p=0.007$). 3. ES reduced bladder opening pressure in 16 individuals (57.1%) immediately after the treatment, by a mean of 4.5 cm H₂O. 4. At follow-up (2 yr) intravesical pressure at maximum flow was lower than baseline in 21 individuals (79%), by a mean of 9.6 cm H₂O ($p>0.05$).

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Martens et al. 2011 Netherlands Prospective Controlled Trial N=101	<p>Population: Gender: males=80, females=21; 73 SCI individuals with dorsal rhizotomy and Brindley stimulator (46 still used stimulator (Brindley group), 27 did not (Rhizotomy group); 28 control; Complete injury and detrusor overactivity.</p> <p><i>Brindley group:</i> Mean age: 48 yr, Mean time post-injury: 21 yr, Mean follow-up time: 13 yr. <i>Rhizotomy group:</i> Mean age: 47 yr, Mean time post-injury: 19yr, Mean follow-up time: 14 yr.</p> <p>Intervention: Brindley stimulator or Rhizotomy.</p> <p>Outcome Measures: Qualiveen Questionnaire, SF 36, Specific Impact of Urinary Problems score and clinical outcomes, quality of life (QoL).</p>	<ol style="list-style-type: none"> 1. The Brindley group had better QoL scores on every item in Qualiveen scale including limitations, constraints, fears, and bad feelings compared to control group (p=0.046). 2. The Brindley group also had a higher score in SF-36 compared to the rhizotomy and control group. The Brindley group reported a lower rate of urinary tract infection (UTI) and higher continence rate. 3. Fifty two percent of individuals in the brindley group reported complete continence compared to the control group (p=0.002) and the Rhizotomy Group (p=0.214).
Sievert et al. 2010 Germany Prospective Controlled Trial N=16	<p>Population: Detrusor areflexia. Mean age: 31yr; Gender: males=16, females=0; Level of injury: T2/3-11=16; Severity of injury: complete=16, incomplete=0.</p> <p>Intervention: Individuals with areflexic bladder were offered bilateral sacral neuromodulation treatment. Subjects refusing treatment (n=6) served as controls.</p> <p>Outcome Measures: Bladder pressure, detrusor contractions, erectile function, urinary tract infection rate (UTI).</p>	<ol style="list-style-type: none"> 1. Improvement in bladder pressure and autonomic detrusor contractions was seen in the treatment group. 2. 2 individuals in the treatment group reported improved erectile function. 3. Individuals in the treatment group reported a mean of 0.5 UTIs/yr, while individuals in the control group reported 3.8.
Bycroft et al. 2004 UK Prospective controlled trial N=12	<p>Population: SCI: Age range 19-46 yr; Gender: males=7, females=5; Level of injury: thoracic=7; Severity of injury: complete=7; Time post-injury=18-63 mo.</p> <p>Intervention: A multi-pulse magnetic stimulator and coil was used to apply magnetic stimulation to sacral nerve roots at half capacity and near full capacity through single and intermittent bursts. In spinal cord injured individuals, stimulation was during neurogenic detrusor overactivity; while normal individuals received stimulation during voiding.</p>	<ol style="list-style-type: none"> 1. No significant bladder pressure rise was seen in either single or intermittent bursts of magnetic stimulation of the sacral nerve roots. 2. Magnetic stimulation in spinal cord injured individuals resulted in suppressed detrusor overactivity and suppressed voiding in normal individuals.

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	Outcome Measures: Bladder pressure, suppression of detrusor contractions.	
Previnaire et al. 1996 France Prospective Controlled Trial N=20	Population: Mean age at injury: 32.4 yr; Gender: males=18, females=2; Time post-injury: 43.55mo; Level of injury: C4-T12; Severity of injury: tetraplegia complete=8, tetraplegia incomplete=4, paraplegia complete=4, paraplegia incomplete=4. Intervention: Continuous electrical stimulation of dorsal penile or clitoris nerve via surface electrodes. Outcome Measures: Bladder capacity and perineal contraction, adverse effects.	<ol style="list-style-type: none"> 1. No significant difference in bladder capacity between T1, T2, T2. 2. No significant difference between the mean bladder capacities. 3. Significant increase in bladder capacity with electrical stimulation at twice the threshold compared with baseline and threshold cystometries. 4. The current of twice the threshold evoked a clinical perineal contraction in all individuals, threshold stimulation did not. 5. No adverse effects.
Goldman et al. 2008 USA Prospective Controlled Trial N=21	Population: Mean age: 52.7 yr (range 31-78 yr); Gender: males=0, females=21. Intervention: Dorsal genital nerve stimulation. Outcome Measures: Bladder diaries, 24hr pad tests, and adverse event queries.	<ol style="list-style-type: none"> 1. 47% of subjects reported $\geq 50\%$ reduction in incontinence episodes. 2. Pad weight was reduced by $\geq 50\%$ 3. 7 subjects experienced 9 adverse events.
Bourbeau et al. 2018 USA Pre-Post N=5	Population: Mean age=66 \pm 8.4yr; Gender: N/S; Etiology: SCI=5; Time since injury=25.6 \pm 17.3yr. Intervention: Participants received genital nerve stimulation (GNS). GNS was delivered through two circular electrodes applied to the dorsum of the penis. The cathode was placed at the base of the penis and the anode 2 cm distally. For females, one electrode was placed above the clitoris and the other on the lower labia majora or inner thigh. Participants underwent three one-month testing periods (baseline, stimulation, post-stimulation). A portable stimulator was used at home by the participants during the stimulation phase only (one-month duration). Outcome measures were assessed at baseline, and at the end of the stimulation and post-stimulation periods (each lasting one month). Outcome Measures: Incontinence episodes (IE); bladder capacity	<ol style="list-style-type: none"> 1. There was a significant decrease in IE from baseline to stimulation period ($p<0.001$). 2. There was a significant increase in IE at post-stimulation compared to the stimulation phase. Moreover, IE were still significantly lower than baseline ($p<0.001$). 3. There was no significant difference in bladder capacity across all time periods ($p>0.05$). However, bladder capacity did increased acutely during each urodynamics in response to GNS regardless of time period ($p<0.001$).

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<p>Brose et al. 2018 USA Pre-Post N=24</p>	<p>Population: Mean age=60±11yr; Etiology: SCI=24. Time since injury=13±4 yr; Inclusion criteria: presence of neurogenic detrusor over-activity (NDO).</p> <p>Intervention: Genital nerve stimulation (GNS) was applied across two round surface electrodes. The cathode was placed on the proximal, dorsal end of the penis and the anode 2 cm distally (alternatively, the anode was a surface electrode placed on the mon pubis). For the female participants, the cathode was placed directly superior to the clitoris and the anode on the left lateral labia majora. Biphasic, charge-balanced, cathodic-leading pulses were delivered at 20 Hz. Outcome measures were assessed at baseline and post-intervention.</p> <p>Outcome Measures: Bladder capacity; bladder contractile inhibition.</p>	<ol style="list-style-type: none"> 1. Bladder capacity increased significantly (p=0.007). 2. 19 of 24 participants had delayed bladder contractions.
<p>Gad et al. 2018 USA Pre-Post N=7</p>	<p>Population: Mean age=38.57±7.71yr; Gender: males=4, females=3; Etiology: SCI=7; Time since injury=5.66±7.23yr; Inclusion criteria=SCI at T11 or above; use intermittent catheterization to manage lower urinary tract (LUT).</p> <p>Intervention: Participants received transcutaneous spinal cord stimulation (TSCS) delivered by 2.0 cm-diameter electrodes. Day1: Spinal stimulation was delivered at 0.5 Hz (individually at T11 and L1) with current starting at 10 mA and increasing at increments of 10-200 mA until tolerable or responses plateaued. Day 2: Transcutaneous electrical spinal stimulation for LUT functional augmentation (TESSLA) was delivered at 30 Hz and the bladder was filled until a detrusor contraction occurred. Stimulation was subsequently turned off and the bladder was emptied fully. The bladder was then filled to 75% and TESSLA was delivered at 1 Hz at T11 to initiate voiding. Outcome</p>	<ol style="list-style-type: none"> 1. TESSLA delivered at 1 HZ resulted in improved VE, flow rate, detrusor-sphincter coordination, and decreased PVR (p<0.05). 2. TESSLA delivered at 30 HZ at T11 resulted in significant improvements in bladder capacity and improved detrusor sphincter coordination during voiding (p<0.05). 3. When urodynamic studies were repeated after TESSLA was turned off, there was a reversal to baseline values.

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	<p>measures were assessed at baseline and during TESSLA.</p> <p>Outcome Measures: Volume at first detrusor contraction (Vdet); voiding efficiency (VE); post-void residual (PVR); sensation of fullness; sensation of detrusor contraction; detrusor-sphincter dyssnergia; max. change in detrusor pressure during voiding; max. change in Pura during voiding.</p>	
<p>Knight et al. 2017 UK Pre-Post N=6</p>	<p>Population: Gender: males=6; females=0; Etiology: SCI=8; Inclusion criteria: male subjects between the ages of 18-75 with a complete or incomplete supra-sacral SCI of at least 24 mo duration; presence of neurogenic detrusor overactivity (NDO).</p> <p>Intervention: Conditional neuromodulation (CN) was applied using biphasic balanced pulses. Amplitude for each participant was determined based on sensory threshold or maximum tolerated. The bladder was filled at a physiological rate (15 mL/min) with CN applied simultaneously. A 60 s stimulation was triggered each time EMG threshold was met. Outcome measures were assessed at baseline and during CN.</p> <p>Outcome Measures: Maximum cystometric capacity (MCC); maximum detrusor pressure (Pdet).</p>	<ol style="list-style-type: none"> 1. There was a significant increase in MCC ($p<0.03$) during NC. 2. There was a significant decrease Pdet ($p<0.03$) during NC.
<p>Castano-Botero et al. 2016 Colombia Pre-Post N=104</p>	<p>Population: Neurogenic detrusor overactivity; Mean age: 38.0 yr; Gender: males=95, females=9; Level of injury: cervical=34, thoracic=68, lumbar=2; ASIA classification: A=96, B=8; Mean time post-injury: 72.8 mo; Injury etiology: traumatic spinal cord injury=103, other=1.</p> <p>Intervention: Sacral anterior root stimulation (SARS), which involved laminectomy, posterior rhizotomy, implantation of electrodes, and tunneling.</p> <p>Outcome Measures: Urinary infection, urinary incontinence, autonomic dysreflexia, cystometric bladder capacity, post-void residual (PVR) volume, adverse events.</p>	<ol style="list-style-type: none"> 1. The percentage of urinary infection ($p<0.001$), urinary incontinence ($p<0.001$), and autonomic dysreflexia ($p<0.001$) significantly decreased post-treatment. 2. Post-treatment, the mean bladder capacity was 362 mL, with 94% of participants having a bladder capacity greater than 400 mL and 91% of participants achieving effective voluntary voiding (PVR<50 ml). 3. In terms of adverse events, 6% required a suburethral mesh, 2% had an infection, 2% had electrode extrusion, 2% had

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		receiver block extrusion, and 1% had device failure at 6 mo.
McCain et al. 2015 United States Pre-Post N=10	<p>Population: Bladder and sphincter spasticity; Gender: males=9, females=1; Level of injury: cervical=5, thoracic=5; ASIA classification: A=4, B=4, C=1, D=1.</p> <p>Intervention: The bladder was filled with sterile saline at 20 ml/min until reflexive bladder contractions were observed. During reflex contractions, patterned electrical stimulation was randomly applied to the S2/S3 dermatome in 25 sec intervals.</p> <p>Outcome Measures: Urethral sphincter pressure, vesical pressure, adverse events.</p>	<ol style="list-style-type: none"> 1. Of the six participants with detectable urethral reflex activity, none demonstrated urethral reflex suppression in response to any of the stimulation patterns. Stimulation did not have any significant effect on urethral pressure or bladder pressure. 2. No participants reported pain or adverse sensation during stimulation. One participant experienced two episodes of elevated blood pressure with a filled bladder, and three participants experienced one or more lower limb spasms.
Ojha et al. 2015 India Pre-Post N=15	<p>Population: Detrusor overactivity; Posterior tibial nerve (PTN group): Mean age: 32.3 yr, Gender: males=9, females=1; Level of injury: C6-T3=1, T4-T10=6, T11-L3=3; Severity of injury: complete=6, incomplete=4; ASIA classification: A=5, B=1, C=3, D=1; Median time post-injury: 9.5 mo. Dorsal penile nerve (DPN group): Mean age: 42.8 yr; Gender: male; Level of injury: T4-T10=3, T11-L3=2; Severity of injury: complete; ASIA classification: A=4, B=1.</p> <p>Intervention: Individuals with intact F-wave were recruited into the PTN study (n=10) and those with an absent F-wave were recruited into the DPN study (n=5). Individuals received electrical stimulation for 20 min per session each day for 14 consecutive days at the assigned site.</p> <p>Outcome Measures: Reflex volume, cystometric capacity, maximum detrusor pressure, voiding diary improvement (no change or an increase in number of leaks and decrease in maximum volume of urine voided were considered to denote lack of improvement).</p>	<ol style="list-style-type: none"> 1. In the PTN study, the post-intervention mean reflex volume increased by 37.9 ml, the mean maximum pressure decreased by 8 cm H₂O, and the mean cystometric capacity increased by 56 ml. There were no significant differences for any parameter comparing pre- and post-treatment. 2. In the DPN study, the post-intervention mean reflex volume increased by 46.8 ml, the mean maximum pressure decreased by 42.4 cm H₂O, and the mean cystometric capacity increased by 59.6 ml. There were no significant differences for any parameter comparing pre- and post-treatment. 3. In the PTN study, 9 participants improved and 1 did not, with a statistically significant binomial distribution test (p=0.021). 4. In the DPN study, 5 participants improved and 0 did not, with a non-statistically significant binomial distribution test (p=0.062).
Lee et al. 2012 Korea Pre-Post N=6	<p>Population: Age range 33-59 yr; Gender: males=6, females=0.</p> <p>Intervention: Semi-conditional stimulation parameters were set</p>	<ol style="list-style-type: none"> 1. The capacity of the bladder increased in all individuals after 2-4 wk of treatment.

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	<p>during cystometry (CGN) and semi-conditional stimulation on dorsal penile nerve (DPN) by surface electrodes applied from 14 to 28 d, at home.</p> <p>Outcome Measures: Bladder contraction, clinical bladder capacity, bladder compliance, initial bladder volume, maximum bladder volume.</p>	<ol style="list-style-type: none"> 2. Clinical bladder capacity measured by the voiding volume upon reflex voiding, and clean IC increased from 201.67±106.10ml to 383.33±51.64ml after treatment. 3. Bladder compliance improved from 3.30±1.89 ml per cm H₂O before treatment to 11.26±9.18ml per cm H₂O after treatment. 4. V_{initial} increased from 45.17±23.84 to 165.5±156.5ml after treatment. 5. V_{maximum} increased from 203.67±77.55 to 359.50±70.43ml after treatment.
<p>Possover 2009 Switzerland Pre-Post N=8</p>	<p>Population: Mean age: 42±9 yr; Level of injury: Thoracic; Severity of injury: complete.</p> <p>Intervention: SCI individuals with previous explantation of a dorsal implanted Brindley Finetech controller underwent the LION procedure, a laparoscopic transperitoneal technique of implantation of neural electrodes.</p> <p>Outcome Measures: Urodynamic assessment (Detrusor contraction), complications collected during follow-up for 3-27 mo.</p>	<ol style="list-style-type: none"> 1. 6 of 8 individuals were able to have procedure (remaining 2 had damage to sacral nerves). 2. Immediate detrusor contraction of up to 60cm of H₂O in women and 90cm in men was seen after bilateral stimulation of S3/S4. 3. At follow-up (up to 27 mo), complete bladder emptying still occurred. 4. Complete control of spasticity and autonomic dysreflexia was seen with bilateral implantation of the neuromodulation electrodes. 5. No complications were seen postoperatively.
<p>Radziszewski et al. 2009 Poland Pre-Post N=22</p>	<p>Population: Mean age: 32 yr; Gender: males=18; females=4; Level of injury: C=3, L=19.</p> <p>Intervention: SCI individuals were administered transcutaneous electrical stimulation of bladder for 15 min over 30 successive days.</p> <p>Outcome Measures: Urodynamics (cystometric capacity, flow velocity, residual urine), adverse events. Urodynamic assessment conducted pre- and immediately following 30 d treatment period and 2 mo post-treatment.</p>	<ol style="list-style-type: none"> 1. A significant increase in cystometric capacity of urinary bladder (p=0.001) and peak flow velocity (p<0.001), while a significant decrease of residual urine (p=0.008) was seen immediately after electrical stimulation and at 2 mo follow-up compared to baseline. However, no significant change was seen between immediately post stimulation and after 2 mo. 2. No significant changes were seen in opening pressure and intravesical pressure at peak urine flow. 3. No adverse events were reported.
<p>Kutzenberger 2007 Germany Pre-Post N=464</p>	<p>Population: SCI individuals with neurogenic detrusor overactivity. Mean age: 33, Gender: males=244,</p>	<ol style="list-style-type: none"> 1. Sacral deafferentation (SDAF) resulted in treatment of detrusor overactivity in 442 individuals.

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	females=220; Level of injury: paraplegia=274, tetraplegia=190. Intervention: SCI individuals underwent sacral deafferentation and implantation of a sacral anterior root stimulator for neurogenic detrusor overactivity. Outcome Measures: Continence, urinary tract infections (UTIs).	2. 385 individuals achieved continence. 3. SDAF and sacral anterior root stimulation (SARS) resulted in decrease incidence of UTIs from 6.3/yr to 1.2/yr.
Lee et al. 2005 Korea Pre-Post N=7	Population: Mean age: 39.85 yr; Gender: male=7, female=0; Mean time post-injury: 67.28 mo; Level of injury: C6-T11; Severity of injury: ASIA A=2, ASIA B=2, ASIA C=3. Intervention: Percutaneous or transcutaneous electrical stimulation for 1 minute. Outcome Measures: Infused volume of saline, duration of suppression at first and last reflex, peak detrusor pressure.	1. No significant difference of infused volume of saline at first or last reflex contraction. 2. No significant difference for duration of suppression for first and last reflex contraction. 3. No significant difference in P_{ini} , P_{max} and P_{sup} . 4. Peak detrusor pressure was effectively suppressed by both percutaneous and transcutaneous electrical stimulation. 5. No medical complications in either stimulation technique.
Hansen et al. 2005 Denmark Pre-Post N=16	Population: Gender: males=14, females=2; Level of SCI: C4/5-L4/5; Severity of injury: complete=8, incomplete=6; Time post-injury=3 mo–36 yr. Intervention: Stimulation of the penile/clitoral nerve was performed on individuals with a custom made battery driven stimulator. Amplitude of stimulation was increased until the bulbocavernosus reflex was elicited and an event driven stimulation of amplitude of 2 times bulbocavernosus was used. Outcome Measures: Bladder capacity, bladder pressure, prevalence of leakage, tolerance.	1. At least 1 inhibited detrusor contraction was seen in 13 out of 16 individuals who underwent penile/clitoral nerve stimulation. 2. Automatic event driven electrical stimulation resulted in 40% increase in bladder capacity and 69% decrease in storage pressure. 3. Only one individual had leakage. 4. Stimulation was tolerated by all but one individual.
Kutzenberger et al. 2005 Germany Pre-Post N=464	Population: Gender: males=244, females=220; Level of injury: paraplegic=464. Intervention: Individuals underwent sacral deafferentation and implantation of anterior root stimulator. Outcome Measures: Success rate, continence, voiding, urinary tract infection (UTI) prevalence. Mean follow-up time= 6.6 yr (minimum>6 mo).	1. 437 individuals had successful sacral deafferentation. 2. 385 achieved continence. 3. Voiding voluntarily through anterior sacral root stimulation was seen in 420 individuals. 4. There was a decrease in urinary tract infections from 6.3/yr preoperatively to 1.2/yr postoperatively.

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Spinelli. et al. 2005 Italy Pre-Post N=15	<p>Population: Neurogenic detrusor overactivity; Mean age: 38 yr; Gender: males=8, females=7.</p> <p>Intervention: Individuals with neurogenic detrusor overactivity underwent chronic pudendal nerve stimulation. Measures were assessed at baseline and 6 mo post-treatment.</p> <p>Outcome Measures: Urodynamic evaluation measuring cystometric capacity and maximum pressure.</p>	<ol style="list-style-type: none"> 1. Urodynamic evaluation for 7 individuals who completed 6 mo follow-up: 2. Maximum cystometric capacity, ↑ from 153.3±49.9 to 331.4±110.7mL (p<0.01). 3. Maximum pressure, decreased from 66.0±24.3 to 36.8±35.9 cm H₂O (p=0.059).
Kirkham et al. 2002 UK Pre-Post N=5	<p>Population: Age Range 32-46 yr; Level of injury: thoracic=5; Severity of injury: complete=5.</p> <p>Intervention: Finetech-Brindley stimulator was implanted in individuals without rhizotomy of the posterior roots.</p> <p>Outcome Measures: Bladder capacity, bladder pressures.</p>	<ol style="list-style-type: none"> 1. Postoperatively 2 individuals no longer presented with detrusor hyperreflexia. 2. Neuromodulation resulted in increased bladder capacity of all individuals. 3. 2 of 3 individuals had their bladder capacity increase more than double through continuous stimulation. 4. Intense stimulation in 3 individuals resulted in bladder pressures greater than 70cm H₂O.
Hohenfellner et al. 2001 Germany Pre-Post N=27	<p>Population: Mean age: 44.9 yr (18-63 yr); Gender: males=8, females=19; Underlying neurological disorder: lesions of spinal cord=16; pelvic surgery=6; cerebral lesions=3; inflammatory disease of central nervous system (CNS)=2.</p> <p>Intervention: Investigate the therapeutic value of sacral neuromodulation for rehabilitation of hypersensitive, hyperreflexic, or areflexic bladders.</p> <p>Outcome Measures: Day and night time frequency; first desire to void (mL); bladder capacity (mL).</p>	<ol style="list-style-type: none"> 1. Test simulation was successful in 13 individuals. 2. In 2 of 3 individuals with failure to empty, the residual urine volume was reduced from 30 mL to 0 mL. 3. Therapeutic effect lasted 11 to 96 mo (mean 54 mo).
Creasey et al. 2001 USA Pre-Post N=23	<p>Population: SCI: Mean age: 40 yr; Gender: males=16, females=7; Severity of injury: Complete; Level of injury: suprasacral (C4-T12); Median time post-injury=7 yr.</p> <p>Intervention: Implantation of externally controlled neuroprosthesis for stimulating the sacral nerves and posterior sacral rhizotomy. Collected at baseline, 3 mo and 12 mo post-implantation.</p>	<ol style="list-style-type: none"> 1. At 3 mo, 19/21 were successful in voiding more than 200mL of urine on demand, while 17/21 achieved residual volumes of less than 50mL. These results were maintained at 12 mo and were compared to 4/23 and 3/23 respectively prior to implantation (p<0.001). 2. Median voided volume □ (p<0.001) and residual volume ↓ (p<0.001) as compared to baseline.

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
	Outcome Measures: Voided and residual volumes, catheter use, urinary tract infections (UTIs), anticholinergic use, autonomic dysreflexia, incontinence, satisfaction.	<ol style="list-style-type: none"> 3. Continence was improved in 12 of 17 who completed 12 mo diaries 4. By 12 mo 18/23 people used the system as their primary bladder management method. 5. Decrease in median number of reported UTIs/person/yr from 3 to 2 at 12 mo, number of people using anticholinergics (17 to 2 at 12 mo) and number of people experiencing autonomic dysreflexia (8 to 2 at 12 mo). 6. Most people were satisfied with device. 7. Also helped with bowel management. 15 of 17 reduced time spend on bowel management; median time was halved ($p<0.001$).
Kirkham et al. 2001 England Pre-Post N=14	<p>Population: SCI: Gender: males=14, females=0; Level of injury: C6 – L1; Time post-injury>1 yr.</p> <p>Intervention: Different patterns of dorsal penile nerve stimulation (continuous or conditional which was a one minute burst triggered by a rise in detrusor pressure of 10cm H₂O) assessed during urodynamic evaluation.</p> <p>Outcome Measures: Urodynamic parameters (bladder capacity, bladder compliance). Collected prior and during/following stimulation.</p>	<ol style="list-style-type: none"> 1. Both continuous and conditional stimulation increased bladder capacity. 2. Continuous stimulation increased bladder compliance. 3. Of 6 subjects in which both stimulation methods were tested, 4 showed increased bladder capacity with the conditional versus continuous method but the difference was not significant. 4. The authors suggest the conditional neuromodulation method would be effective for use in an implanted device.
Egon et al. 1998 France Pre-Post N=96	<p>Population: SCI: Mean age: 34.3 yr (males), 31.4 yr (females); Gender: males=68, females=28; Level of injury: paraplegia=55, tetraplegia=41; Time post-injury: 6.9 yr (males), 6.1 yr (females); Follow-up time=5.4 yr (males), 5.8 yr (females).</p> <p>Intervention: ≥6 mo follow-up of those implanted with Finetech-Brindley sacral anterior root stimulator and in most cases posterior sacral rhizotomy.</p> <p>Outcome Measures: Urodynamic assessment prior and at follow-up as noted above.</p>	<ol style="list-style-type: none"> 1. Bladder capacity increased from 242±120 to 567±51mL for males and from 118±80 to 560±43 ml for females. 2. 56 of 65 surviving males and 26 of 28 females were all continent. All but 1 female was incontinent prior. 5 individuals required an anticholinergic for continence. 3. 58 males and 25 females used the stimulator for bladder emptying with a residual volume of <50 ml. 4. Urinary tract infections (UTIs) ↓. 4 reported at least 1 UTI after, 35 prior. 5. Some reported ↑ spasticity which was transitory, pre-existing

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
		autonomic dysreflexia in 22 with bladder filling ceased. 6. 2 stimulators became infected, 5 stimulators failed, 3 had cable failures.
Previnaire et al. 1998 France Pre-Post N=6	<p>Population: Mean age: 41.7±13.0 yr; Gender: males=5, females=1; Time post-injury: 9.3±5.5 mo; Severity of injury: tetraplegia incomplete ASIA B=3, tetraplegia incomplete ASIA C=1, paraplegia incomplete ASIA B=2.</p> <p>Intervention: Pudendal nerve maximal electrical stimulation (MES) consisting of daily stimulation periods of 20 min, repeated five times a week, during 4 weeks, with continuous electrical stimulation of the penis or of the clitoris via bipolar surface electrodes (rectangular stimuli of 0.5 ms pulse duration, 5 Hz frequency).</p> <p>Outcome Measures: Bladder capacity (mL) before and after MES.</p>	1. There were no differences between cystometric bladder capacity volumes before or after MES.
Van Kerrebroeck et al. 1997 Netherlands Pre-Post N=52	<p>Population: Mean age: 28.5 yr; Gender: males=41, females=11; Level of injury: cervical=11, thoracic=41; Mean time post-injury=6.4 yr.</p> <p>Intervention: A Finetech-Brindley sacral anterior root stimulator was implanted and a complete posterior sacral root rhizotomy was performed on all individuals.</p> <p>Outcome Measures: Bladder capacity, compliance, continence, urinary tract infections. Individuals were followed up 6 weeks after surgery, every 3 mo in the first yr, every 6 mo in the second yr, and once a yr afterwards.</p>	<p>1. Significant increase postoperatively was seen in bladder capacity at 6 wk and 6 mo (p=0.000) and compliance at 6 mo (p=0.000).</p> <p>2. Complete continence at 6 mo was achieved in 38 individuals during the day and 45 during the night.</p> <p>3. 38 individuals had no infection since the operation at 6 mo.</p>
Van Kerrebroeck et al. 1996 Netherlands Pre-Post N=52	<p>Population: Mean age: 32.9 yr; Gender: males=29, females=23; Etiology of injury: trauma=50; Level of injury: cervical=11, thoracic=41; Severity of injury: complete=52.</p> <p>Intervention: Individuals underwent complete posterior sacral root rhizotomy and had a Finetech-Brindley sacral anterior root stimulator implanted.</p> <p>Outcome Measures: Bladder capacity, continence, residual urine, urinary tract infections,</p>	<p>1. Bladder capacity increased significantly in all individuals.</p> <p>2. Complete continence was seen in 43 of the 52 individuals.</p> <p>3. 41 individuals were able to use the stimulator alone to empty the bladder.</p> <p>4. The prevalence of urinary tract infections decreased from 4.2 per yr to 1.4 per yr.</p> <p>5. One individual had the implant removed due to infection.</p>

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
	complications. Follow up was done 6 wk after surgery and every 3 mo during the first yr.	
Wheeler et al. 1994 USA Pre-Post N=9	<p>Population: Mean age: 33.6 yr; Time post-injury: 2-26 yr.</p> <p>Intervention: Pelvic floor stimulation via dorsal penile stimulation, consisting of stimulation frequencies of 2 and 5 pps and a max current of 50 mA.</p> <p>Outcome Measures: Cystometric (CMG) bladder evaluation (filling bladder pressure and capacity, bladder contractile activity and sphincter electromyographic activity) and urologic status.</p>	<ol style="list-style-type: none"> 1. Two subjects successfully completed the study. 2. The most effective stimulating parameters was 5pps, 250msec pulse width and 40ma current. 3. In one of the individual who was satisfied with the protocol, bladder filling volumes increased from 110 to 150mL.
Wheeler et al. 1992 USA Pre-Post N=6	<p>Population: Mean age: 36 yr; Gender: males=6, females=0; Time post-injury: 2-11 yr (mean 5.3 yr); Injury level: C6-T12</p> <p>Intervention: Dorsal penile stimulation using a stimulation parameter of 5 pulses per second and pulse duration of 0.35 msec.</p> <p>Outcome Measures: Cystometrographic filling volumes [baseline to post stimulation volumes (mL), percent of volume change from baseline to stimulation].</p>	<ol style="list-style-type: none"> 1. There was a significant increase in filling volume from before to during stimulation (127mL to 328 mL; mean 76% increase).
Robinson et al. 1988 England Pre-Post N=22	<p>Population: SCI: Mean age: 30 yr; Gender: males=20, females=2; Level of injury: paraplegia=15, tetraplegia=7.</p> <p>Intervention: Implantation of Brindley anterior sacral root stimulator.</p> <p>Outcome Measures: Urodynamics, intravenous urography, continence. Collected prior and following implantation. Length of follow-up not stated.</p>	<ol style="list-style-type: none"> 1. No group results reported. 2. 16/22 using implant (11 continent, 5 incontinent). 3. Of 5 incontinent, 4 had hyperreflexia and these were unable to use stimulator with sufficient frequency. 4. 4 had hydronephrosis; 2 resolved after implant while 2 required sphincterotomy. 5. Total of 6 individuals required sphincterotomy. 6. 6 were able to sustain an erection, though not useful for intercourse due to associated stimulator induced muscle spasm. 7. Dyssynergia was noted as the main complication (n=6).
Wheeler et al. 1986 USA Pre-Post N=15	<p>Population: SCI: Mean age: 47 yr; Gender: males=15; Level of injury: C5-T12; Time post-injury=4 mo-16 yr.</p>	<ol style="list-style-type: none"> 1. No group results reported. 2. In general, slightly more individuals had enhanced bladder function with treatment

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
	<p>Intervention: 4 to 8 wk of quadriceps muscle reconditioning by functional electrical stimulation (FES) bilaterally intended for strength and spasticity.</p> <p>Outcome Measures: Urodynamic assessment, strength (force transducer), spasticity (pendulum test). Collected prior and following stimulation program.</p>	<p>than those with no change or reduced bladder function.</p> <ol style="list-style-type: none"> 3. 7 people had increased bladder capacity with pressure that decreased or stayed the same. 4. 6 people had decreased bladder capacity with pressure that increased or stayed the same; however 2 of these results were confounded by resolution of spinal shock. 5. Changes in bladder function were correlated with changes in strength and spasticity.
Vodusek et al. 1986 USA Pre-Post N=10	<p>Population: Mean age: 24.9 yr; Gender: males=8, females=2; Time post-injury 5-96 mo (mean 30.2 mo); Level of injury: T=6, C=4.</p> <p>Intervention: Electrical stimulation via the dorsal of the penis or dorsal clitoral nerve consisting of a repetitive stimulation (1Hz) with rectangular stimuli (0.2 or 0.5ms) and rate of 5 to 10Hz during bladder filling.</p> <p>Outcome Measures: Micronutrient threshold (before, during and after stimulation; cc and percent).</p>	<ol style="list-style-type: none"> 1. Micronutrient threshold increased on stronger stimulation in seven individuals. 2. Post stimulation cystometry revealed a much lower micronutrient threshold than that obtained during stimulation.
Krebs et al. 2017 Switzerland Post-Test N=111	<p>Population: Median age=50yr (28-77); Gender: males=59; females=52; Etiology: SCI=111; Time since injury=11.7yr; Inclusion criteria: individuals who received sacral intradural deafferentation of S2-S5 and implantation of an intradural anterior root stimulator after laminectomy from L4 to S2.</p> <p>Intervention: Medical records of individuals who underwent sacral deafferentation (SDAF) and implantation of a sacral route stimulator were reviewed. Outcome measures were assessed at 10 different time points post-intervention.</p> <p>Outcome Measures: Max. detrusor pressure (Pdet); detrusor compliance (Dcom);</p>	<ol style="list-style-type: none"> 1. Pdet during stimulation showed a significant decrease over time ($p<0.001$). 2. Men had a significantly higher Pdet during stimulation compared to women ($p<0.001$). 3. There was no significant interaction effect between gender and time on Pdet during stimulation ($p>0.05$). 4. Pdet during the storage phase showed a significant decrease over time ($p<0.001$). 5. Dcom showed a significant increase over time ($p<0.001$). 6. Dcom was not significantly different in males and females ($p>0.05$).
Yoo et al. 2009 USA Post-Test N=7	<p>Population: Age range 22-66 yr; Gender: males=6, females=1; Level of injury: C5-T12.</p> <p>Intervention: Randomized sequence of 6 trials that combined</p>	<ol style="list-style-type: none"> 1. A DE bladder contraction was observed in 6/7 individuals. 2. A BCR was elicited in 5/7 participants

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
	<p>two stimulus amplitudes and three stimulation frequencies of intra-urethral electrical stimulation.</p> <p>Outcome Measures: Distension evoked (DE) bladder contractions; bulbocavernosus reflex (BCR), proximal versus distal urethra activity, and detrusor pressure.</p>	<p>3. Electrical stimulation of the proximal urethra evoked sustained bladder activity in 3/7 participants</p> <p>4. In 2 of the 7 participants, electrical stimulation of the distal urethra evoked excitatory bladder responses.</p> <p>5. P_{det} of proximal urethra was significantly greater than "non-responsive" bladder activity ($p<0.05$)</p> <p>-P_{det} of distal urethra was significantly greater than "non-responsive" bladder activity ($p<0.05$).</p>
Wollner et al. 2016b Switzerland Case Series N=50	<p>Population: Neurogenic lower urinary tract dysfunction; Mean age: 46.3 yr; Gender: males=20, females=30; Level of injury: cervical=16, thoracic=7, lumbar=12, sacral=4; ASIA classification: A=3, B=2, C=11, D=19; Mean time post-injury: 9.5 yr; Injury etiology: spinal cord injury=35, myelomeningocele=2, multiple sclerosis=2, morbus Parkinson=1, other=10.</p> <p>Intervention: Charts were reviewed for individuals who had received sacral neuromodulation (SNM) using bilateral tined leads implanted in the S3 or S4 sacral foramina. Successful test stimulation with >50% symptom improvement and individual satisfaction resulted in individuals receiving permanent implantation.</p> <p>Outcome Measures: Test success, continence, frequency of bladder drainage per 24 hr, pad use in 24 hr, maximum bladder capacity, maximum detrusor pressure, compliance, individual satisfaction, post-void residual, complications.</p>	<p>1. Of the 50 participants undergoing the test phase, 26/39 neurogenic detrusor overactivity (NDO) participants and 9/11 urinary retention participants experienced test success and received permanent implantation.</p> <p>2. There were 8 complications, with 2 infections and 6 technical defects.</p> <p>3. In neurogenic overactive bladder participants, there were significant decreases in frequency of bladder drainage per 24 hr ($p<0.05$) and pad use in 24 hr ($p<0.01$) post-treatment, while there was a significant increase for compliance ($p<0.046$). There were no significant changes in terms of maximum bladder capacity or maximum detrusor pressure.</p> <p>4. For the 26 successful NDO participants, 21 reported complete continence and 5 were incontinent.</p> <p>5. For participants with chronic neurogenic urinary retention, all nine successes were able to void spontaneously and achieve continence. Post-treatment, there was a significant decrease in post void residual, while pad use, frequency of bladder evacuation, maximum bladder capacity, detrusor pressure, and</p>

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
		<p>compliance did not show significant changes.</p> <p>6. Of the 32 participants with SNM use at last follow-up, 21 were very satisfied, 9 were satisfied, 1 was unchanged, and 1 was unsatisfied.</p>
Chinier et al. 2016 France Case Series N=96	<p>Population: Mean age: 36 yr; Gender: males=72, females=24; Level of injury: C7-C8=29, T1-T9=54, T10-L2=13; ASIA classification: A=89, B-D=7; Mean time post-injury: 6.5 yr.</p> <p>Intervention: Records were reviewed for individuals who had received a Brindley neurostimulator implantation.</p> <p>Outcome Measures: Stress incontinence, maximum urethral closure pressure (MUCP).</p>	<ol style="list-style-type: none"> 1. Compared to 93.8% of participants being incontinent prior to treatment, 10.4% experienced stress incontinence at one year post-treatment. 2. Compared to baseline, there was a significant decrease in the mean MUCP at 2-6 mo post-treatment. 3. Incompetent bladder neck ($p<0.001$) and previous urethral surgery ($p=0.003$) were significantly associated with stress incontinence. Age, gender, injury level, compliance, and MUCP were not significant predictors of stress incontinence.
Krebs et al. 2016 Switzerland Case Series N=130	<p>Population: Charcot spinal arthropathy (CSA) group (n=11): Mean age: 36 yr; Gender: males=6, females=5; Level of injury: paraplegia=9, tetraplegia=2; Severity of injury: complete; Mean time post-injury: 13.7 yr.</p> <p>Intervention: Medical records were reviewed for individuals who had underwent sacral deafferentation and sacral anterior root stimulation (SDAF/SARS), also known as the Brindley procedure.</p> <p>Outcome Measures: Occurrence of CSA, time to diagnosis of CSA, stimulation failure or inadequate SARA-driven micturition (SARS dysfunction).</p>	<ol style="list-style-type: none"> 1. The proportion of CSA occurrence was significantly higher in participants with SARS dysfunction (7/41) compared to those without (4/89) ($p=0.036$). 2. The proportion of CSA occurrence was significantly higher in participants with SARS (11/130) compared to those without (17/3735) ($p<0.00001$). 3. CSA occurred a median of 8 yr after SDAF/SARS or 21 yr after spinal cord injury.
Krasmik et al. 2014 Switzerland Case Series N=137	<p>Population: Mean age: 40.0 yr; Gender: males=81, females=56; Level of injury: cervical=53, thoracic=81, lumbar=3; Severity of injury: complete=132, incomplete=5; ASIA classification: A=132, B=4, C=1; Mean time post-injury: 11.6 yr.</p> <p>Intervention: Charts were reviewed for individuals who had underwent sacral deafferentation and sacral anterior root stimulation</p>	<ol style="list-style-type: none"> 1. With a mean follow-up of 14.8 yr, compared to pre-operatively, there were significantly fewer participants with high detrusor pressure ($p<0.001$), low detrusor compliance ($p<0.001$), renal reflux ($p<0.001$), one of more urodynamic risk factor ($p=0.002$), antimuscarinic treatment ($p=0.03$), urinary tract infections

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
	<p>(SDAF/SARS), also known as the Brindley procedure.</p> <p>Outcome Measures: Detrusor pressure >40 cm H₂O or detrusor compliance <20 ml/cm H₂O or renal reflux (deafferentation failure), residual urine >100 mL or stimulator defect (stimulation failure), urinary incontinence, symptomatic urinary tract infection (UTI), urodynamic risk factors, antimuscarinic treatment, autonomic dysreflexia, complications.</p>	<p>(p<0.001), and incontinence (p<0.001).</p> <ol style="list-style-type: none"> There were 17 participants with deafferentation failure, 14 participants with stimulation failure, and 6 participants with deafferentation and stimulation failure. Mean bladder capacity significantly increased (p<0.001) and mean number of symptomatic UTI significantly decreased (p<0.001). There were 84 complications leading to surgical revisions and 43 participants required additional urological interventions.
Lombardi et al. 2014 Italy Case Series N=85	<p>Population: Neurogenic non-obstructive urinary retention (N-NOR); Mean age: 38.8 yr; Gender: males=52, females=33; Severity of injury: incomplete; ASIA classification: C=61, D=22; Etiology of injury: traumatic=62, vascular=3, myelitis=21.</p> <p>Intervention: Data were reviewed for individuals who had undergone the percutaneous first stage of sacral neuromodulation (SNM).</p> <p>Outcome Measures: Success of first stage SNM (responder), first sensation of bladder filling, volume of first sensation of bladder filling per ml, compliance, ability to void, maximum flow rate, detrusor pressure at maximum flow rate (PdetQmax), post void residual (PVR), or maximum urethral closure pressure.</p>	<ol style="list-style-type: none"> At the end of the first stage of SNM, there were 36 responders and 49 non-responders. For non-responders post-treatment, there were no significant differences compared to baseline in terms of first sensation of bladder filling, volume of first sensation of bladder filling per ml, compliance, ability to void, maximum flow rate, PdetQmax, PVR, or maximum urethral closure pressure. For responders post-treatment, there were significant increases for first sensation of bladder filling (p<0.01), ability to void (p<0.01), maximum flow rate (p<0.01), PdetQmax (p<0.01), and PVR (p<0.01). Significant decreases compared to baseline were observed for PVR (p<0.01), and no significant differences were observed in terms of bladder capacity, compliance, or maximum urethral closure pressure. The only significant predictive parameter for first stage SNM success was reported first sensation of bladder filling during cystometric filling at baseline (p=0.02). Complete N-NOR, duration of N-NOR, age

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
		over 40 yr, female gender, ASIA D, and traumatic etiology had no significant effect.
Gurung et al. 2012 England *Follow-up from Khastgir et al. 2003 Case Series N=19	<p>Population: Mean age: 28.9 yr (12-52); Gender: males=12, females=7; Mean follow-up time: 14.7 yr (10.5-20.3); Mean time from injury to surgery: 4.5 yr (0.3-22 yr); Level of injury: Suprasacral=19.</p> <p>Intervention: Augmentation ileocystoplasty (AIC).</p> <p>Outcome Measures: Mean maximum cystometric capacity (MCC), Maximum detrusor pressure (MDP), and quality of life (QoL) questionnaire.</p>	<ol style="list-style-type: none"> 1. The increase in MCC was significant ($p<0.001$). 2. The reduction of MDP was significant ($p<0.001$). 3. QoL questionnaire showed 13/14 were satisfied with the outcome of the procedure, 1 individuals described being 'unhappy', 14 individuals reported no change in sexual function, 2 individuals reported being more constipated in recent years.
Lombardi & Del Popolo 2009 Italy Case Series N=24	<p>Population: Mean age: 46 yr; Gender: males=14, females=10; retrospectively divided into 2 groups - urinary retention group with urodynamic evidence of underactive bladder and overactive bladder syndrome group.</p> <p>Intervention: SCI individuals implanted with a sacral neuromodulation system (Medtronic).</p> <p>Outcome Measures: Voiding symptoms collected with diary (number of voids, voided volume per void, number of urinary leakage episodes, pad use and nocturia for the overactive category, number of clean intermittent self-catheterization (CISC) for retention category) and adverse events collected at 1, 3, 6 mo and every 6 mo thereafter for a mean follow-up period of 60.7 mo (range=18-132 mo).</p>	<ol style="list-style-type: none"> 1. Individuals in the urinary retention group: 2. Increase in catheterized volume per catheterization, mean urinary frequency, mean voided volume, $p<0.05$. 3. Decrease in mean number of CISC, $p<0.05$ 4. Individuals in the overactive bladder syndrome group: 5. Decrease in mean urinary frequency, mean number of urinary incontinence, mean pads used and nocturia, $p<0.05$ 6. Increase in mean voided volume, $p<0.05$ 7. 22 adverse events were reported – most prevalent were change in stimulation sensation ($n=8$), loss of efficacy ($n=4$) and pain/spasticity in leg ($n=3$).
Vastenholt et al. 2003 Netherlands Case Series N=37	<p>Population: SCI: Mean age: 43 yr; Gender: males=32, females=5; Severity of injury: paraplegia=23, tetraplegia=14; Mean time post-injury=87 mo; Mean follow up time=86 mo.</p> <p>Intervention: Long-term follow-up of those implanted with sacral anterior root stimulator.</p> <p>Outcome Measures: Qualliveen questionnaire for quality of life (QoL) and impact of urinary problems, plus questions about effectiveness, side effects, advantages.</p>	<ol style="list-style-type: none"> 1. 32 of 37 still use the stimulator - complete continence for 21 during day and 26 at night. 27 reported an overall improvement in continence. 2. Urinary tract infections (UTIs) decreased with stimulator with majority saying they had >3/yr before and 0-2/yr after. 3. Significant increase in QoL as compared to a SCI reference group reported previously with various methods of management.

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
		<p>4. External technical failures=1/17 yr for cable breaks and 1/38 yr for transmitter defects.</p> <p>5. Internal technical failures=1/66 user-yr.</p> <p>6. Top advantages included reduction of UTI by 68%, increased social life by 54%, and increased continence by 54%.</p>
<p>Katz et al. 1991 USA Case Series N=33</p>	<p>Population: SCI: Mean age: 40 yr; Gender: males=31, females=2; Level of injury: paraplegia=12, tetraplegia=21; Mean time post-injury=83.6 mo.</p> <p>Intervention: Implantation of epidural dorsal spinal cord stimulator at T1 (tetraplegia) or T11-T12 (paraplegia) intended primarily for spasticity relief.</p> <p>Outcome Measures: Urodynamic parameters. Collected prior and 3 mo to 1 yr post-implantation.</p>	<p>1. For the most part, 17 of 23 evaluable individuals had no change in urodynamic values and mean urodynamic parameters showed no change ($p>0.05$).</p> <p>2. 6 of these subjects had changes in lower urinary tract function but these changes were not systematic.</p>
<p>Madersbacher et al. 1982 Austria Case Series N=29</p>	<p>Population: SCI: Age range=8-60 yr; Gender: males=26, females=3; Level of injury: C5-S1; Severity of injury: incomplete; Time post-injury=3 mo.</p> <p>Intervention: Impulse packages applied to a saline filled bladder. Minimum of ~50 stimulations for up to 90 min daily until maximal improvement is attained. Data collected prior to treatment and at un-specified follow-up time.</p> <p>Outcome Measures: Urodynamic assessment, incontinence.</p>	<p>1. No group results reported.</p> <p>2. 17 of 29 became continent, 10 others became socially dry without need for pads and urinals.</p> <p>3. 26 gained perfect bladder sensation. 25 achieved satisfactory bladder contractions.</p> <p>4. 28 had residual urine below 50 cc.</p> <p>5. At one yr, individuals reported a reduced effect.</p>

Summarized Level 5 Evidence Studies:

Sanders et al. (2011) reported that individuals would choose minimally invasive electrode methods to improve bladder function as compared to more invasive methods such as use of the Brindley device (with or without rhizotomy).

Discussion

Sacral neuromodulation or sacral anterior root stimulation combined with sacral deafferentation is the most well studied method of triggering bladder emptying via electrical stimulation. The evidence for these techniques is level 4, with retrospective case series and prospective pre-post study designs (Robinson et al. 1988; Van Kerrebroeck et al. 1996; Van Kerrebroeck et al. 1997; Egon et al. 1998; Creasey et al. 2001; Vastenholt et al. 2003; Kutzenberger et al. 2005; Kutzenberger 2007; Lombardi & Del Popolo 2009; Possover 2009; Krebs et al. 2017). Typical participant

characteristics for these studies include: detrusor overactivity; incomplete bladder emptying and frequently recurrent UTI; incontinence; and vesicoureteric reflux and refractory to conservative treatment. In each of these studies, a large percentage of subjects did become continent and were able to successfully void with these devices, whereas bladder compliance was mostly unsatisfactory with pre-implantation bladder management methods. These findings appear to persist as reports have noted continued improvement with successful continence rates of 73-88% over an average follow-up period up to 8.6 years (Egon et al. 1998; Vastenholt et al. 2003; Kutzenbergen et al. 2005; Kutzenberger 2007; Lombardi & Del Popolo 2009). Of note, Lombardi and Del Popolo (2009) conducted a study that included individuals with underactive bladder (n=13) in addition to those with overactive bladder (n=11) and reported similar results for both groups (i.e., reduction in incontinence and increased voiding volume). However, 30.8% of persons in the underactive bladder group had a loss of efficacy over the follow-up period (mean of 60.7 months) as compared to none in the overactive bladder group.

A systematic review of electrical nerve stimulation, based on 20 published studies (of which 14 used the Brindley device), supports electrical nerve stimulation as an option for bladder management in SCI individuals despite a lack of randomized controlled trials to determine optimal efficacy. Studies already mentioned above that overlapped with the 20 studies synthesized in Ren et al (2016) included Van Kerrebroeck et al. 2016, Egon et al. 1998, Creasey et al. 2001, Kutzenberger et al. 2005, and Lombardi & Del Popolo 2009.

Several of these investigators reported a significant decrease in UTIs among participants, even after long-term use (Van Kerrebroeck et al. 1996; Egon et al. 1998; Vastenholt et al. 2003; Creasey et al. 2001; Kutzenberger et al. 2005; Kutzenberger 2007; Martens et al. 2011) and autonomic dysreflexia (Van Kerrebroeck et al. 1996; Egon et al. 1998; Creasey et al. 2001; Kutzenberger et al. 2005; Kutzenberger 2007; Possover 2009). Some investigators performed satisfaction surveys and reported that most participants remained satisfied with the device, even after many years. In particular, Vastenholt et al. (2003) and Martens et al. (2011) gave a Qualiveen questionnaire for assessing bladder health-related QoL and impact of urinary problems. In the study by Vastenholt et al. (2003), the top three advantages noted by stimulator users was a reduction in UTIs (68% reporting), improved social life (54%) and improved continence (54%). Martens et al. (2011) reported improved QoL scores (Qualiveen and SF-36), a significantly better Specific Impact of Urinary Problems score and continence rate, in addition to reduced UTIs for individuals undergoing a Brindley procedure. For individuals with incomplete SCI who are refractory to pharmacological treatments for neurogenic non-obstructive urinary retention, SNM is a viable “mini-invasive” option based on statistically significant Qmax increased and decreased post-void residual volume ($p<0.01$). Of the 33% (11/34) of “inconstant responders”, subsequent implants to additional sacral roots were responsible for a return to the responder state (Lombardi et al. 2014).

Percutaneous bipolar radiofrequency ablation of sacral nerves S2 and S3 was reported to reduce urinary incontinence and improve QoL in 10 individuals for at least 2 years (Jo et al. 2016), based on a pre-post study design. Similar findings were

reported in another RCT with 10 individuals even though pre/post intervention differences in maximum cystoetric capacity and maximum detrusor pressure during filling were not significantly different between treatment and control groups (Kim et al. 2015).

In an RCT that compared the effectiveness of pulsed electromagnetic field therapy (PEMFT) to TENS on bladder dysfunction after SCI, 80 individuals were randomized to two groups (Fergany et al., 2017). The TENS group received 20 mins of treatment three times a week for 20 sessions, and group B received PEMFT for 20 mins for 20 sessions (Fergany et al., 2017). The authors found that both groups showed significant improvement in bladder capacity and urinary flow with the PEMFT showing significantly greater improvement than the TENS group (Fergany et al., 2017).

Bladder training with transcutaneous electrical nerve stimulation (TENS) compared to those randomized to pelvic floor biofeedback (PFBFB) revealed significant improvements in bladder volume at first desire to void ($p=0.001$), maximum cystometric capacity ($p=0.001$), detrusor pressure at maximum flow rate ($p=0.02$), and maximum flow rate ($p=0.001$). Only maximum flow rate improved significantly ($p=0.042$) with PFBFB. (Shendy et al. 2015).

Another non-invasive option, percutaneous tibial nerve stimulation (PTNS) was compared to solifenancin succinate (SS) in a randomized study that showed equivocal efficacy ($p<0.05$) for increased volume per catheterization, total daily leakage volume and I-QoL without changes in fluid intake, ICI frequency (Chen et al. 2015). A pre-post study of 10 individuals comparing PTNS to dorsal penile nerve (DPN) stimulation also showed equivocal bladder function improvements (Ojha et al. 2015). An advantage of PTNS was avoidance of dry mouth experienced by the SS group where 2 individuals subsequently discontinued SS treatment. (Chen et al. 2015)

Pre and post assessments of patterned afferent stimulation of sacral dermatomes did not reveal suppression of urethral sphincter reflexes in individuals with SCI despite beneficial results recorded in animal studies (McCoin et al. 2015).

Although invasive, sacral neuromodulation (SNM) can be tested for bladder management efficacy before permanent stimulator implantation is considered. Of the 50 individual charts reviewed by Wollner et al. (2016b), records showed that 31 were still satisfied or very satisfied with the device at last followup of at least 6 months post-transplantation (1 individual was reported as unsatisfied). Furthermore, selection of preoperative condition of the striated sphincter and bladder neck were shown to be key factors in postoperative incontinence risk assessment (Chinier et al 2016). Spinal instability is another negative predictor of sacral deafferentation (SDAF) and sacral anterior root stimulation (SARS) success as shown in a retrospective analysis of 130 charts yielding 4 times greater likelihood for developing Charcot spinal arthropathy (CSA) after SDAF/SARS. Nevertheless, SDAF/SARS remains an effective treatment option for neurogenic lower urinary tract dysfunction (NLUTD) as long as individual factors like the social environment, staff education, or handling

ability is considered when bladder management options are discussed for individuals with a complete SCI (Krasnik et al. 2014).

Posterior rhizotomy was performed in addition to implantation of a sacral root stimulator in most reports (Castano-Botero et al. 2016; Creasey et al. 2001; Van Kerrebroeck et al. 1996; Egon et al. 1998; Kutzenberger et al. 2005; Kutzenberger 2007; Martens et al. 2011). The stated benefit of this deafferentation is the abolition of dyssynergia and high intravesical pressures, reduced risk of hydronephrosis and reflex incontinence. The negative cost is the loss of bowel reflexes and reflex erections. Nonetheless, most authors report improved bowel management in many of their individuals (since the stimulator is activated during the bowel routine), and a great improvement in autonomic dysreflexia (Van Kerrebroeck et al. 1996; Egon et al. 1998; Creasey et al. 2001; Kutzenberger 2007). In the study by Robinson et al. (1988) sphincterotomies were performed on three individuals with persistent reflex incontinence, and/or upper tract deterioration, while three individuals were given sphincterotomies pre-implantation to prevent anticipated autonomic dysreflexia. Thus, sphincterotomy has shown some success as an option for producing some of the benefits attributed to posterior rhizotomy.

A primary purpose of posterior rhizotomy is the attainment of an areflexic bladder, thus allowing a more compliant reservoir with the potential for greater bladder capacity under lower pressure. Results from all investigations measuring capacity have shown this to be true with significant increases in bladder capacity at lower pressures associated with combined sacral anterior root stimulation and sacral deafferentation (Creasey et al. 2001; Van Kerrebroeck et al. 1996; Egon et al. 1998; Kutzenberger et al. 2005; Kutzenberger et al. 2007). Several investigations have been conducted using different approaches aimed at conditioning the bladder with different forms of stimulation so as to achieve the same effect of increasing bladder capacity under low-pressure conditions in persons with SCI with overactive bladder and intact dorsal sacral nerves (Madersbacher et al. 1982; Kirkham et al. 2001; Kirkham et al. 2002; Bycroft et al. 2004; Hansen et al. 2005; Fergany et al. 2017). Additionally, rhizotomy alone (without a stimulator) has shown to result in higher QoL scores over matched controls (Martens et al. 2011).

Of note, Kirkham et al. (2002) implanted the same sacral anterior root stimulator used in the majority of investigations (i.e., Finetech-Brindley stimulator) in a small group of individuals (n=5) without posterior rhizotomies and therefore configured the stimulator to deliver both anterior and posterior sacral root stimulation. The conditioning posterior root stimulation was effective in producing increased bladder capacity in 3 of 5 subjects and the anterior root stimulation was able to elicit bladder emptying, but with significant residual volumes. It is important to note that the two remaining subjects sustained posterior root damage and were not included in post-operative testing. This preliminary trial suggests there is a possibility of achieving success with sacral anterior root stimulation without necessitating the destructive posterior root ablation. Krebs et al. (2017) reviewed medical charts of individuals who received sacral deafferentation and implantation of an anterior sacral root stimulator with no accompanying posterior rhizotomy. The authors found that maximum

detrusor pressure had a significant decrease over time with detrusor compliance showing a significant increase (Krebs et al. 2017).

Others have conducted more mechanistic investigations of conditioning stimuli delivered to the thoracolumbar, pudendal, dorsal penile or clitoral nerve (Gad et al., 2018; Opisso et al. 2013; Martens 2011; Goldman et al. 2008; Opisso et al. 2008; Spinelli et al. 2005; Previnaire et al. 1996; Kirkham et al. 2001; Wheeler et al. 1994; Bourbeau et al., 2018; Brose et al. 2018) or magnetic stimulation applied over the sacral nerves (Bycroft et al. 2004; Fergany et al., 2017) and achieved demonstrations of detrusor inhibition or increased bladder capacity under lower pressure. Authors looked at stimulation of the thoracolumbar area of spine as opposed to sacral stimulation, and found significant improvements in bladder capacity and detrusor sphincter coordination during voiding (Gad et al. 2018). A small (n=11; Opisso et al. 2013) study of three days of dorsal genital nerve stimulation demonstrated the feasibility of at home, self-administered electrical stimulation to increase bladder capacities and void volumes. Previous work by this group (Opisso et al. 2008) showed that training towards self-administration versus automated stimulation was effective in select individuals to achieve suppression of undesired detrusor contractions and ultimately increased bladder capacity. Similar results were achieved with conditional stimulation, using implanted or surface electrodes on the dorsal genital nerve to suppress involuntary detrusor contractions (Martens et al. 2011; Horvath et al. 2009; Dalmose et al. 2003; Bourbeau et al., 2018). In a small pilot study of GNS, Bourbeau et al. (2018) showed a significant decrease in incontinence episodes. The same authors followed up with a larger sample size and found that GNS improved bladder capacity as well (Brose et al. 2018). However, further developmental work on larger groups of individuals in more rigorous study designs would be required before these or modified approaches could be incorporated clinically as an approach that permits bladder stimulation in the absence of deafferentation. For example, semi-conditional stimulation, which conserves battery life, was also shown to be significantly effective for detrusor overactivity inhibition to increase bladder volume in individuals with SCI (Lee et al. 2011). External stimulators, electrodes, cables and tolerance to electrical stimulation in the presence of preserved sensation are considered by individuals to be hindrances to acceptability of this intervention (Opisso et al. 2013).

Knight et al. (2018) investigated a novel wearable device to control detrusor overactivity in eight SCI subjects using conditional neuromodulation. Transrectal stimulation was delivered through the device in response to simultaneously recorded external anal sphincter (EAS) contraction as a marker for neurogenic detrusor overactivity (NDO). The effect of conditional neuromodulation on bladder capacity and maximum detrusor pressure was investigated in addition to reliability of dyssynergic sphincter contraction as a marker for NDO. Conditional neuromodulation through the novel device showed a statistically significant increase in bladder capacity and reduction in maximum detrusor pressure in 75% of test subjects. EAS activity was a reliable surrogate for detection of NDO. This is the first study to date that shows conditional neuromodulation can be delivered and triggered via a single biocompatible device placed in the anal canal.

Lee et al. (2005) reported on a group of seven subjects with SCI where transcutaneous versus percutaneous electrical stimulation of the DPN was compared for effectiveness of bladder storage functionality. Although the percutaneous method was superior to the limitations of surface electrodes (e.g., daily donning/doffing, consistent placement and impedance) used for the transcutaneous method, the materials available for percutaneous electrodes are not yet sufficiently durable for long term use. Furthermore, percutaneous stimulation electrodes require precise positioning and potentially introduce a source of infection risk.

In a subsequent report, Lee et al. (2012) presented data from a small (n=6) group of males with SCI and complicated bladder function, using surface electrical stimulation to modulate bladder function. The stimulation paradigm consisted of initial current delivery to the dorsal penile nerve voluntarily triggered after perception of the first bladder contraction and followed by cyclic on-off stimulation parameters pre-determined during a 2-3 day admission to rehabilitation. Vesicoureteral reflux resolved in four cases and bladder wall deformity improved in 5 of the 6 cases, after treatment. Despite the improvement to bladder capacity and compliance, only short-term clinical efficacy was reported. To be a viable longer-term viable solution, not only would long-term follow-up data be required but also individual reported correlates would be required given the potential technical difficulties of this semiconditional stimulation treatment. Dexterity requirements for those with tetraplegia and interference from urine and sweat are among the possible feasibility and acceptability deterrents for this new treatment option.

The importance of current strength of pudendal nerve stimulation for short-term detrusor hyperreflexia inhibition has been explored in chronic suprasacral SCI (Previnaire et al. 1996; Wheeler et al. 1992; Vodusek et al. 1986). During cystometries, current strength at 2.0-3.5 times the bulbocavernosus reflex threshold was required to achieve functional inhibition. However, the subsequent study by Previnaire et al. (1998) determined that daily (i.e., 20 min/day, 5x/wk for 4 wk) stimulation at strengths equal to or above 99 mA applied to the pudendal nerve did not achieve efficacious inhibition of detrusor hyperreflexia.

Yoo et al. (2009) investigated the utility of an intraurethral stimulating catheter to selectively activate the proximal or distal segments of the urethra in 7 individuals with overactive bladder activity secondary to SCI. Although the study confirmed the existence of the pudendal nerve portion of the micturition reflex, further study of the stimulation parameters is required to be able to overcome detrusor dyssynergia and achieve bladder emptying.

Further developmental work would be required before these or modified approaches could be incorporated clinically to improve bladder function when afferent connectivity is intact. Recently, Possover et al. (2009) reported a new surgical technique applied to persons with SCI involving laparoscopic transperitoneal implantation of neural electrodes to pelveoabdominal nerves, which they have termed the “LION procedure” (i.e., Laparoscopic Implantation of Neuroprosthesis). With this method, which is far less invasive than the traditional

dorsal approach for stimulator implantation, the risk associated with immediate or long-term complications (e.g., meningitis, encephalitis, infections) is significantly reduced. In addition, the destructive procedures of rhizotomy and laminectomy are not necessary. Possover (2009) conducted this procedure on a series of eight persons previously having an explanted Brindley-Finotech stimulator, six of whom had viable sacral nerves. This resulted in adequate detrusor contractions enabling complete bladder emptying still present at follow-up (3-27 months). Individuals undergoing this procedure returned home after only a 3-5 day hospital stay and there were no reported complications.

Another approach has been to apply stimulation to the bladder itself, most appropriately done during initial rehabilitation (Madersbacher et al. 1982; Radziszewski et al. 2009). Radziszewski et al. (2009) applied daily 15-minute bouts of transcutaneous electrical stimulation directly to the bladder for 30 days in individuals seen by the Rehabilitation Department of a Military Hospital (time since injury not reported). These authors demonstrated significant increases in bladder capacity and peak flow velocity and a significant decrease in residual urine volume immediately following stimulation and persisting at two months follow-up compared to baseline. Continued efficacy was reported by the same group in 2013 (Radziszewski et al. 2013).

A similar approach was reported by Madersbacher et al. (1982) in which stimulation, in the form of impulse packages applied to a saline filled bladder, was administered over a variable treatment period after which the treatment effect persisted up to one year when most subjects reported a definite waning of the benefits. Unlike other studies involving sacral neuromodulation, this was conducted on those more recently injured with 17 of 29 becoming continent and 10 others becoming socially dry without need for pads and urinals. This study involved a case series design but would have been much more powerful with the inclusion of a control group, given the potential for natural bladder recovery in individuals with more recent injuries. Further research would also be needed to examine safety information related to bladder pressure during voiding, and follow-up of any potential renal changes before considering this intervention.

Sievert et al. (2010) also capitalized on the concept of neural plasticity through early (upon confirmation of bladder acontractility) sacral neuromodulation and reported no instances of detrusor overactivity and urinary incontinence with normal bladder capacity, reduced UTI rates and improved bowel and erectile functionality without nerve damage. Although follow-up was reported for greater than 2 years, further investigations are needed to augment the small sample size (n=10).

Other investigators have examined the effects on the urinary system associated with stimulation directed towards other targets. For example, Katz et al. (1991) tested the effect of epidural dorsal spinal cord stimulation, intended primarily for spasticity relief, at T1 (for those with tetraplegia) or T11-T12 (for those with paraplegia). Wheeler et al. (1986) investigated the effect of 4 to 8 weeks of quadriceps muscle reconditioning by surface electrical stimulation (FES) bilaterally, intended primarily for strength and spasticity. In each case, these techniques had marginal effects on

bladder function. However, in the latter experiment it was noted that some subjects did achieve beneficial changes in bladder function and that these tended to be most noticeable in the same subjects that showed positive improvements in strength and spasticity.

Conclusions

There is level 4 evidence (from six pre-post studies, five case series, and one observational study) that ongoing use of sacral anterior root stimulation (accompanied in most cases by posterior sacral rhizotomy) is an effective method of bladder emptying resulting in reduced incontinence for the majority of those implanted. This is associated with increased bladder capacity and reduced post-void residual volume.

There is level 1b evidence (from one RCT; Fergany et al. 2017) that PEMFT may improve bladder capacity and urinary flow more than TENS when stimulating the sacral roots.

There is level 4 evidence (from four pre-post studies and two case series study) that sacral anterior root stimulation (accompanied in most cases by posterior sacral rhizotomy) may be associated with reducing UTIs and autonomic dysreflexia.

There is level 4 evidence (from one pre-post study and one case series study; Madersbacher et al. 1982; Radziszewski et al. 2009) that direct bladder stimulation may result in reduced incontinence, increased bladder capacity and reduced residual volumes (with two year efficacy data from one study group) but requires further study as to its potential for larger scale clinical use.

There is level 4 evidence (from various single studies) that other forms of neuroanatomically-related stimulation (e.g., electrical conditioning stimulation to posterior sacral, thoracolumbar, anal, pudendal, dorsal penile or clitoral nerve or surface magnetic sacral stimulation) may result in increased bladder capacity but require further study as to their potential clinical use. These non- or minimally invasive techniques are preferred by individuals over more invasive methods such as use of the Brindley device, with or without rhizotomy.

There is level 2 evidence (from a one prospective controlled trial; Sievert et al. 2010) that reports early sacral neuromodulation may improve management of lower urinary tract dysfunction. Further investigation is required to confirm the results and substantiate the hypothesis of resultant plastic changes of the brain.

There is level 4 evidence (from one case series study; Katz et al. 1991) that epidural dorsal spinal cord stimulation at T1 or T11 originally intended for reducing muscle spasticity may have little effect on bladder function.

There is level 4 evidence (from one pre-post study; Wheeler et al. 1986) that a program of functional electrical stimulation exercise involving the quadriceps

muscle originally intended for enhancing muscle function and reducing muscle spasticity has only marginal (if any) effects on bladder function.

Sacral anterior root stimulation (accompanied in most cases by posterior sacral rhizotomy) enhances bladder function and is an effective bladder management technique through the program (surgery and follow-up) requires significant expertise.

Direct bladder stimulation may be effective in reducing incontinence and increasing bladder capacity but requires further study.

Pulsed electromagnetic stimulation may be more effective than transcutaneous electrical nerve stimulation when stimulating the sacral roots for improving bladder capacity and urinary flow.

Posterior sacral, thoracolumbar, pudendal, dorsal penile or clitoral nerve stimulation may be effective to increase bladder capacity but requires further study.

Posterior sacral, pudendal, dorsal penile or clitoral nerve stimulation may be effective to increase bladder capacity but requires further study.

Early sacral neural modulation may improve management of lower urinary tract dysfunction but requires further study.

Epidural dorsal spinal cord stimulation (T1 or T11) and functional electrical stimulation of the lower limbs are not effective in enhancing bladder function.

4.4.8 Sphincterotomy, Artificial Sphincters, Stents and Related Approaches for Bladder Emptying

Transurethral sphincterotomy and related procedures, such as insertion of artificial sphincters, sphincteric stents or balloon dilation of the external urinary sphincter, provide a means to overcome persistent dysynergia (Chancellor et al. 1999; Juma et al. 1995; Chancellor et al. 1993a; Chancellor et al. 1993b; Patki et al. 2006; Seoane-Rodriguez et al. 2007). Often these are performed when intermittent catheterization is not an option because of a lack of manual dexterity and when more conservative options have proven unsuccessful (Chancellor et al. 1999; Juma et al. 1995). With the success of transvaginal tape implantation in individuals of non-neurogenic stress incontinence, Pannek et al. (2012) sought to evaluate its use for neurogenic stress incontinence in females with SCI but results were unfavourable.

Table 19 Sphincterotomy, Intraurethral Stent Insertion and Related Approaches for Bladder Emptying

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
Chancellor et al. 1999 USA RCT PEDro=5 N=57	<p>Population: SCI with detrusor-external sphincter dyssynergia=26, sphincterotomy=31: Mean age: 34.5 yr versus 39.1 yr; Gender: males=57; Level of injury: cervical=40, thoracic=17; Mean time post-injury=8.7 yr versus 8.0 yr.</p> <p>Intervention: Sphincterotomy versus placement of a sphincteric stent (UroLume prosthesis).</p> <p>Outcome Measures: Urodynamic parameters (maximum detrusor pressure, bladder capacity, post-void residual urine volume), length of hospitalization, quality of life (QoL). Collected pre-operatively and 3, 6, 12 and 24 mo post-op.</p>	<ol style="list-style-type: none"> 1. Significant ↓ in detrusor pressure ($p<0.05$) relative to baseline with both treatments and no difference between sphincterotomy and stent at any time. 2. No significant change in bladder capacity with either treatment at any time. 3. Significant ↓ in post-void residual volume ($p<0.05$) at some time points but not others – no difference between treatments. 4. The need for catheterization, initially required in 50% of the sphincterotomy group and 71% of the stent group, was reduced to just 3, 4, 1, & 1 and 1, 0, 1 & 2 individuals respectively at each follow-up period. 5. There was little difference in subjective assessment of impact of bladder function on QoL or in the incidence of complications between the treatment groups. 6. Those in the stent group spent less time in the hospital for the procedure ($p=0.035$).
El-Azab et al. 2014 Egypt Prospective Controlled Trial N=40	<p>Population: Tension-free vaginal tape (TVT group): Median age: 34 yr; Gender: female; Injury etiology: spinal cord injury=16, myelomeningocele=3, spinal cord tumor=1. Pubovaginal sling (PVS group): Median age: 36 yr; Gender: female; Injury etiology: spinal cord injury=14, myelomeningocele=4, lumbar disc surgery=2.</p> <p>Intervention: Individuals with neurogenic stress urinary incontinence received TVT (n=20) or PVS (n=20).</p> <p>Outcome Measures: Time to failure, Urogenital Distress Inventory Short Form-6 (UDI-6), Incontinence Impact Questionnaire Short Form-7 (IIQ-7), voiding dysfunction, post-void residual urine volume (PVR), urge urinary incontinence (UUI), low</p>	<ol style="list-style-type: none"> 1. Four participants in TVT group and three participants in PVS group had objective treatment failure at their last follow-up. The time to treatment failure was not significantly different between groups. 2. Both groups had significant decreases in UDI-6 and IIQ-7 after treatment. The UDI sub-item of frequency was significantly more reduced in the PVS group ($p=0.012$) and the total IIQ-7 was significantly more reduced in the IIQ-7 group. 3. After treatment, the median PVR was significantly lower in the TVT group compared to the PVS group.

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
	compliance, unstable bladder contractions, complications.	<ol style="list-style-type: none"> 4. All participants in PVS group had voiding dysfunction compared to only 12 participants in TVT group. 5. The prevalence of de novo UUI was significantly higher after TVT than after PVS. 6. At one year follow-up, two TVT participants had low compliance and four had unstable bladder contractions, compared to two PVS participants with unstable bladder contractions. 7. Complications were infrequent for both groups, with only one TVT participant experiencing vaginal mesh erosion. The overall reoperation rate for failure was 20% in TVT and 15% in PVS.
Rivas et al. 1994 USA Prospective Controlled Trial N=46	<p>Population: Mean age: 34 yr (range 18-58); Gender: males=46, females=0. All individuals had detrusor-external sphincter dyssynergia and voiding pressure >60 mm H2O.</p> <p>Intervention: Individuals who chose endoluminal urethral sphincter prosthesis (Urolome; n=26) were compared to those who chose conventional external sphincterotomy (n=20). Subjects were followed-up 6-20 mo.</p> <p>Outcome Measures: Voiding pressure, residual urine volume, cystometric capacity, complications.</p>	<ol style="list-style-type: none"> 1. After both interventions, similar results were achieved: voiding pressure dropped at 6 mo and 12 mo ($p<0.001$), residual urine volume dropped by 12 mo ($p<0.001$) and cystometric capacity remained constant ($p>0.05$). 2. Prosthesis placement was associated with a significantly shorter operation, length of hospitalization, lower hospitalization cost, and less bleeding ($p<0.01$ for all) than sphincterotomy. 3. The complications of stent insertion were device migration ($n = 4$) and secondary bladder neck obstruction ($n = 2$); one individual with continuing reflux required bilateral ureteral implantation. 4. The complications of sphincterotomy were bleeding necessitating transfusion ($n = 2$), recurrent obstruction ($n = 2$), and erectile dysfunction ($n = 1$).
Hobson & Tooms 1992 USA Prospective Controlled Trial N=22	<p>Population: SCI=12; Level of injury: paraplegia=7, tetraplegia=5, Able-bodied=10.</p> <p>Intervention: Radiographic views of spinal/pelvic postural alignment at three different postures, including: neutral sitting (PIM), trunk bending</p>	<ol style="list-style-type: none"> 1. Person with SCI will sit in PIM with pelvis tilted 15° more than non-injured individuals. 2. P2 causes forward rotation of pelvis (8° in able-bodied, 12° in SCI).

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
	right 15° (PIR), and forward trunk flexion 30° (P2). Outcome Measures: Spinal and pelvic alignment.	<ol style="list-style-type: none"> 3. PIM posture with 100° reclined backrest causes lordotic angle of 26° in SCI, and 22° in able-bodied (not significant). 4. In PIM posterior pelvic tilt causes 4cm anterior displacement of ischial tuberosities compared to able-bodied. 5. P2 causes ischial tuberosities to move posteriorly (2.7cm for SCI, 1.6cm for able-bodied). Difference is insignificant between groups.
Ke & Kuo 2010 Taiwan Pre-Post N=22	<p>Population: Mean age at diagnosis of bladder neck dysfunction (BND)=46.7 yr; Gender: males=19, females=3; Severity of injury: ASIA scale- A=11; B=4; C=4; D=3; Level of injury- C=13; T=9</p> <p>Intervention: Transurethral Incision of the Bladder Neck (TUI-BN)</p> <p>Outcome Measures: Urodynamic parameters, complications</p>	<ol style="list-style-type: none"> 1. 9 individuals reported spontaneous voiding after catheter removal postoperatively. Urinary retention was reported in 3 individuals. 2. 19 individuals reported an open urethral sphincter during voiding after the surgery. 3. Clinical signs of detrusor-external sphincter dyssynergia disappeared in 6 individuals and the degree of autonomic dysreflexia improved in 15 individuals. 4. 18 individuals reported satisfactory improvement in QoL index post-surgery. No complication was reported.
Bersch et al. 2009 Switzerland Pre-Post N=51	<p>Population: Gender: males=37, females=14; SCI: 37; Level of injury: C=4, T=25, L=22; Meningomyelocele=8; Other=6; Mean follow-up time=95.9 mo</p> <p>Intervention: Implantation of the modified artificial sphincter</p> <p>Outcome Measures: Subjective and objective cure rates</p>	<ol style="list-style-type: none"> 1. 36 individuals were objectively and subjectively cured; 46 became completely continent in daily living. 2. Median bladder capacity was 465mL; median detrusor compliance was 41.7 mL/cm H₂O. 3. 16 individuals reported 18 revisions, only one implant need to be permanently removed.
Mehta & Tophill 2006 UK Pre-Post 29	<p>Population: SCI with detrusor-external sphincter dyssynergia; Mean age: 45 yr; Gender: males=29; Level of injury: paraplegic=12, tetraplegic=17; mean time post-injury=12.8 yr.</p> <p>Intervention: Memokath stents were placed in men with suprasacral SCI.</p> <p>Outcome Measures: Effectiveness, complications. Mean follow-up of 21 mo (0-47 mo).</p>	<ol style="list-style-type: none"> 1. Initially all individuals found memokath to be effective in preventing incontinence. 2. At the last follow-up, 30 of 33 stents had been removed and 23 of these were due to complications. 3. The most common causes of stent removal included: 4. Persistent haematuria in 3 individuals.

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
		<ol style="list-style-type: none"> Urinary tract infections (UTIs) in 4 (early) and 6 (later). Acute retention in 2. Migration in 7. Stent blockage by encrustation or prostatic in growth in 14.
Chancellor et al. 1995 USA Pre-Post N=41	<p>Population: SCI with overactive bladder with detrusor-external sphincter dyssynergia; Mean age: 35.7 yr; Gender: males=41; Level of injury: cervical=34.</p> <p>Intervention: Placement of a sphincter stent (UroLume). Several stent lengths were used: 2, 2.5, and 3 cm.</p> <p>Outcome Measures: Voiding pressure, residual urine, and bladder capacity were measured at 3, 6, 12, and 24 mo although other follow-up occurred up to 44 mo (mean 18 mo).</p>	<ol style="list-style-type: none"> All subjects achieved spontaneous reflex voiding without incontinence. Voiding pressures significantly decreased from 77cm H₂O preoperatively to 35cm H₂O at 12 mo and 33cm H₂O at 24 mo after stent insertion (p=0.001). Post-void residual urinary volume decreased from 202mL preinsertion to 64mL at 24 mo, (p=0.001) postinsertion. No significant difference was seen in maximum cystometric capacity before and after insertion. No significant changes in any of the urodynamic parameters were seen after 24 mo of follow up between individuals with and those without previous external sphincterotomy. Hemorrhage requiring blood transfusion, obstructive hyperplastic epithelial overgrowth, stent encrustation or stone formation, nor soft tissue erosion occurred in any individuals. Erectile function was not affected. Complete stent epithelialization was seen in 34 individuals in just 6 mo. Stent repositioning or removal was required in 3 individuals in the first mo and 2 individuals in one yr.
Juma et al. 1995 Pre-Post N=63	<p>Population: SCI: Mean age: 53 yr; Level of injury: cervical=32, thoracic=25, lumbar=6; Severity of injury: complete=32, incomplete=32; Mean time post-injury=27 yr; Mean follow-up since last sphincterotomy=11 yr; Mean number of sphincterotomies=1.74.</p>	<ol style="list-style-type: none"> No statistical comparisons reported 25/63 had upper tract pathology (12 renal calculi, 11 renal scarring, 1 atrophic kidney, 1 renal cyst). 19 of these were deemed significant. Risk of significant upper tract complications in presence or

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
	<p>Intervention: Follow-up evaluation of those having sphincterotomy.</p> <p>Outcome Measures: Complications since sphincterotomy as determined by following: urinalysis, urine culture, urinary tract infection (UTI), urea, creatine levels, intravenous pyelogram (IVP), renal ultrasound, urodynamics, cystoscopy and voiding cystourethrogram (as indicated). Collected at follow-up at mean of 11 (2-30) yr since last sphincterotomy.</p>	<p>absence of bacteria was 38% and 13% respectively.</p> <ol style="list-style-type: none"> 30/63 had lower tract complications (5 bladder calculi, 10 recurrent UTI, 3 urethral diverticula, 6 urethral stricture or bladder neck stenosis and 6 recurrent epididymitis). Risk for lower tract complications ↑ with ↑ in leak point pressure; 50% for those with leak point pressure of >70cm H₂O; reduced to 25% when leak point pressure of <30 cm H₂O. Mean post-void residual remained high (496mL).
Abdill et al. 1994 USA Pre-Post N=25	<p>Population: SCI with detrusor-external sphincter dyssynergia; Mean age: 32.8 yr; Gender: males=25; Level of injury: paraplegic=2, tetraplegic=23; Mean time since injury=7.2 yr.</p> <p>Intervention: Surgical insertion of a wire mesh stent (UroLume).</p> <p>Outcome Measures: Bladder capacity, residual urine volume, and voiding pressure. Measures were taken at 1, 3, 6, and 12 mo post operation.</p>	<ol style="list-style-type: none"> All subjects achieved spontaneous reflex voiding without incontinence and were managed with condom catheterization. Significant decrease was seen postoperatively in: Voiding pressure ($p<0.001$). Residual urine volume ($p<0.01$). No statistical difference was seen in bladder capacity after stent insertion. Complications included hydronephrosis and reflux which did not resolve in one individual and had to undergo bilateral urethral, reimplantation which resulted in a urinary tract infection, and migration of sphincter prosthesis was seen in 3 individuals.
Chancellor et al. 1993b USA Pre-Post N=17	<p>Population: MS=1, SCI=16; Mean age: 34.7 yr; Gender: males=17, females=0; Level of injury: paraplegia=4, tetraplegia=13; Mean time post-injury=13 yr.</p> <p>Intervention: Transurethral balloon dilation of external urinary sphincter.</p> <p>Outcome Measures: Urodynamic parameters (voiding pressure, bladder capacity, post-void residual urine volume), cystoscopy, UTIs, autonomic dysreflexia and monitoring of renal and erectile function. Collected prior and 3, 6, 12 mo post procedure.</p>	<ol style="list-style-type: none"> Of all 17 individuals previously managed by indwelling Foley catheter, 15 now used condom catheters and 2 voided on their own. Significant ↓ in voiding pressure ($p=0.008$) relative to baseline at all follow-up times. No change in bladder capacity ($p=0.30$) at any follow-up time. Significant ↓ in post-void residual volume ($p<0.05$) at all follow-up times. Positive urine cultures (i.e., UTI) in 15/17 prior to surgery but only in 5,

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
		<p>8 and 4 of the individuals at 3, 6 and 12 mo respectively.</p> <ol style="list-style-type: none"> Subjective autonomic dysreflexia improved in all 9 who had previously complained of this. Pre-existing hydronephrosis in 2 resolved. 3 had subjectively improved erectile function. Post-procedural complications included bleeding (1), development of new obstructions (2), stricture (1).
Chancellor et al. 1993c USA Pre-Post N=25	<p>Population: SCI: Mean age: 32.8 yr; Gender: males=25; Level of injury: paraplegia=2, tetraplegia=23; Mean time post-injury=7.2 yr.</p> <p>Intervention: Insertion of a sphincteric stent (UroLome prosthesis).</p> <p>Outcome Measures: Urodynamic parameters (voiding pressure, bladder capacity, post-void residual urine volume) and various complications. Collected pre-operatively and 3, 6, 12 mo post-op.</p>	<ol style="list-style-type: none"> Significant ↓ in voiding pressure ($p<0.001$) relative to baseline at all follow-up times. No significant change in bladder capacity ($p=0.57$) at any follow-up time. Significant ↓ in post-void residual volume ($p<0.01$) at all follow-up times. Positive urine cultures (i.e., UTI) occurred in 22 of 25 individuals prior to surgery but only in 9, 11 and 4 of the individuals at 3, 6 and 12 mo respectively. Subjective autonomic dysreflexia improved in all 19 who had previously complained of this. Pre-existing hydronephrosis in 5 individuals resolved in 4.
Chartier-Kastler et al. 2011 France Post-test N=51	<p>Population: mean age: 35 yr (18-58 yr); Gender: male=51, female=0; SCI=35; Myelomeningocele=16; Mean follow-up time: 83 mo (6-208 mo); Mean LOS=14.7 d.</p> <p>Intervention: Artificial urinary sphincter insertion.</p> <p>Outcome Measures: Morbidity, adverse events, removal rate of artificial urinary sphincter (AUS).</p>	<ol style="list-style-type: none"> The study reported 33 complications in 24 individuals which required a new procedure. The average time before refitting was 74 mo. Five infections (which led to device removal) and five erosions were observed. At the end of the study, 15 individuals had dropped out, 11 had a working AUS during study period. The average AUS lifespan was 88 mo. The most common complication was early postoperative refitting to adjust cuff size.
Losco et al. 2015 United Kingdom Case Series N=27	<p>Population: Mean age: 56 yr; Gender: female; Level of injury: above T12=2, T12 and below=22, sacrectomy=3.</p>	<ol style="list-style-type: none"> At mean follow-up period of 5.2 yr, 22 participants were dry and one participant was happy with the improvement.

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
	<p>Intervention: Records were reviewed for those with neurogenic stress urinary incontinence who had received placement of mid-urethral synthetic transobturator tapes.</p> <p>Outcome Measures: Complete correction of stress incontinence without the need to wear incontinence pads (Dry), individual satisfaction, change in bladder management, complications, occurrence of de novo overactive bladder (OAB).</p>	<ol style="list-style-type: none"> 2. Twenty-five participants had no change in bladder management and two required clean intermittent self-catheterization. 3. Two participants developed de novo OAB, three participants developed transient thigh pain, and no participants had bladder injuries, vaginal injuries, or tape erosions.
Vainrib et al. 2014 United States Case Series N=46	<p>Population: Mean age: 21.8 yr; Level of injury: cervical=33, thoracic=13; Mean time post-injury: 355.4 mo.</p> <p>Intervention: Records were reviewed for individuals receiving repeat bladder neck incision (BNI) with or without external sphincterotomy (ES).</p> <p>Outcome Measures: Success rate, durability of success, complications, neurogenic detrusor overactivity (NDO), decreased bladder compliance.</p>	<ol style="list-style-type: none"> 1. The 46 participants included in the analyses represent the 47.4% failure rate for initial BNI/ES. 2. For the first revision, the success percentage was 50.0%, with the mean durability of success at 105.6 mo and the mean durability of failure at 70.4 mo. 3. For the second revision, the success percentage was 68.2%, with the mean durability of success at 115 mo and the mean durability of failure at 65 mo. 4. For the third revision, the success percentage was 85.7%, with the mean durability of success at 148 mo and the mean durability of failure at 24 mo. 5. There were few complications noted perioperatively in any of the participants regardless of the number of procedures required. 6. Preoperative percentage of participants with NDO before the first 3 redo interventions were 84.2%, 88.9%, and 75%, while there was decreased bladder compliance in 10.5%, 22.5%, and 25% of participants. 7. The most common indications for surgery failure and need for repeat surgery were elevated residual for the first repeat BNI/ES, recurrent urinary tract infections for the second, and elevated residual for the third.
Pannek et al. 2012 Switzerland Case Series N=9	<p>Population: Median age: 45.1 yr (range=27-6 yr); Gender: males=0, females=9; Level of injury: Paraplegia=4, Tetraplegia=5; Severity</p>	<ol style="list-style-type: none"> 1. The 2 individuals with diapers still used the same amount of diapers at follow-up, while the median number of incontinence pads was

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
	<p>of injury: complete=4, incomplete=5; Mean time post-injury=11.8 yr (range=0.5-29 yr)</p> <p>Bladder drainage was obtained using either intermittent catheter (IC) (n=7), spontaneous voiding (n=1) or suprapubic catheter (n=1). For all individuals, genuine stress urinary incontinence due to neurogenic bladder dysfunction was proven prior to surgery by testing for a stable detrusor in the filling phase, normal bladder compliance and bladder capacity</p> <p>All individuals used incontinence devices prior to surgery (diapers (2) (each using 2/24hr), incontinence pads (7) (median=4/24hr) resp.). All individuals underwent a thorough medical history including counting the number of incontinence devices used/d, vaginal examination, renal ultrasound and video-urodynamic testing. Follow-up examination took place at 3 mo post-surgery, and once every yr after that</p> <p>Median time between surgery and follow-up exam=6.8 mo.</p> <p>Intervention: NA – Data analysis of stress urinary incontinence pre- and post transobturator sub-urethral tape (TOT) surgery</p> <p>Outcome Measures: Use of incontinence devices, bladder capacity, detrusor compliance, maximum detrusor pressure, valsalva leak point pressure (LLP)</p>	<p>reduced from 4 to 2.6/24hr in the other 7 individuals.</p> <ol style="list-style-type: none"> Of the nine individuals, only 3 showed improvement post-surgery - 2 of the 7 individuals using incontinence pads were now continent at follow-up (i.e. did not use any pads) and 1 individual reduced their pad use by 50%. Median bladder capacity pre versus post-surgery was 467 ml versus 379 ml resp. which was not statistically significant. Median detrusor compliance pre versus post-surgery was 120ml/cm H₂O versus 106.7ml/cm H₂O resp. which was not statistically significant. Median maximum detrusor pressure pre versus post-surgery was 11cm H₂O versus 12cm H₂O resp. which was not statistically significant. No new onset of detrusor overactivity was detected post-surgery. In 6 of the 9 individuals with LPP pre-surgery, the Median LPP pre versus post-surgery increased from 28cm H₂O to 41.2cm H₂O resp. Of the 6 individuals who did not experience treatment success, 5 underwent second-line treatment (artificial sphincter (3) or urinary diversion (2) resp.).
<p>Abdul-Rahman et al. 2010 UK Case Series N=6</p>	<p>Population: Mean age: 41.8 yr (26-65 yr); Level of injury: C=11, T=1; 6 individuals followed to 20 yr.</p> <p>Intervention: External urethral sphincter stents</p> <p>Outcome Measures: Urodynamic variables/ video cystometrogram (VCMG), adverse events</p>	<ol style="list-style-type: none"> VCMG showed a significant sustained reduction of maximum detrusor pressure ($p<0.01$) and duration of detrusor contraction ($p<0.05$) at 20 yr follow-up. 5 of 6 individuals developed bladder neck dyssnergia within first 9 yr of follow-up; all successfully treated with bladder neck incision (BNI) No problems with stent migration, urethral erosion, erectile dysfunction or autonomic dysreflexia noted. Two individuals lost to follow-up at 1 and 3 yr, but were

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
		complication free; two developed encrustation requiring stent removal; 1 individual died due to unrelated causes, and another developed bladder cancer and underwent cystectomy 14 yr post-insertion.
Pan et al. 2009 Australia Case Series N=84	<p>Population: Mean age: 35.6 yr; Level of injury: tetraplegia=52, paraplegia=32.</p> <p>Intervention: Charts of SCI individuals that underwent external sphincterotomy were reviewed.</p> <p>Outcome Measures: Success or failure of sphincterotomy based on various clinical criteria. Mean follow-up of 6.35 yr (range=1-20 yr).</p>	<ol style="list-style-type: none"> 57 individuals had failure after initial sphincterotomy. UTI's were the most common reason for sphincterotomy failures followed by detrusor sphincter dyssynergia and upper tract dilation. After a second sphincterotomy for 30 of the 57 individuals for whom the initial sphincterotomy failed, 13 individuals reported success.
Game et al. 2008 France Case Series N=147	<p>Population: Mean age: 41.3 yr; Gender: males=147, females=0; Type/Level of injury: tetraplegia=85, paraplegia=24, MS=24</p> <p>Intervention: Charts of individuals that underwent temporary urethral sphincter stent placement for neurogenic detrusor sphincter dyssynergia.</p> <p>Outcome Measures: Urinary tract infection (UTI), post voiding residual volume, autonomic hyperreflexia with individuals reviewed at 1 and 3 mo post-placement and every 3 mo thereafter.</p>	<ol style="list-style-type: none"> The most common early and late postoperative complication was urinary tract infection. After stent placement: Significant reduction in post-voiding residual volume was seen ($p<0.0001$). Number of individuals experiencing symptoms of autonomic hyperreflexia decreased significantly ($p=0.0003$). Significantly lower mean number of episodes of symptomatic urinary tract infection was seen, ($p<0.0001$). No significant difference in outcome was noted between the Nissenkorn and Diabolo stent. Removal of stent did not result in any complications. 92 of the 147 individuals had permanent urethral sphincter stent placed after removal of the temporary.
Seoane-Rodriguez et al. 2007 Spain Case Series N=47	<p>Population: SCI with overactive bladder with detrusor-external sphincter dyssynergia: Mean age: 52.7 yr; Gender: males=47; Level of injury: cervical=68%, dorsal=23%, lumbar=9%; Severity of injury: AIS A: A=76.7%, B=9.3%, C=14%.</p>	<ol style="list-style-type: none"> There was a significant decrease in detrusor pressure in most individuals, ($p=0.0001$). Post void residual volumes decreased 224cc ($p=0.001$). The presence of urinary tract infection (UTI) diminished by 25% from 67.5 to 42.5%, $p=0.031$.

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
	<p>Intervention: Retrospective review of insertion of intraurethral stent (Memokath or UroLome).</p> <p>Outcome Measures: Detrusor pressure, number of urinary tract infections (UTIs), autonomic dysreflexia, complications in the upper urinary tract, and prosthesis complications with average follow-up of 67 mo (range=14-125 mo).</p>	<ol style="list-style-type: none"> The episodes of dysreflexia also decreased significantly ($p=0.039$). Upper urinary tract complications decreased from 47 to 23% ($p=0.013$). After stent placement, 84% of people that used indwelling catheter previously were able to manage with the external drainage. The most common complication for prosthesis placement was migration, 28%. 4 individuals required stent removal.
Perkash 2007 USA Case Series N=46	<p>Population: Mean age: 47.7 yr; Gender: males=46; Level of injury: tetraplegia=31, paraplegia=15; Severity of injury: AIS A&B=43, C=3</p> <p>Intervention: SCI individuals that underwent transurethral sphincterotomy were followed.</p> <p>Outcome Measures: Post void residual urine, systolic blood pressure (BP), diastolic BP. Mean follow-up time 5.4 ± 3.1 yr.</p>	<ol style="list-style-type: none"> Mean post void residual urine and systolic and diastolic BP decreased significantly post transurethral resection (TURS) ($p<0.0001$). After 1 yr, only 4 individuals still exhibited AD.
Patki et al. 2006 UK Case Series N=9	<p>Population: SCI with urodynamic stress incontinence; Mean age: 38.2 yr; Gender: males=9, females=0; Level of injury: cervical=1, lumbar=3, thoracic=5; Severity of injury: complete=7, incomplete=2.</p> <p>Intervention: Artificial urinary sphincter (American Medical System 800) implantation with the urethral cuff around the bulbar urethra via a perineal approach. These require activation which occurred 6 weeks post-implantation.</p> <p>Outcome Measures: Continence rate, adverse effects, detrusor pressure, and bladder capacity. Follow-up in outindividual clinics at 3 mo, 6 mo, and yearly for a mean of 70.2 mo (3-133 mo).</p>	<ol style="list-style-type: none"> On date of activation there was a 100% continence rate and no individual reported leakage. 2 individuals reported significant recurrent incontinence at 3 mo follow up, with one implant being removed and the other being revised. At the end of 24 mo, a scrotal pump of another individual become infected and was removed. Overall 5 successful implants have had no revisions and have the original implant at a mean follow-up of 105.2 mo. No upper tract change or deterioration in renal function was noted in any individual. More than half of the individuals with working implants recorded higher maximum detrusor pressures at followup. No significant changes were seen in bladder capacity.

Note: AD=Autonomic Dysreflexia; AIS=ASIA Impairment Scale; UTI=Urinary Tract Infection; TURS=Transurethral Modified Sphincterotomy

Discussion

A common surgical method of treating bladder outlet obstruction or detrusor-sphincter dyssynergia has been transurethral sphincterotomy usually conducted in anticipation of emptying the bladder with condom drainage with reflex voiding. Autonomic dysreflexia, a common complication of high volume storage and/or high pressure voiding in those with SCI typically above T6, can be diagnosed with blood pressure monitoring during cystometrogram and urodynamic studies and subsequently better managed after successful transurethral sphincterotomy (Perkash 2007). Perkash (2007) noted a significant ($p<0.0001$) decrease in systolic and diastolic blood pressure after transurethral sphincterotomy as well as improved voiding and post-void residuals. However, although diminished symptoms of autonomic dysreflexia were reported, mean maximum voiding pressures changes were not significant.

Juma et al. (1995) conducted a pre-post test of 63 individuals who had received one or more sphincterotomies with a mean follow-up time of 11 years (range 2-30). This study was directed at describing the risk for long-term complications following this procedure. Although more than half of these individuals had normal upper tract imaging studies, a significant proportion had complications with 25 of 63 individuals having some upper tract pathology (i.e., 12 renal calculi, 11 renal scarring, 1 atrophic kidney, 1 renal cyst), with nineteen of those deemed significant. Risk of significant upper tract complications in presence or absence of bacteria was 38% and 13%, respectively. Thirty out of 63 individuals had lower tract complications (i.e., 5 bladder calculi, 10 recurrent UTI, 3 urethral diverticula, 6 urethral stricture or bladder neck stenosis and 6 recurrent epididymitis). These authors noted that the most reliable urodynamic measure for predicting potential complications following sphincterotomy appeared to be an increase in leak point pressure. Complication rates of 50% were noted for those with leak point pressure of >70 cm H₂O, whereas rates were reduced to 25% when leak point pressure was <30 cm H₂O.

Despite possible upper renal tract protection and extended periods of satisfactory bladder function (i.e., 81 months), long-term outcome data (Pan et al. 2009) caution that high rates of recurring bladder dysfunction symptoms (68%) require approaching sphincterotomy as a staged intervention given that 36% (30/84) of individuals required a second procedure to achieve the mean extended period of satisfactory bladder function. When considering these studies, it is uncertain if these high complication rates would be comparable in the event individuals had continued with their previous form of bladder management as often surgical procedures are performed only if other more conservative methods are unsuccessful. A controlled trial is required to address this issue. For cases where DESD is paired with bladder neck dyssynergia, (which should be confirmed with videourodynamic study), Ke & Kuo (2010) have shown that transurethral incision of the bladder neck (TUI-BN) may restore contractility of the detrusor. Post-void residual volume decreased and QMax increased significantly after TUI-BN and an

open urethral sphincter was noted in 19 of 22 individuals studied postoperatively. In addition, autonomic dysreflexia during micturition was also reduced or eliminated in 15 of 17 individuals with preoperative autonomic dysreflexia (Ke & Kuo 2010).

One alternative to sphincterotomy is placement of a stent passing through the external sphincter thereby ensuring an open passage. Several studies have been conducted examining the long-term outcomes associated with different types of stents including a wire mesh stent (UroLume) (Chancellor et al. 1993b, Abdill et al. 1994, Rivas et al. 1994; Chancellor et al. 1995; Abdul-Rahman et al. 2010) and a nickel-titanium alloy tightly coiled stent (Memokath; Mehta & Tophill 2006). Long-term outcomes of each of these stents were also investigated in a retrospective case series study of 47 consecutive male individuals (Seoane-Rodriguez et al. 2007). All of these studies involved either retrospective case series reviews or prospective pre-post study designs and demonstrated effective treatment of incontinence initially while the stent was in place although some studies also showed the necessity for stent removal/replacement due to migration or other complications. In particular, Mehta and Tophill (2006), in a case series of 29 persons with SCI with a follow-up of up to 47 months, suggested that the “working life” of the Memokath stent was 21 months. They noted that complications most commonly leading to removal included stent blockage by encrustation, migration (especially in single-ended models), UTIs and persistent haematuria. Others have noted similar issues but typically have reported lower rates of complications leading to stent removal (Abdill et al. 1994, Chancellor et al. 1995, Seoane-Rodriguez et al. 2007; Abdul-Rahman et al. 2010). Despite these issues, when the stents are in place they appear to be effective, resulting in significant reductions in voiding pressure and post-void residual urine volumes although no significant changes have been noted in bladder capacity (Chancellor et al. 1993b; Abdill et al. 1994; Chancellor et al. 1995; Seoane-Rodriguez et al. 2007; Abdul-Rahman et al. 2010). In addition, reduced incidence of UTIs and autonomic dysreflexia has typically been reported (Chancellor et al. 1993c; Seoane-Rodriguez et al. 2007). Game et al. (2008) advocate for a trial period with a temporary stent early post-injury based on the percentage of individuals (~30%) not choosing placement of a permanent stent or in whom the stent did not provide the expected results. This reversible management option is however, limited by the available materials for temporary stenting. Rivas et al. (1994) reported a clear individual bias in favour of the stent because of its short- and long-term reversibility. The authors also concluded that the stent was equivalent to external sphincterotomy in terms of urodynamic values and superior for reasons of reduced surgery, hospitalization, costs and hemorrhage as an adverse event.

Chancellor and colleagues (1999) also conducted a RCT (n=57) comparing the outcomes associated with sphincterotomy as compared to placement of the stent (UroLume) prosthesis. This study was deemed a low quality RCT, largely because blinding and concealed allocation was not possible given the nature of the intervention. Similar measurement procedures and overall findings were noted as reported for the studies above (i.e., Chancellor et al. 1993c) with significant decreases in voiding detrusor pressure and post-void residual urine volumes and no significant changes reported for bladder capacity and no differences noted between sphincterotomy and stent for any measure at any time point (i.e., 3, 6, 12 and 24

months). The need for catheterization, initially required in 50% of the sphincterotomy group (n=26) and 71% of the stent group (n=31), was reduced to no more than four individuals at all follow-up timepoints for both groups. There was little difference in subjective assessment of impact of bladder function on QoL or in the incidence of complications between the treatment groups although those in the stent group spent less time in the hospital for the procedure.

Chancellor et al. (1993b) also have examined another procedure with similar rationale as that associated with sphincterotomy. This investigation involved a pre-post trial design (n=17) of transurethral balloon dilation of the external urinary sphincter. Again, similar methods were employed as the studies noted above and findings were also similar. Of all 17 individuals previously managed by indwelling Foley catheter, 15 used condom catheters post-procedure and two voided on their own. Significant decreases were noted in voiding pressure ($p=0.008$) at all follow-up times (i.e., 3, 6 and 12 months). No changes were observed in bladder capacity ($p=0.30$); significant reductions in post-void residual urine volumes ($p<0.05$) were observed at all follow-up times. Positive urine cultures (i.e., UTI) were noted in 15 of 17 subjects prior to surgery but only in 5, 8 and 4 individuals at 3, 6 and 12 months, respectively. Subjective autonomic dysreflexia improved in all nine individuals who had previously experienced AD.

Bladder neck incision (BNI), with or without external sphincterotomy (ES) is one of several primary treatment options for SCI individuals who are unable or unwilling to perform clean intermittent catheterization (CIC). Vainrib et al (2014) report 50-85.7% success rate after 3 BNI/ES procedures and recommend that individuals should be advised of the need for repeat surgery when considering this treatment option.

Patki et al. (2006) reported a small retrospective case series investigation (n=9) of an implantation of an artificial urinary sphincter (AUS; American Medical System 800). This device has evolved over the years to where it is now easier to implant surgically, has a longer life and a higher success rate in achieving incontinence (~80% with more recent models). In this trial, all individuals achieved successful incontinence with no self-reported leakage upon activation of the system. However, by 3-month follow-up, two individuals reported significant recurrent incontinence, with one implant being removed and the other being revised; by a mean follow-up of 105.2 months, 5 of 9 implants had been successful with no revisions. Overall, more than half of the individuals with working implants recorded higher maximum detrusor pressures although no upper tract change or deterioration in renal function was noted in any individual. A retrospective analysis in 2009 by Bersch et al. of individuals (n=51) who underwent implantation of an artificial sphincter at the bladder neck using a port instead of a pump suggested this approach to be highly successful, reliable, safe and a cost-effective treatment option (even with implant revisions). Additionally, a retrospective review by Chartier-Kastler et al. (2011) determined an artificial urinary sphincter device was effective in restoring urinary continence in males, in the majority of cases reviewed, with a decrease in urethral erosion by placement of the device around the bladder neck, providing more credence to consideration for SCI individuals.

Based on the success of safety and efficacy of tension-free vaginal tape for stress incontinence in females with neuropathic bladders (N=12; NSCI=3), Hamid et al. (2003) concluded that tension-free vaginal tape (TVT) was safe for the treatment of women with neuropathic intrinsic sphincter deficiency. Pannek et al. (2012), with the promise of the work of Hamid et al. (2003) and a long history of success in improving continence for women with non-neurogenic stress incontinence, sought to evaluate the use of transobturator tape (TOT) for women suffering from stress incontinence of neurogenic origin secondary to SCI. Even by eliminating sources of variability for success such as material type and surgical competence, the results of this case series (n=9) yielded unfavourable results. Low cough or valsalva induced leak point pressure incontinence and high complication rates of the procedure led the authors to conclude that the TOT was not a viable option for the treatment of SCI related neurogenic stress incontinence. Other attributions to the interventional failure in this individual population were thought to be related to the specific type and grade of detrusor deficiency and the prevalence of pelvic deformity development (Hobson & Tooms 1992) such as a posteriorly tilted pelvis that would interfere with the position of the obturator foramen. Sharing in the lack of understanding for the mechanism of TOT success is the team of Losco et al. (2015) who postulated a more homogenous study population of women with neuropathic bladders, bladder and outlet pathology as the explanation for their positive results. 22 of 27 individuals (82%) reported complete dryness from SUI post-TOT surgery. A further comparison of TVT to the traditional pubovaginal sling (PVS) for the treatment of neurogenic stress urinary incontinence (nSUI) reported equivocal success (El-Azab and El-Nashar 2015). However, while all individuals required clean intermittent catheterization (CIC) post-PVS, 50% of TVT individuals did not require de novo CIC.

Conclusions

There is level 2 evidence (from one prospective controlled trial; El-Azab et al. 2014) in support of tension-free vaginal tape (TVT) and pubovaginal slings as both effective for neurogenic stress urinary incontinence, with TVT associated with 50% of individuals not needing de novo CIC post-surgery.

There is level 4 evidence (from one case series study; Vainrib et al. 2014) that 1-3 successive BNI/ES procedures are required to achieve 50-85.7% success rate, respectively, in neurogenic detrusor overactivity.

There is level 4 evidence (from one case series study; Perlash 2007) that sphincterotomy is effective in reducing episodes of autonomic dysreflexia associated with inadequate voiding.

There is level 4 evidence (from one case series study; Pan et al. 2009) that sphincterotomy, as a staged intervention, can provide long-term satisfactory bladder function.

There is level 2 evidence (from a one RCT and several level 4 studies; Chancellor et al. 1999) that both sphincterotomy and implantation of a sphincteric stent are effective in reducing incontinence, with little need for subsequent

catheterization, and both treatments are associated with reduced detrusor pressure and reduced post-void residual volume but not with changes in bladder capacity. The only significant difference in these two treatments was the reduced initial hospitalization associated with the stent, given the lesser degree of invasiveness.

There is level 4 evidence (from one pre-post study and one case series study; Chancellor et al. 1993c; Seoane-Rodriguez et al. 2007) that implantation of a sphincteric stent may result in reduced incidence of UTIs and bladder-related autonomic dysreflexia over the short-term although several studies have demonstrated the potential for various complications and subsequent need for re-insertion or another approach over the long-term.

There is level 4 evidence (from one pre-post study; Juma et al. 1995) that over the long-term, previous sphincterotomy may contribute to a high incidence of various upper and lower tract urological complications.

There is level 4 evidence (from one case series study; Game et al. 2008) that advocates for placement of a temporary stent early after injury as a reversible option that allows individuals to choose from the range of permanent stent placement to less invasive bladder management methods such as intermittent catheterization.

There is level 4 evidence (from one pre-post study; Chancellor et al. 1993b) that transurethral balloon dilation of the external sphincter may permit removal of indwelling catheters in place of condom drainage, and also may result in reduced detrusor pressure and post-void residual volume but not with changes in bladder capacity.

There is level 4 evidence (from one case series study and one pre-post study; Patki et al. 2006; Bersch et al. 2009) that implantation of an artificial urinary sphincter may be useful in the treatment of incontinence in SCI but further study is required.

There is level 4 evidence (from one pre-post study; Ke & Kuo 2010) that transurethral incision of the bladder neck may be useful in bladder neck and voiding dysfunction.

There is level 4 evidence (from one case series study; Pannek et al. 2012) that sub-urethral transobturator tape implantation is not effective in managing neurogenic stress incontinence in females living with SCI.

There is level 4 evidence (from one case series study; Losco et al. 2015) that mid-urethral transobturator tape implantation is effective in managing neurogenic stress incontinence in females living with SCI.

Surgical and prosthetic approaches (with a sphincterotomy and stent respectively) to allow bladder emptying through a previously dysfunctional external sphincter both seem equally effective resulting in enhanced drainage although both may result in long-term upper and lower urinary tract complications.

Artificial urinary sphincter implantation and transurethral balloon dilation of the external sphincter may be associated with improved bladder outcomes but require further study.

4.5 Other Miscellaneous Treatments to Enhance Bladder Emptying

In addition to those noted in the previous sections, there are a variety of other approaches that have been investigated to address the consequences of neurogenic bladder associated with SCI. These include the use of desmopressin acetate (DDAVP) as an adjuvant therapy to manage the effects of an overactive bladder otherwise refractory to conventional treatment such as nocturnal enuresis (i.e., night-time emission of urine) or the requirement for too frequent catheterizations. It is important to note that overactive bladder may be caused by other urologic abnormalities (e.g., benign prostatic hyperplasia, or UTI) that can coexist with other consequences of neurogenic bladder secondary to SCI. Therefore, urodynamic evaluation is critical to assessing overactive bladder before adjuvant therapy is administered. If needed, DDAVP is a synthetic analogue of antidiuretic hormone most commonly administered by intravenous infusion for treatment of bleeding disorders. It can also be taken in the form of a pill or intranasal spray for reducing urine production as in the present application (Chancellor et al. 1994; Zahariou et al. 2007). DDAVP is thought to bind to V2 receptors in renal collecting ducts to increase water reabsorption.

Others have employed alternative approaches such as electroacupuncture (Cheng et al. 1998) or nerve crossover surgery / spinal root anastomoses (Livshits et al. 2004; Lin et al. 2008; Lin et al. 2009) to enhance recovery of bladder function. The utility of spinal root anastomosis in SCI came from groups rediverting the ipsilateral C7 root to repair brachial plexus injuries with significant long-term effects of motor and sensory function of the upper extremities as a result of compensatory action of the other nerve roots (Gu et al. 2005). Since the brachial and sacral plexuses are organized similarly, the redirection of local lower extremity nerve roots has been considered a possible, albeit highly invasive, treatment option.

Table 20 Other Miscellaneous Treatments

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
Desmopressin Acetate		
Zahariou et al. 2007 Greece Pre-Post N=11	<p>Population: SCI in inindividual rehabilitation: Gender: males=7, females=4; Level of injury: above T6=6, below T6=5.</p> <p>Intervention: Desmopressin acetate (DDAVP) was given intranasally (20µg before bedtime) in association with other standard therapy including anticholinergic drugs (Oxybutynin 5mg, 1x3 daily), evening antibiotic prophylaxis and clean intermittent catheterization (IC).</p> <p>Outcome Measures: Urine production/ output, clean IC rate. Urine samples collected at 6am and 6pm.</p>	<ol style="list-style-type: none"> DDAVP produced a statistically significant increase in urine production rate during the day ($p<0.001$) and a decrease in nocturnal urine production ($p<0.001$). DDAVP treatment showed a significant increase on urine asmolality during the night ($p<0.001$). Treatment produced a significant decrease in individuals performing clean intermittent catheterizations in the night while still maintaining continence. No serious adverse effects were seen.
Chancellor et al. 1994 USA Case Series N=7	<p>Population: SCI with detrusor hyperreflexia unresponsive to conventional therapy: Age range 22-52 yr; Gender: males=3, females=4.</p> <p>Treatment: 10ug/d intranasal desmopressin acetate (DDAVP) over 1 mo.</p> <p>Outcome Measures: Episodes of nocturia, time between catheterizations.</p>	<ol style="list-style-type: none"> No statistical results reported. Decreased nocturia for 4 individuals treated at night (Nocturnal enuresis eliminated in 2 individuals). Increased duration between catheterizations for 3 individuals treated during the day.
Locomotor Training		
Hubscher et al. 2018 USA Prospective Controlled Trial N=12	<p>Population: Activity-based training (ABT): Mean age=27.37±5.63yr; Gender: males=5, females=3; Etiology: SCI=8. Time since injury=4.25±3.55yr. Non-trained (NT): Mean age=30.25±4.49yr; Gender: males=4, females=0; Etiology: SCI=4; Time since injury; 6.70±2.23yr. Inclusion criteria (both groups): clear indications that the spinal shock period has concluded as determined by the presence of muscle tone, deep tendon reflexes or muscle spasms, and discharged from standard inindividual rehabilitation.</p> <p>Intervention: Participants in the ABT received locomotor training (LT) alone or LT+ stand training. LT was completed on a treadmill using body weight support consisting of a harness and lift. 1hr/d, for 80 d.</p>	<ol style="list-style-type: none"> BC, VE, Tdet, and size of bladder contraction increased significantly post-intervention for the ABT group ($p<0.05$). LPP decreased significantly post-intervention for the ABT group ($p<0.05$). There was no significant change in BC, VE, Tdet, and size of bladder contraction for the NT group ($p>0.05$).

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
	<p>Participants who received LT + stand training received the same locomotor training with the addition of stand training through the use of a custom designed standing frame with horizontal bars anterior and lateral to the participant for upper extremity support and balance assistance. Stand training was 1 hr/d separated at least 3 hr from LT. Participants in NT received standard care (no training). Outcome measures were assessed at baseline and post-intervention.</p> <p>Outcome Measures: Bladder capacity (BC); voiding efficiency (VE); leak point pressure (LPP); size of bladder contraction; detrusor contraction time (Tdet).</p>	
Electroacupuncture		
<p>Gu et al. 2015 China RCT PEDro=7 N=107</p>	<p>Population: Urinary retention; Mean age: 35.7 yr; Gender: males=80, females=27; ASIA classification: B=37, C=53, D=17.</p> <p>Intervention: Individuals were randomized to Clean intermittent catheterization (CIC) (group 1) (n=35), Electroacupuncture combined with CIC (group 2) (n=38), or Sham acupuncture combined with CIC (group 3).</p> <p>Outcome Measures: Residual urine volume, voided volume, bladder balance, frequency of CIC.</p>	<ol style="list-style-type: none"> 1. At 1 mo follow-up, group 2 had a significantly higher number of bladder participants compared to group 1 ($p=0.019$) or group 3 ($p=0.019$). 2. At 1 mo follow-up, group 2 participants had significantly lower frequency of CIC compared to group 1 ($p<0.001$) or group 3 ($p<0.001$), and group 3 was also significantly lower than group 1 ($p<0.01$). 3. In terms of residual urine volume at 1 mo follow-up, group 2 was significantly lower than group 3 ($p<0.001$) and group 3 was significantly lower than group 1 ($p=0.018$). 4. At 1 mo follow-up, group 2 had a significantly higher voided volume compared to 1 ($p<0.001$) and group 3 ($p<0.001$), with no significant differences between groups 1 and 3. 5. At 3 mo follow-up, significant differences were found between groups in terms of residual urine volume ($p<0.001$), with groups ordered as 1, 3, and 2 in terms of decreasing volume.

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
		6. At 3 mo follow-up, significant differences were found between groups in terms of voided volume ($p<0.001$), with groups ordered as 1, 3, and 2 in terms of increasing volume.
Xia et al. 2014 China RCT PEDro=6 N=42	<p>Population: Neurogenic bladder; Treatment group: Mean age: 37.2 yr, Gender: males=13, females=8; Time post-injury: 2.4 mo; Control group: Mean age: 37.5 yr; Gender: males=14, females=7; Mean time post-injury: 2.6 mo.</p> <p>Intervention: Individuals were randomized to 1) Treatment group (n=21): Acupuncture treatment, consisting of 10 stimulations over 2 weeks or 2) Control group (n=21): Bladder training, including interval water drinking, timed voiding, and intermittent catheterization.</p> <p>Outcome Measures: Bladder capacity, residual urine volume, bladder pressure, rectal pressure, detrusor pressure, bladder compliance, International Prostate Symptom Score (IPSS), and efficacy rate.</p>	<ol style="list-style-type: none"> 1. Compared with control group, the treatment group had significantly increased bladder capacity and compliance, and significantly reduced residual urine volume, bladder pressure, rectal pressure, and detrusor pressure ($p<0.05$). 2. IPSS values for both groups were significantly lower post-treatment ($p<0.05$), with treatment group scores significantly lower than control group score ($p<0.05$). 3. The total efficacy rate in the treatment group was significantly higher than the control group ($p=0.043$).
Cheng et al. 1998 Taiwan RCT PEDro=4 N=60	<p>Population: SCI: Acupuncture versus Control Group; Mean age: 39.4 yr versus 34.3 yr; Gender (M/F): 24/8 versus 23/5; Level of injury: above T11=34, below T11=26; Severity of injury: Frankel A=25, B=35; Time post-injury=23.7 d versus 26.1 d.</p> <p>Intervention: Electroacupuncture to 4 points (CV3, CV4, UB32 bilateral)+conventional bladder training=32 versus control group of conventional bladder training=28.</p> <p>Outcome Measures: Time from SCI-bladder balanced, urodynamic assessment in n=20 of acupuncture group.</p>	<ol style="list-style-type: none"> 1. ↓ time to achieve bladder balancing for those with upper motor lesions - acupuncture versus control, 57.1 ± 22.5 d versus 85.2 ± 27.4 d ($p<0.005$). 2. Similar for lower motor neuron lesions, 55.4 ± 22.6 d versus 83.4 ± 26.1 d ($p<0.01$). 3. If it was started within 3 wk of SCI, bladder balancing was achieved sooner, 46.6 ± 13.2 d versus 65.8 ± 15.4 d ($p<0.005$). 4. No significant changes seen in urodynamic assessment associated with 1st acupuncture session but ↑ in bladder capacity and ↓ voiding pressure seen by time bladder was balanced.
Rectus Abdominus Detrusor Myoplasty (RADM)		
Agarwal et al. 2018 India Pre-Post N=5	<p>Population: Median age=38.31yr; Gender: males=5, females=0; Etiology: SCI=5. Time since injury=1-3yr; Inclusion criteria: acontractile/hypocontractile bladder.</p>	<ol style="list-style-type: none"> 1. There was no significant difference in PVRV post-intervention ($p>0.05$). 2. There was a significant increase in BCI ($p<0.007$), Pdet ($p<0.006$), and Vmax ($p<0.013$).

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
	Intervention: All participants underwent rectus abdominus detrusor myoplasty (RADM). Outcome measures assessed preoperatively and post-operatively. Outcome Measures: Post-void residual volume (PVRV); detrusor pressure (Pdet); urine flow rate (Vmax); bladder contractility index (BCI)	3. All individuals no longer had recurrent UTIs or vesicoureteral reflux post-intervention or at follow up (15 mo post-intervention).
Sphincterectomy		
Takahashi et al. 2018 Japan Pre-Post N=37	Population: Mean age=35.4±2.4yr; Gender: males=13; female=4; Etiology: incomplete SCI=12; complete SCI=25; Time since injury=17.9±3.7yr. Intervention: Medical records of individuals who underwent external sphincterectomy (ES) for treatment of detrusor overactivity (DO) or detrusor-sphincter dyssnergia (DSD) and were followed for at least 5 years were reviewed. External sphincterectomy was performed using electrocautery. Adequate division of the striated muscles of the external sphincter were achieved by an incision from the midprostatic urethra through the bulbomembraneous junction. Individuals were divided into two groups; success and failure. Success was defined as individuals who maintained reflex voiding using a condom catheter and did not need to change their lower urinary tract management. Failure was defined as individuals who required a change in lower urinary tract management due to deterioration of voiding efficiency or autonomic dysreflexia. Individuals underwent urodynamic assessment pre- and post-operatively (2-3 months, and 1,3,5,10,15,20 years after ES). Outcome Measures: Mean bladder pressure (MBP); bladder volume at first DO (VDO); maximum bladder capacity (MBC).	1. MBP of all individuals decreased over time. The decrease in MBP was observed for more than 10 years after ES. Both the success and failure groups showed similar trends as all individuals for MBP over time. 2. VDO increased gradually over time. 3. The presence of DO increased after ES up until 10 years, after which there was a marked decrease.
Nerve Crossover Surgery - Spinal Root Anastomoses		
Sievert et al. 2016 Germany	Population: Mean age: 30 yr; Gender: males=6, females=2; Level	1. At a mean follow-up of 71 mo post-treatment, no participants

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
Pre-Post N=8	<p>of injury: cervical=4, thoracic=4; ASIA classification: A; Mean time post-injury: 83 mo.</p> <p>Intervention: Four individuals with detrusor sphincter dyssynergia and four individuals with detrusor overactivity underwent the Xiao procedure, consisting of the creation of an artificial somato-autonomic reflex arch through intradural anastomosis.</p> <p>Outcome Measures: Occurrence of voiding upon stimulation of skin, bladder capacity, maximum detrusor pressure, bladder compliance.</p>	<p>could void upon stimulation of the skin, as assessed by videourodynamics or individual diary.</p> <p>2. No significant improvements in terms of bladder capacity, maximum detrusor pressure, and bladder compliance were observed post-treatment.</p>
Rasmussen et al. 2015 Denmark Pre-Post N=10	<p>Population: Neurogenic bladder dysfunction; Mean age: 43.3 yr; Gender: males=9, females=1; Level of injury: cervical=4, thoracic=6; ASIA classification: A=7, B=3; Mean time post-injury: 6.5 yr.</p> <p>Intervention: The Xiao procedure, which involved creation of an artificial somato-autonomic reflex arch through intradural anastomosis.</p> <p>Outcome Measures: Maximum cystometric bladder capacity, bladder compliance, detrusor overactivity, urinary leakage, detrusor contractions/relaxations during stimulation, International Spinal Cord Injury Data Set, Lower Urinary Tract Function Basic Data Set.</p>	<p>1. No participant could void voluntarily at baseline or follow-up; bladder emptying and changes in detrusor pressure could not be induced by stimulating the reflex arch.</p> <p>2. Compared to baseline, no significant differences were observed after treatment in terms of maximum cystometric bladder capacity, or bladder compliance.</p> <p>3. Significantly less leakage ($p=0.03$) was observed at follow-up compared to baseline.</p> <p>4. In terms of the International Spinal Cord Injury Data Set and Lower Urinary Tract Function Basic Data Set, neurogenic bladder dysfunction symptoms did not change from baseline to follow-up, with no consistent changes observed in terms of bladder emptying, incontinence episodes, means of bladder emptying, or use of medication.</p> <p>5. Three participants subjectively reported less urinary incontinence, 1 reported decreased incidence of urinary tract infections, 1 reported fewer kidney stone symptoms, 2 reported improved bowel emptying, 4 reported no change, and 1 reported increased intervals between catheterizations.</p>

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
Lin & Hou, 2013 China Pre-Post N=9	<p>Population: Mean age: 36 yr (range 29-51); Gender: males=7, females=2; Level of injury: L1 vertebral body fracture =6, L2 vertebral body fracture=3; Mean time post-injury: 8 mo (range=6-12 mo); all individuals urinated via bladder stoma with no residual urine in the bladder=4 or after applying abdominal pressure when the residual urine volume was>100 mL=5.</p> <p>Intervention: All individuals underwent a standard laminectomy from L5-S3, and S1 ventral nerve root (VR) surgery was performed strength tests of the muscles innervated by the S1 nerve (i.e. gastrocnemius, soleus, abductor hallucis, and extensor digitorum brevis resp.) were completed on the second day post-surgery and at 1,3,6 and 12 mo postoperatively</p> <p>Outcome Measures: Muscle strength (Medical Research Council (MRC) Grade), Bladder capacity, Urine volume, Residual urine volume, Max detrusor pressure, Maximum flow. Urodynamic tests were completed at 1, 3, 6, 12, 18, 24 and 36 mo postoperatively.</p>	<ol style="list-style-type: none"> 1. Mean follow-up time: 30 mo (range=18-36 mo) 2. On the second day post-surgery, the power of the S1-innervated muscles decreased by 1 (MRC) grade, while at 3 mo the muscles of all individuals had recovered to their preoperative strength levels. 3. By 8-12 mo postoperatively, 7/9 individuals (78%) had recovery of bladder storage, voiding functions (able to void voluntarily), no nocturnal urinary incontinence, and had also regained bladder sensory function (i.e. able to sense a full bladder and perceive the desire to void). 4. Pre- and postoperative urodynamic tests showed significant improvements in bladder function by 12 mo. 5. Of the 7 individuals responding to treatment, average bladder capacity pre- versus post-op decreased from 496±75 ml to 377±64 ml resp. which was statistically significant (p=0.0042) 6. Of the 7 individuals, urine volume pre- versus post-op increased from 44±16.2 ml to 320.6±44.2 ml resp. which was statistically significant (p=0.0000) 7. Of the 7 individuals, residual urine volume pre- versus post-op decreased from 186±35 ml to 43±10 ml resp. which was statistically significant (p=0.0000) 8. Of the 7 individuals, maximum detrusor pressure pre- versus post-op increased from 3.6±1.8 cm H₂O to 85±30 cm H₂O resp. which was statistically significant (p=0.0005) 9. Of the 7 individuals, maximum flow rate pre- versus post-op increased from 3.0±0.8 ml/s to 31.4±7.2 ml/s resp. which was statistically significant (p=0.0001)

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
		10. The frequency of urinary tract infections gradually decreased after 6 mo and disappeared completely as voiding recovered.
Lin et al. 2009 China Pre-Post N=12	<p>Population: SCI individuals with detrusor-external sphincter dyssynergia; Mean age: 30 yr; Gender: males=8, females=4; Level of injury: C=2, T=10</p> <p>Intervention: Spinal root anastomosis of S1 to S2 ventral root.</p> <p>Outcome Measures: Incontinence, bladder capacity, flow rate, urinary tract infection (UTI), adverse events and were followed for up to 6 yr (mean=3 yr).</p>	<ol style="list-style-type: none"> 9 individuals had recovery of bladder storage without nocturnal urinary incontinence. An increase was seen in average bladder capacity ($p=0.0011$) and maximum flow rate ($p=0.0002$) postsurgery. Residual urine ($p=0.0004$) and maximum detrusor pressure ($p=0.0435$) decreased post surgery. At 6 mo post surgery, incidence of urinary tract infections stopped. Adverse effects included cerebrospinal fluid leakage and headache.
Lin et al. 2008 China Pre-Post N=10	<p>Population: Complete conus medullaris injury with atonic bladder; Mean age:38 yr; Gender: males=6, females=4; Level of injury: T12=3, L1=5, L2=4; Severity of injury: complete</p> <p>Intervention: Spinal root anastomosis of T11 to S2 ventral root.</p> <p>Outcome Measures: Bladder capacity, urine volume, residual urine volume, max detrusor pressure, max flow collected at regular intervals up to 2 yr.</p>	<ol style="list-style-type: none"> 7 individuals found improvements in bladder storage and voiding functions. Significant improvement in urodynamic outcomes were seen 2 yr post reconstruction: <ul style="list-style-type: none"> Bladder capacity, $p=0.0031$ Urine volume, $p=0.0026$ Residual urine volume, $p=0.0005$ Max detrusor pressure, $p=0.00001$ Max flow, $p=0.0001$ Mild postoperative spinal fluid leakage was seen in 1 individual.
Xiao et al. 2003 China/USA Pre-Post N=15	<p>Population: SCI individuals with detrusor-external sphincter dyssynergia; Mean age:39 yr; Severity of injury: AIS A</p> <p>Intervention: L5-S3 ventral root anastomosis to establish a new reflex pathway.</p> <p>Outcome Measures: Residual urine volume, urinary tract infections, detrusor pressure, adverse events.</p>	<ol style="list-style-type: none"> 10 individuals had recovery of bladder storage and emptying functions. A decrease was seen in average residual urine (332 to 31mL) and incidence of urinary tract infections 8 mo post surgery. Two individuals were still dependent on a stimulator for voiding. Post surgery, 4 individuals showed almost normal bladder activity on a cystometrogram (CMG) and electromyography.

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
		5. Significant improvement was seen in mean detrusor pressure ($p<0.05$). 6. 3 individuals had mild postoperative spinal fluid leakage for 2 to 5 d. 7. Bowel control was also regained in individuals who regained bladder control.
Bladder Cancer		
Lee et al. 2014a Taiwan Cohort N=272005	<p>Population: Spinal cord injury (SCI cohort): Mean age: 52.2 yr; Gender: males=34173, females=20228; Level of injury: cervical=29565, thoracic=16451, lumbar=16451, unclassified=77. No spinal cord injury (Non-SCI cohort): Mean age: 52.2 yr; Gender: males=136692, females=80912.</p> <p>Intervention: Data from the National Health Insurance Research Database were accessed for the SCI group with each member randomly frequency matched with four non-SCI people.</p> <p>Outcome Measures: Bladder cancer diagnosis, prostate cancer diagnosis, death.</p>	1. The overall incidence of bladder cancer was 12% lower in the SCI cohort than the non-SCI cohort with a non-significant adjusted hazard ratio of 0.91. 2. The overall incidence of prostate cancer was 33% lower in the SCI cohort than the non-SCI cohort with a significant adjusted hazard ratio of 0.73 ($p<0.01$). No significant differences in bladder cancer risk were found between different levels of SCI and non-SCI.
Bladder Stones		
Eyre et al. 2015 United Kingdom Cohort N=112	<p>Population: Median age: 44 yr; Gender: males=83, females=39; Level of injury: cervical=15, thoracic=87, lumbar=9, unknown=1; Frankel classification: A=68, B=34, C=6, D=1, unknown=3.</p> <p>Intervention: Spinal cord injury individuals with bladder stones received either simple washout (n=11), Mauermeyer stone punch (n=49), electrohydraulic lithotripsy (EHL) (n=15), combination of stone punch and EHL (combined) (n=36), or open cystolithotomy (n=1).</p> <p>Outcome Measures: Post-operative complications, length of stay.</p>	1. Of the 112 participants, 19 had a post-operative complication (0 associated with simple washout, 5 associated with stone punch, 3 associated with EHL, 10 associated with combined, and 1 associated with open cystolithotomy). 2. In the multivariable model for complication predictors, cervical injury ($p=0.033$) and the combined procedure ($p=0.046$) were associated with increased odds for complications. Age, sex, Frankel classification, and bladder management method had no significant differences in terms of complications. Of the 106 participants with length of stay data, the multivariable predictors of increased length of stay were complication ($p<0.001$) and combined procedure ($p=0.028$).

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
		Age, sex, Frankel classification, and bladder management method had no significant differences in terms of complications.
Bartel et al. 2014 Switzerland Case Series N=2825	<p>Population: Bladder stone group (n=93): Mean age: 50 yr; Gender: males=69, females=24; Level of injury: cervical=34, thoracic=49, lumbar=9, sacral=1; Severity of injury: complete=75, incomplete=18; ASIA classification: A=53, B=22, C=13, D=5; Injury etiology: trauma=74, multiple sclerosis=10, other=9; Time post-injury: 9.5 yr.</p> <p>Intervention: Charts were reviewed for spinal cord injury individuals who had a bladder stone.</p> <p>Outcome Measures: Bladder management method, period to stone development, bladder stone recurrence rate.</p>	<ol style="list-style-type: none"> 1. Of the 2825 SCI individuals, 93 had bladder stones (2.8%). 2. In terms of bladder management methods, bladder stones were observed in 11% of suprapubic catheter, 6.6% of transurethral catheter, 2% of intermittent catheterization, and 1.1% of reflex micturition. 3. In terms of period to stone development, the mean for suprapubic catheter was 59 mo, transurethral catheter was 31 mo, intermittent catheterization was 116 mo, and reflex micturition was 211 mo. The bladder stone recurrence rate was 28% for suprapubic catheter, 40% for transurethral catheter, 22% for intermittent catheterization, and 0% for reflex micturition.
Other		
Virseda et al. 2014 Spain Case Control N=76	<p>Population: Vesicoureteral reflux (VUR); Mean age: 48.9 yr; Gender: males=60, females=16; Level of injury: cervical=21, thoracic=49, lumbar=6; Mean time post-injury: 179 mo.</p> <p>Intervention: Records were reviewed for VUR individuals who had undergone endoscopic treatment by a bulking treatment, comparing treatment successes to failures.</p> <p>Outcome Measures: Recurrence rate, time post-intervention, gender, age, bulking agent, reflux grade, neurogenic detrusor overactivity (NDO), stress urinary incontinence, bladder capacity, filling pressure, maximum flow rate.</p>	<ol style="list-style-type: none"> 1. Overall, resolution of VUR was achieved in 61% of participants, with the recurrence rate being 37% for participants undergoing a first intervention and 50% for those undergoing a second intervention. 2. Cured participants were significantly younger than non-cured participants (p=0.033). 3. No significant differences between groups were observed in terms of gender or bulking agent. 4. The percentage of cure was significantly higher with lower reflux grade (p=0.020). 5. The odds of reflux persistence in NDO participants was 4.57 times greater than those without NDO (p=0.008). 6. The odds of reflux persistence in participants without SUI was significantly greater than those with SUI (p=0.032).

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
		7. No significant associations with treatment success were found for bladder capacity, filling pressure, or maximum flow rate. In the multivariable analysis, presence of NDO ($p=0.012$) and reflux grade ($p=0.017$) independently influenced the cure of VUR.

Summarized Level 5 Evidence Studies:

Nahm et al. (2015) reported that despite lower rates of bladder and prostate cancer in people with SCI vs people without SCI, bladder cancer related mortality is higher with more severe injuries. Sammer et al. (2015) suggested that screening strategies to prevent bladder cancers may be considered for people with SCI where those with more severe injuries are more at risk.

Discussion

Desmopressin Acetate

Zahariou et al. (2007) and Chancellor et al. (1994) conducted a pre-post ($n=11$) and a case series ($n=7$) investigation, respectively, to investigate the use of intranasal DDAVP as an alternative therapy to reduce urine production in the hopes of reducing nocturnal emissions or reducing the need for overly frequent catheterization during the day. In each case, DDAVP was employed as an adjuvant therapy in addition to standard therapies of anticholinergics and intermittent catheterization which had resulted in less than satisfactory results. With use of DDAVP just before bedtime, Zahariou et al. (2007) reported a statistically significant increase in urine production rate during the day ($p<0.001$) and a decrease in nocturnal urine production ($p<0.001$). After DDAVP treatment, participants had reduced or complete elimination of nocturnal enuresis (Chancellor et al. 1994; Zahariou et al. 2007). In addition, the proportion of persons requiring clean IC in the night while still maintaining continence was greatly reduced (Zahariou et al. 2007) and three individuals used DDAVP during the day at work and were able to achieve an additional 3.5 hours between catheterizations (Chancellor et al. 1994). These improvements persisted for a mean of 12 months. These small-scale studies provide only preliminary evidence and encourages further study, although DDAVP is in fairly widespread use for SCI-related neurogenic bladder.

Locomotor Training

A prospective controlled trial by Hubscher et al. (2018) studied the effects of locomotor training (LT) for improving motor outcomes post-SCI, specifically whether it can improve bladder, bowel and sexual function. Eight subjects used LT on a treadmill using body-weight support therapy, or LT and standing training. Filling cystometry documented significant increases in bladder capacity, voiding efficiency

and detrusor contraction time as well as significant decreases in voiding pressure post-training relative to baseline. Questionnaires revealed a decrease in the frequency of nocturia and urinary incontinence for several research participants as well as a significant decrease in time required for defecation and a significant increase in sexual desire post-training. Authors concluded that these results suggest that an appropriate level of sensory information provided to the spinal cord, generated through task-specific stepping and/or loading, can positively benefit the neural circuitries controlling urogenital and bowel functions.

Electroacupuncture

Another adjunctive therapy that has been investigated is the use of electroacupuncture (EA). For example, Cheng et al. (1998) conducted a RCT (n=60) investigating the effectiveness of electroacupuncture administered in combination with conventional bladder management method (i.e., clean intermittent catheterization (CIC), tapping and trigger point stimulation) as compared to those not receiving electroacupuncture. Their primary outcome measure was the time to achieve bladder balancing which was defined as the time when: 1) the individual could easily pass adequate urine at low pressure, 2) residual urine of approximately 100 ml or less and 3) absent UTIs. Although employing a randomized, controlled design, some limitations (i.e., lack of blinding, concealed allocation or intent to treat) constrained the level of evidence assigned to this trial (i.e., Level 2). Regardless, those receiving electroacupuncture had a reduced time to achieve bladder balancing for both those with upper motor lesions ($p<0.005$) and lower motor neuron lesions ($p<0.01$). In addition, if electroacupuncture was started within three weeks of SCI, bladder balancing was achieved sooner than those who started after three weeks ($p<0.005$). Gu et al. (2015) also reported the superiority of EA+CIC effectiveness (vs CIC alone) in reducing residual urine volume ($p<0.001$) and frequency of CIC ($p<0.001$), increased voided volume ($p<0.001$), and promoting the balance of vesical function ($p<0.05$). Similarly, EA with bladder function training vs bladder function training alone is significantly more effective in increasing bladder volume and compliance, decreased residual urine volume, bladder pressure, rectal pressure, and detrusor pressure ($p<0.05$) (Xia et al. 2014). Modest improvements were also reported with bladder function training alone. The treatment group also had lower IPSS (International Prostate Symptom Score that describes various characteristics of urination) and better therapeutic efficacy ($p<0.05$) compared to controls.

Rectus Abdominus Detrusor Myoplasty (RADM)

Urinary bladder dysfunction in the form of acontractile/ hypocontractile bladder is very common after spinal cord injury and it may lead to recurrent urinary tract infection (UTI), stones formation, and deteriorating renal function. This is conventionally treated through the use of life-long clean intermittent catheterization (CIC) or an indwelling catheter (IC). For these individuals, another option is to use innervated skeletal muscle wrap around the bladder to augment detrusor function and voluntary evacuation of bladder. Agarwal et al. (2018) studied five individuals that underwent Rectus Abdominis Detrusor Myoplasty (RADM) to treat acontractile/hypocontractile bladder. These individuals were assessed by urodynamic study for post void residual volume (PVRV), detrusor pressure (Pdet), urine flow rate (Vmax), and bladder contractility index (BCI). Complete spontaneous

voiding was achieved in all individuals. RADM elicits a statistically significant reduction in PVRV and statistically significant increase in urine flow rate, bladder contractility and detrusor pressure after six months. Another effect of treatment was all recurrent UTIs ceased in subjects.

Sphincterectomy

External sphincterotomy (ES) in the treatment of SCI individuals with detrusor sphincter dyssynergia (DSD) is used to achieve low pressure urine storage and low pressure emptying of the bladder. By decreasing bladder outlet obstruction, reflex voiding can be performed with a lower bladder pressure, leading to more effective voiding, lesser incidence of UTI, preservation of upper urinary tract function, and reduction of autonomic dysreflexia (AD). Takahashi et al. (2018) conducted a long-term follow-up study after ES to determine if urodynamic parameters improved after the therapeutic procedure in male SCI individuals with DSD. Of the 37 SCI individuals studied, 27 are still managed with reflex voiding to a condom catheter (success group), while 10 needed to change their bladder management. Mean maximum bladder pressure (MBP) was maintained at a low level over 20 years after ES. However, neurogenic detrusor overactivity (NDO) gradually decreases over time, which might be one of the reasons for failure after ES.

Nerve Crossover Surgery - Spinal Root Anastomoses

Reports regarding microanastomosis to reinnervate the paralyzed bladder reveal recovery of neurogenic bladder dysfunction. These include surgical anastomosis of the intercostal nerve (Livshits et al. 2004; n=11), T11 nerve root (Lin et al. 2008, n=10), L5 nerve root (Xiao et al. 2003, n=15) or the S1 nerve root (Lin et al. 2009, n=12; Lin & Hou. 2013, n=9) to the S2 or S3 spinal nerve roots. Mean follow-up of individuals was between 2 to 3 years and restitution of bladder function was observed in the majority of individuals. Significant results were reported for pre and post-surgical findings including reduced bladder capacity with increased urine volume under increased force of detrusor contractions and increased voiding pressure. There was also reduced residual urine volume and both detrusor tone and sphincter resistance were increased. Results from individual subjects in Livshits et al. (2004) were presented for each of these showing consistency across these measures although statistical analysis techniques were inappropriate consisting of individual Wilcoxon signed rank tests for each variable. Individual self-report measures showed increases within a few months following surgery. Similar findings were evident in 100%, 67%, 71%, and 78% of individuals undergoing T11, L5, and S1 microanastomosis, respectively (Lin et al. 2009, Xiao et al. 2003, Lin et al. 2008 and Lin & Hou 2013). Full recovery of renal function and an absence of UTI was observed at follow-up (i.e., 6-18 months). Of the 7 of 9 individuals in the Lin and Hou (2013) study that recovered full bladder storage and voiding function, the return of bladder sensation (able to sense full bladder and desire to void) also accompanied the lack of nocturnal urinary incontinence by 8-12 months postoperatively. Important considerations of this surgical approach are that it is far more invasive than other approaches (i.e., indwelling catheterization); and some individuals do not show any improvement postoperatively. In particular, accidental voiding may be triggered by unintentional dermatomal stimulation or Achilles tendon stretch. Furthermore, considering the potential for up to 30% failure rates and serious side effects (i.e. neuromas) this

invasive procedure must be weighed cautiously against other approaches to treatment of bladder dysfunction. However, more recently, 2 small, independent pre-post studies confirmed that the Xiao procedure for intradural anastomosis to improve bladder function, was ineffective (Sievert et al. 2016, Rasmussen et al. 2015).

Bladder Cancer

Contrary to morbidity rates for many secondary conditions in spinal cord injured individuals, the overall incidence of bladder and prostate cancer is reported to be lower by 12 and 33%, respectively for a cohort of people with SCI vs non-SCI (Lee et al 2014; n=27,2005). Although Nahm et al. (2015, n=45,486) did not confirm lower rates of bladder cancer in people with SCI, they did report that people with SCI are not at increased risk compared to people with SCI. However, this large US database did reveal increased bladder cancer mortality in people with more severe injuries (e.g. AIS A, B, C) with AIS D individuals, who typically do not have problems with neurogenic bladder or UTIs, having the risk of mortality as the general population. This group did not observe an increased mortality rate in ventilator dependent or high cervical injury individuals and postulated that their overall shortened life expectancy might have bypassed the development of bladder cancer. These results advocate for screening strategies to identify at-risk groups with contributing factors for bladder cancer related deaths. Urethro-cystoscopy and/or bladder washing cytology and histology are relevant screening strategies that report 10% and 5%, respectively, identification rates in individuals with at least 5 years' history of neurogenic lower urinary tract dysfunction (Sammer et al. 2015).

Bladder Stones

Compared to the general population, individuals with SCI have a higher risk of bladder stone formation (Chen et al. 2002; Bartel et al. 2014). Secondary complications arising from urinary stasis, hypercalciuria due to immobilization, and long-term catheter use are all contributing factors to the higher prevalence of bladder stone formation in people with SCI. Bartel et al. (2014) associated bladder stones in individuals using suprapubic catheters (SPC, 11%), transurethral catheters (TC, 6.6%), intermittent catheterization (IC, 2%) and reflex micturition (RM, 1.1%). The time interval to bladder stone development for TC, SPC, IC, and RM was 31, 59, 116 months and 211 months, respectively. Similarly, recurrence rates were 40, 28, 22 and 0%, respectively. Conversely, time to recurrence for the TC group was the longest at 31 months and 26 and 14 months for IC and SPC groups, respectively. Once a stone required treatment, Eyre et al. (2015) reported overall complication rates ranging from 0% to 11% to 25% following washout, stone punch and electrohydraulic lithotripsy (EHL) techniques, respectively. Combining stone punch and EHL yielded significantly higher overall rate of complications (38%, $p=0.046$), which was further exacerbated when these combined procedures were carried out on individuals with cervical-level injuries ($p=0.032$). Having a complication, a combined procedure, and age contributed to significantly longer lengths of stay ($p<0.001$) than when stone punch alone is chosen.

Other

Endoscopic application of bulking agents is a treatment option for vesicoureteral reflux (VUR) in individuals with chronic SCI. Virseda et al. (2014) found that the

greatest success was achieved after neurogenic detrusor overactivity (NDO) was first eradicated. Otherwise, individuals with NDO experienced a high failure rate even though reflux was independent of involuntary detrusor contraction. Although individual age, presence of stress urinary incontinence (SUI), bilaterality were also thought to be predictive factors of success, multivariate analysis revealed that only degree of reflux and NDO were independent factors affecting success rate for anti-reflux procedures.

Conclusion

There is level 1a evidence (from three RCTs; Cheng et al. 1998; Xia et al. 2014; Gu et al 2015) that supports using electroacupuncture to significantly improve bladder function, when combined with conventional methods of bladder management.

There is level 2 evidence (from one prospective controlled trial; Hubshcer et al. 2018) that the use of locomotor training may increase bladder capacity, voiding efficiency and detrusor contraction time, as well as significant decreases in voiding pressure post-training.

There is level 4 evidence (from one pre-post study and one case series study; Zahariou et al. 2007; Chancellor et al. 1994) that intranasal DDVAP may reduce nocturnal urine production with fewer night-time emissions and also may reduce the need for more frequent catheterizations in persons with SCI with neurogenic bladder that is otherwise unresponsive to conventional therapy.

There is level 4 evidence (from one pre-post study; Agarwal et al. 2018) that Rectus abdominis detrusor myoplasty (RADM) appears to be a promising option in a individual with acontractile/ hypocontractile bladder to restore the bladder function.

There is level 4 evidence (from one pre-post study; Takahashi et al. 2018) that Mean maximum bladder pressure (MBP) is preserved at a low level following external sphincterotomy (ES), however neurogenic detrusor overactivity (NDO) gradually decreases over time over the years after ES, which would be one of the causes of failure of ES.

There is level 4 evidence (from three pre-post studies; Lin et al. 2009; Lin et al. 2008; Lin & Hou 2013) that nerve crossover surgery (anastomosis of T11 or S1 to S2-S3 spinal nerve roots) may result in improved bladder function in chronic SCI.

The balance of level 4 evidence (from three pre-post studies; Xiao et al. 2003 (positive results), Rasmussen et al. 2015 (negative results); Sievert et al. 2016 (negative results)) suggests that the Xiao procedure (L5-S3 ventral root anastomosis to establish a new reflex pathway) is ineffective for improving bladder function).

There is level 2 evidence (from one cohort study; Lee et al. 2014a, n=27,2005) that reported a lower rate of bladder and prostate cancer in people with SCI vs people without SCI.

There is level 2 evidence (from one cohort study; Eyre et al. 2015) that reports higher complication rates for combined bladder stone procedures vs stone punch alone.

There is level 4 evidence (from one case series study; Bartel et al. 2014) suggesting that bladder stone development occurs with suprapubic, transurethral, intermittent catheter use in descending frequency with reflex micturition have the lowest occurrence.

There is level 3 evidence (from one case control study; Virseda et al. 2014) suggesting the eradication of NDO before proceeding with endoscopic application of bulking agents to treat VUR with a higher success rate.

Electroacupuncture therapy as adjunctive therapy may improve bladder function.

Intranasal DDVAP may reduce nocturnal urine emissions and decrease the frequency of voids (or catheterizations).

Anastomosis of the T11 or S1 (but not L5) to the S2-S3 spinal nerve roots may result in improved bladder function in chronic SCI.

People with SCI seem to have a lower rate of bladder and prostate cancer than people without SCI.

Individuals with severe SCI may have higher bladder cancer related mortality.

Bladder cancer screening may be an option for people with more severe SCI.

Combined techniques for bladder stone removal likely result in higher complication rates than when stone punch is used alone.

Bladder stone occurrence may occur more frequently with catheter use than with reflex micturition.

Endoscopic application of bulking agents to treat VUR may be more successful if NDO is eradicated first.

5.0 Detrusor Areflexia

Detrusor areflexia is observed most commonly in cauda equina lesions where the sacral reflex is disrupted. Detrusor areflexia can also occur below the S2 spinal cord level and involve the conus medularis or peripheral nerves. Clinically, this means that

the bladder cannot empty completely or at all, leading to overdistension and stasis. Additionally, there is frequently incontinence due to lack of external sphincter tone, most often due to increased abdominal pressure on the bladder (i.e. stress incontinence). This can be especially problematic in persons with paraplegia that may require high valsalva forces for activities such as transferring from wheelchairs.

Unfortunately, there is a great paucity of research examining the impact and treatment of detrusor areflexia. Although the goals remain the same as with overactive bladder in SCI, (i.e., avoiding incontinence, stasis, UTI, and upper urinary tract damage), these goals may be achieved differently. In general, the goal is either: 1) stopping leakage and improving storage with medications and intermittent catheterization, or 2) improving emptying, either voluntarily in the incomplete injury, and/or into condom drainage in males with more severe neurogenic bladder impairments. However, further discussion on detrusor areflexia will not occur in this chapter given the extremely sparse evidence base. It should be noted that in two other studies described in the sections pertaining to DESD therapy there were mixed samples with a few subjects with detrusor areflexia. In one instance, subjects with detrusor areflexia comprised all study participants providing level 4 evidence from a single case series (n=10) for the surgical anastomosis of the T11 ventral nerve root to the S2-S3 ventral nerve roots in improving bladder function (e.g., Table 20 for Other Miscellaneous Treatments).

Table 21 Detrusor Areflexia

Author Year Country Research Design PEDro Score Total Sample Size	Methods	Outcome
Shin et al. 2002 Korea Observational N=50	<p>Population: Individuals with traumatic cauda equina injury: <u>Normal compliance group (n=36):</u> Mean age: 32.9 yr; Gender: males (n=20), females (n=16); Mean time from injury: 4.9 mo; Mean time interval between injury and rehabilitation: 3.4 mo; Voiding method: clean intermittent catheterization (n=20), reflex voiding (n=11), foley catheterization (n=3), normal voiding (n=2).</p> <p><u>Low compliance group (n=14):</u> Mean age: 26.2 yr; Gender: males (n=6), females (n=8); Mean time from injury: 7.8 mo; Mean time interval between injury and rehabilitation: 5.9 months; Voiding method: clean intermittent catheterization (n=2), reflex voiding (n=7), foley catheterization (n=5), normal voiding (n=0).</p> <p>Intervention: Urodynamic evaluation; normalization of compliance in individuals in the low</p>	<ol style="list-style-type: none"> 1. No significant difference between the normal compliance and low compliance for age and sex. 2. There was a significantly longer time interval between rehabilitation and time from injury in the low compliance group (p<0.05). 3. In the normal compliance group, clean intermittent catheterizations were used significantly more compared to the low compliance group (p<0.05). 4. The low compliance group had significantly lower mean compliance and mean maximal bladder capacity than the normal compliance group (p<0.01). 5. Mean maximal detrusor pressure was significantly higher in the low compliance group (p<0.01).

	<p>compliance group via Oxybutynin and propiverine.</p> <p>Outcome Measures: Presence of autonomous detrusor contraction (ADC), time since injury, voiding method prior to admission, maximal bladder capacity, maximal detrusor pressure, compliance,</p>	<p>6. ADC observed in 6/14 individuals in the low compliance group, these individuals had significantly lower mean compliance, maximal bladder capacity and higher maximal detrusor pressure ($p<0.05$).</p> <p>7. Normalization of low compliance group led to significantly higher compliances and maximal bladder pressures ($p<0.05$), as well as significantly lower maximal detrusor pressures ($p<0.05$).</p> <p>8. Follow-up of normalization showed ADC to disappear and compliance and maximal bladder capacity to return to normal in 4/6 ADC individuals.</p>
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6.0 Urinary Tract Infections

6.1 Defining Urinary Tract Infections

Urinary tract infections are a common secondary health condition following SCI and a major cause of morbidity (Charlifue et al. 1999; Vickrey et al. 1999). The most prevalent risk indicator of UTI in SCI individuals is an indwelling catheter (Biering-Sorensen et al. 2002) or increased duration of catheterization (Foxman 2003). There are numerous ways that UTIs have been defined within individual studies with respect to either identifying the presence of UTIs and/or establishing treatment success. Although this diversity exists across studies, the criteria identified at the National Institute on Disability Rehabilitation Research (NIDRR) sponsored National Consensus Conference on UTI in 1992 and used in the 2006 Consortium for Spinal Cord Medicine Guidelines for Healthcare Providers, have become generally accepted standards for UTI definition. These stipulate that three criteria must be met before an individual with SCI is diagnosed with an UTI: 1) significant bacteriuria; 2) pyuria (urine containing increased white blood cells); and 3) signs and symptoms, as follows:

- Leukocytes in the urine generated by the mucosal lining
- Discomfort or pain over the kidneys or bladder, or during urination
- Onset of urinary incontinence or leakage around the catheter
- Fever or chills
- Anorexia
- Increased spasticity
- Autonomic hyperreflexia,
- Cloudy, dark, and/or malodorous
- Malaise, lethargy, increased sweating, or sense of unease

Significant bacteriuria varies according to the method of urinary drainage and is defined by the following criteria: a) $\geq 10^2$ colony-forming units of uropathogens per milliliter (cfu/mL) in catheter specimens from persons on intermittent

catheterization, b) $\geq 10^4$ cfu/mL in clean-voided specimens from catheter-free men using condom catheters, c) any detectable concentration of uropathogens in urine specimens from indwelling or SPC, and d) $\geq 10^5$ cfu/mL for spontaneous management. Treatment of asymptomatic bacteriuria is not recommended, except in the cases of pregnancy and those undergoing urologic procedures (Nicolle et al. 2005) as it has been shown to be ineffective and can create antimicrobial resistance. In addition, asymptomatic bacteriuria can be effectively treated with antiseptics and urinary alkalinizers or acidifiers (Salomon et al. 2006).

6.2 Detecting and Investigating UTIs

Detecting a UTI via identification of symptoms by a individual is a critical first step; however, in a prospective case review undertaken by Linsenmeyer and Oakley (2003) only 61% (90/147) of individuals were able to correctly predict the presence of a UTI based on their symptoms. Other methods of detection include urine chemical dipsticks which provide an indication of the presence of nitrites and leukocytes with the benefit of providing a quick turnaround (Faarvang et al. 2000; Hoffman et al. 2004). However, the gold standard for detection is the microbiological evaluation of urine bacterial culture. As noted above, organizations such as NIDRR have defined UTIs at least in part on the results of laboratory investigations documenting the presence, amount and type of bacterial growth that occurs with an infection. This also results in the identification of the antibiotic(s) for which the bacteria species may be susceptible (i.e., sensitivity). These practices are aligned with the recommendations for data capture through the work of the International SCI UTI Basic Data Set working group. This work has been endorsed by the International Spinal Cord Society (ISCoS) Scientific Committee and the American Spinal Injury Association (ASIA) Board. Specifically, the data elements include “date of data collection, length of time of sign(s)/symptom(s), results of urine dipstick test for nitrite and leukocyte esterase, urine culture results and resistance pattern” (Goetz et al. 2013). On resistance patterns, it has been noted that 33% of SCI UTIs are polymicrobial (Dow et al. 2004). The clinician must then decide between a limited or full microbial investigation in selecting the appropriate treatment. The obvious benefit of a full microbial investigation (i.e. accuracy) is offset by potentially adverse effects due to the time delay for the bacterial sensitivity results and the cost of a full investigation. The studies reviewed in the present section examine specific issues associated with the laboratory investigation of UTIs and how these might impact treatment.

Table 22 Investigating UTIs

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
Horton et al. 1998 USA RCT PEDro=6 N=40	Population: SCI, in individuals. Intervention: Urine sample was processed within 4 h of sampling (“fresh”) versus 24 (“refrigerated”) hours of refrigeration.	1. No significant difference between fresh and refrigerated samples in: <ul style="list-style-type: none"> • White Blood Cell (p=0.724),

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
	Outcome Measures: Cultures, colony counts, urinalysis.	<ul style="list-style-type: none"> Number of bacteria (p=0.440) Leukocytes (p=0.782), Colony counts of E. fecalis & Pseudomonas (p=0.317), E. coli, Citrobacter, Streptococcus, Yeast, or Acinetobacter (p=1.0). <ol style="list-style-type: none"> Significant difference between fresh & refrigerated samples with colony counts<50 k: "mixed" organisms (p=0.010) Staph aureus trend only (p=0.066) No cultures/colony count changes in up to 24 h refrigeration to alter treatment or clinically significant urinalysis/culture results.
Darouiche et al. 1997 USA RCT (study 1) Pre-Post (study 2) PEDro=7 Study 1 N=45/40 Study 2 N=12	<p>Population: SCI with symptomatic polymicrobial urinary tract infection (UTI); Age range 23-84 yr; Gender: males=57, females=0.</p> <p>Intervention: Limited versus full microbiological investigation for management of symptomatic polymicrobial UTI (limited=cultures for specific organisms not used to guide antibiotic selection).</p> <p>Outcome Measures: Clinical improvement following symptomatic UTI (criteria defined as presence of bacteria+one symptom) by 4 d after treatment with antibiotic, time to start antibiotic cost of entire therapy and lab tests.</p>	<ol style="list-style-type: none"> No difference in therapy response between full versus limited approach (95% versus 85%, p=0.4); Limited approach antibiotic initiation earlier at 1.2±1.4 d versus 3.3±2.5 d for full approach (p=0.01); Higher proportion of people in limited group required no change in initial antibiotic than with full approach 85% versus 33% (p=0.006); Recurrence at 1 mo due to at least 1 of the originally infecting species was similar for both groups (p=1.0); Costs for limited investigation-directed therapy less at \$157±\$174 versus \$252±\$237 for full approach indicative of a trend but not significantly different (p=0.18)
Shah et al. 2005 USA Prospective Controlled Trial N=85	<p>Population: SCI in individuals with indwelling / suprapubic catheter and suspected of having a urinary tract infection (UTI); Control group=41: Mean age: 55.6 yr; Treatment group=44: Mean age: 64.1 yr.</p> <p>Intervention: Individuals were admitted to two spinal cord units: 1) continued the routine practice of examining urine samples without</p>	<ol style="list-style-type: none"> More clinically significant organisms ($\geq 10^5$ cfu/mL) were found in those whose catheter was not changed versus changed (89/41 individuals versus 60/44 individuals, p=0.01). Fewer non-clinically significant organisms (<10⁵ cfu/mL) were found in those whose catheter was not changed versus

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
	<p>replacing the catheter (Control group); versus 2) nurses replaced catheter before obtaining urine samples (Treatment group) for urinary analysis.</p> <p>Outcome Measures: Prevalence of organisms, types of organisms, laboratory costs.</p>	<p>changed (4/41 individuals versus 19/44 individuals, $p=0.01$).</p> <ol style="list-style-type: none"> 3. Changed catheter group had significantly less multidrug resistant organisms than the control group ($p<0.001$). 7. The changed versus unchanged catheter approach resulted in a total cost reduction of \$15.64 per individual.
<p>Hoffman et al. 2004 USA Pre-Post N=56</p>	<p>Population: SCI>6 mo post-injury who reported recurrent urinary tract infections (UTIs); Mean age: 38.86 yr; Gender: males=42, females=14; Level of injury: tetraplegia=34.</p> <p>Intervention: Comparing dipstick results for Nitrites or leukocyte esterase (LE) to urine culture results.</p> <p>Outcome Measures: Urine samples (nitrate, leukocyte esterase (LE), and culture) and self-report of symptoms, urinary tract infection (UTI) presence and treatment collected monthly over 3 yr and then only for 10 mo over last 2 yr, sensitivity, specificity, undertreatment, overtreatment were assessed.</p>	<ol style="list-style-type: none"> 1. In predicting significant bacteriuria, when either Nitrates or LE separately or both were positive there was a low sensitivity (0.63) and overtreatment rate (0.04) with a high specificity (0.89) and undertreatment rate (0.96). 2. In predicting National Institute on Disability Rehabilitation Research-based UTI, when either Nitrates or LE separately or both were positive there was a low sensitivity (0.64) but also a low specificity (0.52) resulting in a higher overtreatment (0.66) and lower undertreatment rate (0.22) than seen with bacteriuria prediction; overall results suggest using dipstick testing as a treatment guide could result in overtreatment rates of 70% and low rates of undertreatment.
<p>Faarvang et al. 2000 Denmark Pre-Post N=143</p>	<p>Population: Those with spinal cord lesion admitted to individual SCI program.</p> <p>Intervention: 256 morning urine samples were collected from individuals using a standardized 'clean' technique. Analysis was conducted with chemical dipstick and microscopy within 3 hr.</p> <p>Outcome Measures: Prevalence of bacteria compared with nitrite/leukocyte dipstick tests (positive and negative predictive values), types of bacteria.</p>	<ol style="list-style-type: none"> 1. The authors suggested that results comparing positive and negative predictive values indicated that the dipstick and microscopy tests are both equally valuable. 2. True negative predictive value ~0.7 and true positive predictive value of ~0.9. 3. 128 out of 256 urine samples contained significant bacteriuria. 4. Only 87 contained just one microorganism.
<p>Massa et al. 2009 USA Case Series N=51</p>	<p>Population: SCI: Gender: males=34, females=17; Catheterization type: standard catheter=26, hydrophilic catheter=25; Level of injury:</p>	<ol style="list-style-type: none"> 1. "Cloudy urine" had the highest accuracy (83.1%); "leukocytes in the urine" had the highest sensitivity (82.8%); "fever" had

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
	<p>cervical=19, thoracic=26, lumbar=5, sacral=1.</p> <p>Intervention: Analysis of monthly urine culture and urinalysis data, as well as a self-reported questionnaire on urinary tract infection (UTI) signs and symptoms.</p> <p>Outcome Measures: Presence of UTI defined as both a bacteriuria with a colony count of at least 10⁵ colony-forming units/mL and at least 1 sign or symptom of UTI.</p>	<p>the highest specificity (99.0%), but had low sensitivity (6.9%).</p> <ol style="list-style-type: none"> Subjects were able to predict their own UTI with an accuracy of 66.2% and the negative predictive value (82.8%) was substantially higher than the positive predictive value (32.6%).
<p>Tantisiriwat et al. 2007 Thailand Case Series N=76</p>	<p>Population: SCI hospitalized at Rehabilitation Center (Thai Red Cross Society); Mean age: 44.7 yr; Gender: males=50, females=26; Type of neurogenic bladder: detrusor overactivity=39, detrusor underactivity=9.</p> <p>Intervention: Retrospectively chart review to assess urinary tract infection (UTI) prevalence, causative bacteria and susceptibility patterns.</p> <p>Outcome Measures: Prevalence of UTI, causative bacteria, susceptibility to antibiotic.</p>	<ol style="list-style-type: none"> Prevalence of UTI was higher in individuals with neurogenic detrusor overactivity (97.14%) than underactivity (66.67%). Of urine culture performed in 41/68 episodes of UTI, 39 positive cultures identified with <i>E. coli</i> (74.4%), <i>K. pneumonia</i> (12.8%), <i>Enterococcus faecalis</i> (5%) and <i>Proteus mirabilis</i> (5%) most common. <i>E. coli</i> was most susceptible to amikacin (96.1%), ceftazidime (88.9%), and ceftriaxone (75%). <i>K. pneumonia</i> was most susceptible to ceftazidime (80.0%), ceftriaxone (80.0%), amikacin (60.0%) and cotrimoxazole (60%).
<p>Escalrin De Ruz et al. 2000 Spain Case Series N=128</p>	<p>Population: SCI: Mean age: 32.0±14.5 yr; Gender: males=100, females=28.</p> <p>Intervention: Prospective examination of individuals for 38 mo to identify potential risk factors for UTIs.</p> <p>Outcome Measures: Associated factors, methods of urinary drainage, bladder type, urological complications, Functional Independence Measure (FIM) and predisposing factors.</p>	<ol style="list-style-type: none"> Risk factors associated with urinary tract infection were invasive procedures without antibiotic prophylaxis, cervical injury and chronic catheterization. Risk factors associated with repeat infection were a FIM score less than 74 and vesicoureteral reflux.

Discussion

Perhaps understanding risk factors may be the simplest method of initial recognition and management of UTI. Escalrin de Ruz et al. (2000) prospectively followed 128 SCI individuals for 38 months. Logistic regression modeling was performed on demographic characteristics, associated factors, urinary drainage methods, type of bladder dysfunction, urological complications and predisposing

factors of each infection episode. The results showed that individuals who were completely dependent (FIM score <74) and who had vesicoureteral reflux were at the highest risk for UTI.

Beyond functional characteristics (e.g., FIM scores and type of bladder dysfunction), Massa et al. (2009) found that the presence of “cloudy urine” had the highest accuracy (83.1%), and a positive dipstick test for the presence of leukocytes had the highest sensitivity (82.8%, highest true positive results). Although the presence of fever reflected the highest specificity (99.0%), its sensitivity was very low (6.9%) for UTI. The authors concluded from this prospective cohort, that basic objective measures such as cloudy urine and positive dipstick results were better at predicting UTI than the individual's themselves.

However, once a UTI is detected, laboratory investigation using microbiological analysis of urine cultures is important for confirming UTI and guiding treatment. Shah et al. (2005), Hoffman et al. (2004) and Tantisiriwat et al. (2007), reporting centre-based results under a variety of study designs, noted *Enterococcus* species, *Klebsiella pneumoniae*, *Escherichia coli*, *Pseudomonas aeruginosa*, *Staphylococcus aureus* and *Proteus mirabilis* as among the most common species of bacteria present in urine from those suspected of having a UTI. In the associated antibiotic sensitivity tests, Tantisiriwat et al. (2007) noted that *E. coli* was most susceptible to amikacin (96.1%), ceftazidime (88.9%), and ceftriaxone (75%). The efficacy of specific antibiotics investigated in the SCI literature will be summarized in subsequent sections.

Given the cost and the time spent before results can be obtained with bacterial culture (e.g. 18-48 hours), simpler screening methods have been developed for assessing the presence of a UTI. One of these methods involves using a urine “dipstick” which signifies the presence of nitrites or the presence of leukocyte esterase respectively as a potential indicator of UTI. The results of investigations into the sensitivity and specificity of dipstick tests in predicting UTI in individual populations other than SCI have been mixed. Hoffman et al. (2004) conducted an investigation to compare dipstick results for nitrites and leukocyte esterase to urine culture results where each test was conducted monthly over a 5 year period in a community-based SCI sample (n=56). Using NIDRR criteria for UTI, 81% of the total 695 samples collected over the study period met criteria for bacteriuria, and of these, 36% met criteria for a positive UTI. In general, sensitivity (i.e., the ability to correctly identify significant results) was relatively low at 63% even when either the leukocyte esterase or nitrate dipstick was positive; specificity (i.e., the ability to correctly identify samples without significant bacteria) was 89% or higher for any combination of test. When compared to the ability to predict UTIs, the dipstick sensitivity remained relatively low at 63% and specificity was also low at 52% for any combination of dipstick test. Overall results suggest using dipstick testing as a treatment guide could result in inappropriate or delayed treatment and the study authors suggested that individuals with SCI with suspected UTI should be evaluated with urine culture and not dipstick testing (Hoffman et al. 2004). However, a separate investigation comparing positive and negative predictive values for dipstick testing as compared to leukocyte microscopy relative to culture-derived bacteriuria determined that

either method was equally effective with reasonable prediction rates of approximately 80% for each alone or in combination (Faarvang et al. 2000).

Darouiche et al. (1997) found that an adequate clinical response to treatment was not significantly different as a result of limited versus full microbial investigation. Limited investigations were conducted by examining colony morphology, appearance on Gram-stain, catalase test and oxidase test without organism identification and antibiotic susceptibilities. Antibiotic selection was based on recognized hospital-based patterns of antibiotic susceptibilities. Cost savings, at an average of \$183 US per individual, was not significantly less than full investigation but indicated a trend ($p=0.18$). Although this provides good evidence in favour of deferring to a limited microbial investigation for SCI UTI treatment selection, the sample size was small ($N=15$) and warrants further study. It is also unclear from this study if the results are transferable to a setting other than an individual hospital unit (i.e., community-based individuals) and whether treatment is determined in part by relying on the experience of the clinical team in determining treatment.

The results of clinical laboratory analysis are also prone to contamination from a variety of practical issues. For example, sample deterioration between the time of sampling and processing is controversial. Horton et al. (1998) conducted a blinded RCT to investigate the effects of refrigeration on urinalysis and culture results. Samples were split and analyzed at 4 hours ("fresh") and 24 hours ("refrigerated") post-refrigeration. The bacterial counts of "mixed" organisms ($p=0.10$) and *Staphylococcus aureus* ($p=0.66$) were altered with refrigeration but no changes in colony counts would have altered the treatment regimen chosen based on urinalysis or culture results. This study provides a level of confidence for urine samples refrigerated (up to 24 hours) prior to analysis.

In another investigation of a narrower issue involving potential contamination, Shah et al. (2005) demonstrated that the number of clinically significant organisms ($\geq 10^5$ cfu/mL) detected by urine culture were reduced in SCI individuals with indwelling or SPC suspected of having a UTI when the catheter was changed just prior to urine collection as compared to those where it was left unchanged ($p=0.01$). This practice also resulted in a savings of \$15.64 (U.S.) per individual.

Conclusions

There is level 4 evidence (from one case series study; Escalrin de Ruz et al. 2000) that individuals with SCI who are completely dependent (FIM<74) or who have vesicourethral reflux are at highest risk for UTI.

There is level 4 evidence (from one case series study; Massa et al. 2009) that the presence of cloudy urine or a positive urine dipstick test are better predictors of UTI compared with the individual's own subjective impression of their own signs and symptoms.

There is conflicting level 4 evidence (from two pre-post studies; Hoffman et al. 2004; Faarvang et al. 2000) concerning whether dipstick testing for nitrates or leukocyte esterase is recommended to guide treatment decision-making.

There is level 1b evidence (from one RCT; Darouiche et al. 1997) that both limited and full microbial investigation result in adequate clinical response to UTI treatment with antibiotics. Therefore, the cost savings attributed to a limited microbial investigation favours this practice in the investigation of UTI although more rigorous investigation of the individual outcomes and attributed costs is needed.

There is level 1b evidence (from one RCT; Horton et al. 1998) that refrigeration (up to 24 hours) of urine samples prior to sample processing does not significantly alter urinalysis or urine culture results in SCI individuals.

There is level 2 evidence (from one prospective controlled trial study; Shah et al. 2005) that fewer false positive tests showing bacteriuria occur if indwelling or suprapubic catheters are changed prior to collection for urine culture analysis.

Both limited and full microbial investigation may result in adequate clinical response to UTI treatment with antibiotics.

Indwelling or suprapubic catheters should be changed just prior to urine collection so as to limit the amount of false positive urine tests.

Urinalysis and urine culture results of SCI individuals are not likely to be affected by sample refrigeration (up to 24 hours).

It is uncertain if dipstick testing for nitrates or leukocyte esterase is useful in screening for bacteriuria to assist treatment decision-making.

6.3 Non-Pharmacological Methods of Preventing UTIs

The method of bladder management one selects is a primary factor in reducing the risk of UTI in persons with SCI (Trautner & Darouiche 2002). The method chosen should minimize exposure of the urinary system to foreign bodies and reduce their potential for continued residence by draining the bladder effectively.

6.3.1 Intermittent Catheterization and Prevention of UTIs

Most SCI-related, UTI prevention research has focused on various techniques for intermittent catheterization and these types of studies are summarized in Table 23.

Table 23 Intermittent Catheterization and Prevention of UTIs

Author Year Country Score Research Design Total Sample Size	Methods	Outcome
Li et al. 2013 China Review of published articles between 1991- Aug 2011 N=5	<p>Method: Comprehensive literature search of English and Chinese RCT, quasi-RCT (parallel-control, crossover-control, prospective cohort studies) of SCI individuals with bladder dysfunction and using hydrophilic and nonhydrophilic (standard) catheters.</p> <p>Databases: PubMed, EMBASE, CNKI (China National Knowledge Infrastructure), Chinese Biomedical Literature Database, Cochrane Library</p> <p>Level of evidence: 2 – RCT (Note: Research Design/ Description of the 5 included studies not fully defined)</p> <p>Questions/measures/hypothesis: Compare the impact of hydrophilic and nonhydrophilic catheters on the occurrence/incidence of UTIs and hematuria.</p>	<ol style="list-style-type: none"> 1. The use of hydrophilic catheters versus standard catheters reduced the odds of UTI by about 64% (OR=.36, CI=95% (24-54%), $p<.00001$; i.e., there was a significantly lower incidence of reported UTIs in those using hydrophilic catheters than in those using standard catheters). 2. The more individuals that used hydrophilic catheters, the more significant the results. 3. The use of hydrophilic catheters versus standard catheters reduced the odds of hematuria by about 43% (OR=.57, CI=95% (35-92%), $p=.001$). (i.e. there was a significantly lower incidence of reported hematuria in those using hydrophilic catheters than in those using standard catheters). 4. The incidence of hematuria was 45.7% (95/208) in individuals using hydrophilic catheters versus 55% (115/209) in individuals using standard catheters.
Bonfill et al. 2017 Spain RCT PEDro=7 N _{Initial} =489 N _{Final} =440	<p>Population: Silver alloy coating catheter (SAC): Mean age=55.30yr; Gender: males=174, females=69; Etiology: Traumatic SCI=177; Medical SCI=61. Standard catheter (STC): Mean age=57.25yr; Gender: males=179, females=67; Etiology: Traumatic SCI=177; Medical SCI=65.</p> <p>Intervention: Individuals were randomly assigned to either silver alloy coating catheter (experimental group) or standard catheter (control group) for at least 7 days. Outcome measures assessed before and after gentamicin instillations.</p> <p>Outcome Measures: Occurrence of catheter-associated symptomatic UTI; symptomatic bacteraemia; adverse events related to catheterization procedure.</p>	<ol style="list-style-type: none"> 1. There was no significant difference in the occurrence of catheter-associated UTI. 2. Sixteen individuals had adverse events potentially related to catheterization: SAC=12 (4.9%), STC=4 (1.6%) (OR 0.03 [0.00-0.006]). 3. Bacteremia confirmed in three individuals: SAC=1, STC=2.
Lavado et al. 2013 Brazil RCT PEDro=9 N=42	<p>Population: Mean age: Control (C)=38.5±10.6 yr, Intervention (I)=34.1±11.1 yr. Gender: (C)=17 male, 4 female, (Int)=males=18, females=3; Level of injury: C5-L2; Motor level: C8-</p>	<ol style="list-style-type: none"> 1. The mean length of study participation was 17.9 ± 1.8 weeks. 2. The rate of adherence to the exercise programme was 94.6%.

Author Year Country Score Research Design Total Sample Size	Methods	Outcome
	<p>T12; Neurological level: ASIA A, B and C; Time since injury: (C)=4.05±1.6 yr, (I)=4.8±2.2 yr.</p> <p>Intervention: Individuals were randomized into Control (C) or Intervention (I) groups All individuals performed a stress test and had a urine analysis and urine culture completed prior to exercise (i.e. pre-training) and at 16 weeks post-training. Physiotherapy sessions consisted of passive mobilizations, stretching and functional activity training. Control group instructed to maintain their current activities of daily life</p> <p>Intervention training group (Int) had additional physiotherapy sessions consisting of a 16-week programme of aerobic physical training (i.e. cycloergometer of upper limbs, distance with a wheelchair, and general muscle exercise (progressive loading of residual muscle and muscle stretching))</p> <p>Training activity=1 hour, 2 or 3x/week</p> <p>Intensity determined by maximum heart rate (goal of 70-80%), or peak oxygen consumption. Stress tests were completed to verify a significant increase of oxygen consumption in order to demonstrate the effectiveness of a physical training programme</p> <p>Outcome Measures: Estimated peak oxygen consumption (V_{O2peak}), Chronic asymptomatic bacteriuria (CAB)</p>	<ol style="list-style-type: none"> 3. Treatment with antibiotics was required for 2 participants (1 from each group resp.). These 2 cases were considered a negative outcome. 4. No adverse effects related to the physical activity were recorded during the training period. 5. V_{O2peak} before versus after training for the Cont group was 896mL min⁻¹ (range 677-1158) versus 834mL min⁻¹ (range 711-1005), which was not statistically significant. (p=0.906) 6. V_{O2peak} before versus after training for the Int group was 939mL min⁻¹ (range 714-1215) versus 1154mL min⁻¹ (range 1005-1351), which was statistically significant. (p=0.009) 7. The difference in V_{O2peak} between the 2 groups was not statistically significant prior to training (p=0.529), however it was statistically significant after training. (p<0.001) 8. The number of individuals testing negative for CAB before training in the Cont versus Int groups was 8 (38.1%) versus 10 (47.6%) resp, which was not statistically significant. (p=0.755). 9. The number of individuals testing positive for CAB after training in the Cont versus Int groups was 15 (71.4%) versus 3 (14.2%) resp, which was statistically significant. (p<0.001).
<p>Moore et al. 2006 Canada RCT PEDro=4 N=36</p>	<p>Population: SCI individuals undergoing rehabilitation and requiring intermittent catheterization due to neurogenic bladder; Mean age: 40 yr; Gender: males=28, females=8; Level of injury: cervical.</p> <p>Intervention: Comparison of clean versus sterile intermittent catheterization (IC). Laboratory personnel were blinded to subject allocation.</p> <p>Outcome Measures: Prevalence of urinary tract infection (UTI), time to onset of UTI, costs of intermittent</p>	<ol style="list-style-type: none"> 1. No significant difference (p>0.05) between the groups was seen in: <ul style="list-style-type: none"> • Prevalence of UTI. • Time to onset of UTI. • Cost for clean intermittent catheterization/d was half that of sterile (\$7.56 CDN versus \$16.62 CDN). • The most common type of bacteria included Enterococcus and Klebsiella. 2. No adverse effects were reported.

Author Year Country Score Research Design Total Sample Size	Methods	Outcome
	catheterization, types of bacteria, adverse effects. Urine analysis was conducted weekly.	
Prieto-Fingerhut et al. 1997 USA RCT PEDro=2 N=29	<p>Population: SCI during inindividual rehabilitation: Gender: males=16, females=13; Severity of injury: AIS: A-D.</p> <p>Intervention: Comparison of sterile versus non-sterile (clean) intermittent catheterization technique every 4 to 6 hr.</p> <p>Outcome Measures: Number of urinary tract infections (UTIs) over a 3 mo period, cost analysis.</p>	<ol style="list-style-type: none"> 1. There were less UTIs with the sterile versus the non-sterile catheterization program (28.6% versus 42.4%) but this difference was not significant. 2. Sterile catheterization program was 277% more costly.
Pearman et al. 1991 Australia RCT PEDro=5 N=43	<p>Population: SCI individuals: Group A (n=20, males=19, female=1); Group B (n=23, males=17, females=6).</p> <p>Intervention: Individuals were randomized to either Group A or Group B. Group A: Individuals underwent intermittent catheterization by Nelaton catheter with the instillation of Trisdine into the bladder at the end of each catheterisation. Group B: Individuals performed intermittent catheterization with the O'Neil catheter.</p> <p>Outcome Measures: Incidence of significant bacteriuria, which was classified as a catheter specimen of >1000 colony forming units (cfu)/ml.</p>	<ol style="list-style-type: none"> 1. In group A, the mean incidence of significant bacteriuria in males and females was 0.58 and 0.48% per catheterization; while in group B the mean incidence of significant bacteriuria in males and females was 1.16 and 2.93% per catheterization. 2. The instillation of Trisdine in group A resulted in a significantly lower incidence of bacteriuria compared to group B (p<0.001).
Bennett et al. 1997 USA Prospective Controlled Trial N=27	<p>Population: Mean age: 26±7.5 yr (range 17-38); Level of injury: tetraplegic (n=11), paraplegic (n=16).</p> <p>Intervention: <i>Group 1:</i> Individuals performed intermittent catheterization (IC) with an introducer tip catheter (no spontaneous void or external urinary catheter). <i>Group 2:</i> Same as group 1 except IC with nonintroducer tip catheter. <i>Group 3:</i> Individuals performing IC with introducer tip catheter (voiding by reflex and wearing an external urinary catheter). <i>Group 4:</i> Same as group 3 except IC with nonintroducer tip catheter.</p>	<ol style="list-style-type: none"> 1. A significant difference was between individuals using an introducer tip catheter and those who were not, regardless if an external urinary catheter was worn in measured urodynamic parameters (p=0.0121). 2. Furthermore, a significant difference was found between individuals using and not using the introducer tip catheter in the intermittent catheterization only group (p=0.0093).

Author Year Country Score Research Design Total Sample Size	Methods	Outcome
	Outcome Measures: Urodynamic parameters.	
Yadav et al. 1993 India Prospective Controlled Trial N=48	Population: <i>Group A (n=27):</i> Gender: males=26, females=1; Time post-injury=12-96 hr; <i>Group B:</i> Level of injury: paraplegia=19, tetraplegia=2; Chronicity=chronic. <i>Group B (n=21).</i> Intervention: Group A (short-term clean intermittent catheterization (IC) starting on day 1 of hospitalization). Group B (long term clean IC; 1-12 yr). Outcome Measures: Number of UTIs collected over 10 d to 3 mo (A) or over 6 mo (B).	1. Both short-term and long-term groups had relatively low rates of UTI. 2. Group A: 5 subjects had symptomatic UTI between 10 d and 3 mo. 3. Group B: 0.07 episodes per individual per mo symptomatic UTI (33%).
Wyndaele & De Taeye 1990 USA Prospective Controlled Trial N=73	Population: <i>SCI Inindividuals (n=25);</i> Age range 6-59 yr; Gender: males=22, females=3; Level of injury: paraplegia, tetraplegia. <i>Non-SCI (n=48).</i> Intervention: Comparison of individual self-catheterization versus in-hospital catheter team for intermittent catheterization (IC). Outcome Measures: Success in balancing bladder, urinary tract infection (UTI) rate, and urethral trauma collected over inindividual stay.	1. No difference in UTI between groups. 2. No difference in achieving a state of balanced bladder between groups (i.e., able to empty bladder by tapping or straining after a mean of 5 weeks.) 3. No difference in urethral trauma between groups.
Charbonneau-Smith 1993 Canada Cohort N=110	Population: Traumatic SCI on inindividual rehabilitation; 2 groups were similar with respect to median age (30.5 yr versus 30 yr), gender, paraplegics versus tetraplegics, level of lesion and extent of lesion; length of stay (LOS): 4.8 wk versus 11 wk. Intervention: Assessment of no-touch versus traditional straight intermittent catheterization (IC) method. Outcome Measures: Urinary tract infections (UTIs), infection free days, duration of infection, cost of antibiotics, nurse satisfaction with method collected during rehabilitation hospital stay.	1. "No-touch" experimental group had fewer UTIs ($p=0.0001$), and reduced duration of infections ($p=0.0004$). 2. No difference on total cost (including antibiotics) and number of infection-free days (trends were in favour of "No-touch", $p=0.072$, $p=0.125$). 3. Similar number of catheters used despite >2x longer length of stay (LOS) for traditional method. 4. Majority of nurses reported they preferred "No touch" catheter.
Jensen et al. 1995 Norway Pre-Post N=12	Population: SCI rehabilitation inindividuals: Age range 17-72 yr; Gender: males=11, females=1; Time post-injury=3-7 mo. Intervention: Effect of residual urine volume following intermittent	1. Residual urine volumes were not associated with UTIs - Mean & Max residual volumes/UTI correlations: $r=0.19$ & 0.16 ($p=0.52$ & 0.63) respectively. 2. Trend for greater maximal residual urine in hyperactive

Author Year Country Score Research Design Total Sample Size	Methods	Outcome
	catheterization (IC) on urinary track infections (UTIs). Outcome Measures: Residual urine volume as measured by ultrasonography and occurrence of UTIs collected during hospital stay.	versus hypoactive bladder following IC (p=0.06). 3. No differences in hyperactive versus hypoactive bladder for mean residual volumes (p=0.21) or UTIs (p=0.49).
Krebs et al. 2016 Switzerland Case Series N=1104	Population: NLTUD; Mean age; 48 yr; Gender: males=821, females=283; Level of injury: C1-C4=73, C5-C8=249, T1-S5=622, AIS D=87, not determinable=73; Mean duration of NLTUD: 20.3 yr. Intervention: Individuals had previously undergone prophylactic treatment for urological procedures and/or onabotulinumtoxin injections for NDO. Outcome Measures: Assessment of both risk factors (catheterization, type of catheterization) for UTIs as well as prophylactic antibiotic treatment to prevent UTIs.	1. Bladder evacuation method, botulinum toxin injections into the detrusor and prophylactic treatment to prevent UTIs significantly predicted the contraction of symptomatic UTIs and recurrent UTIs (p=0.049). 2. Probability of experiencing a UTI was 10x higher for individuals voiding via a transurethral indwelling catheter compared to those voiding spontaneously. 3. Bladder voiding by TUC increased the probability 5x of recurrent symptomatic UTIs. 4. OnabotulinumtoxinA injections only increased the odds of symptomatic UTIs by 1.7x.
Mukai et al. 2016 Japan Case Series N=259	Population: Neurogenic bladder; Median age: 47 yr; Gender: males=220, females=39; Level of injury: cervical=86, thoracic=138, lumbar=34, sacral=1; Injury etiology: traumatic=207, non-traumatic=52; ASIA classification: A=166, B=32, C=30, D=26, E=5. Intervention: Individuals who required clean intermittent catheterization (CIC) for neurogenic bladder were reviewed determine potential risk factors for febrile urinary tract infections (UTI). Outcome Measures: Gender, ASIA classification, pyuria, bacteriuria, number of CIC performance per day, anticholinergic use, β -3 agonist use.	1. A total of 67 participants had febrile UTI during the follow-up period. 2. There were no significant associations for pyuria or bacteriuria with febrile UTI. 3. Anticholinergic use, β -3 agonist use, number of CIC per day were not significantly associated with febrile UTI occurrence. 4. In the multivariable analysis, gender being males (p=0.0431) and ASIA classification being C or more severe (p=0.0266) were significantly associated with an increased risk for febrile UTI occurrence.

Summarized Level 5 Evidence Studies:

Krassioukov et al (2015) reported a direct link between significantly increased UTI frequency and catheter reuse ($p < 0.001$). Although UTIs have many associated negative consequences to all people with SCI, the impact of UTIs emerging at critical times may have much more devastating consequences for subgroups (e.g. during

competition for elite athletes) which may warrant consideration for sterile techniques. Addressing lack of health education and available resources would be strategies to undertake to shift routines in favour of sterile catheter use. However, even if CIC is the method of choice, males ($p=0.431$) and those more severely injured (AIS C, B, A, $p=0.0266$) experience significantly higher rates of febrile UTI. Martins et al. (2013) reported 71% of individuals used clean intermittent catheterization, 18.4% ($n=7$) used condom catheters, 7.8% ($n=3$) used suprapubic drainage, and 2.6% ($n=1$) used tapping. 65.7% of individuals tested positive for asymptomatic bacteriuria where *E.coli* was the most prevalent (60%). Antibiotic resistance rates from bacteria were 73.3% to Ampicillin, 60% to Sulfamethoxazole-Trimethoprim, and 33.3% to Norfloxacin. The high prevalence of prophylactic and emergent antibiotic treatment of bladder management related infections has increased catheter-associated urinary tract infections (CAUTI) in spinal cord injury individuals (Dedeic-Ljubovic et al. 2009). Regular rectal swab surveillance, disposable aprons and glove use, and strictly monitored cleaning procedures (materials, instruments, infected individuals and environmental) are among the necessary activities to prevent multi-drug resistant *P. aeruginosa* (MDRP).

Discussion

During individual rehabilitation, IC is generally the preferred method of bladder management and several prospective studies have compared sterile techniques with traditional or clean techniques of IC (Charbonneau-Smith 1993; Prieto-Fingerhut et al. 1997; Moore et al. 2006). Notably, Moore et al. (2006) and Prieto-Fingerhut et al. (1997) employed RCT designs and showed no statistically significant differences in the number of UTIs occurring in individuals using the sterile technique versus the clean technique. Conversely, Charbonneau-Smith (1993) conducted a prospective trial and did find significantly reduced UTI rates for a sterile “no-touch” technique as compared to historical controls undergoing a traditional sterile method. Given the nature of the historical comparison confounding variables may affect this result. Both authors noted the greater expense associated with the sterile approach, making it a less attractive option in the absence of evidence for improved positive outcomes. On the other hand, Krebs et al. (2016) found that the use of transurethral indwelling catheters (TIC) increased the odds of symptomatic UTIs and recurrent UTIs by more than 10- and 4-fold, respectively. As such, the authors recommended that TIC “should be avoided whenever possible”. Also significantly increased are UTIs resulting from IC use ($p \leq 0.014$) and botulinum toxin injections into the detrusor ($p=0.03$).

Another strategy for decreasing the incidence of UTI is through the use of antiseptic-coated indwelling catheters. Bonfill et al (2017) conducted an RCT comparing catheters coated with silver alloy to standard catheters supplied by the trial site. No significant difference was found between incidence of symptomatic UTIs between the experimental and control groups (7.41% vs 7.72%, respectively). The generally low overall incidence of UTIs in the study was attributed to the pragmatic design whereby cultures were only performed in participants with a clinical suspicion of UTI.

A meta-analysis of five RCTs comparing the impact of hydrophilic catheters on UTIs in people with SCI found a reduction in the number of UTIs (reduced by 64%) when the hydrophilic catheters were used (compared to non-coated catheters; Li et al. 2013). The coating on the hydrophilic catheters also reduced urethral trauma (reduced odds of hematuria by ~43%). Despite the general positive effect of hydrophilic catheters versus uncoated catheters, no significant difference was found in single studies for episodes of bacteriuria (Sutherland et al. 1996), number of UTIs (Vapneek et al. 2003) and frequency of symptomatic UTIs (Cardenas & Hoffman 2009). However, the reduced number of UTIs requiring antibiotics, significantly reduced UTI frequency and episodes of hematuria across multiple studies would generally advocate for the use of hydrophilic catheters.

An interesting RCT finding reported by Lavado et al. (2013) found a significant reduction of positive urinary cultures in individuals randomized to 16 weeks of moderate aerobic physical conditioning compared to controls who were asked to maintain their daily life activities (Lavado et al. 2013). Increased peak oxygen consumption in participants of the intervention group suggested a correlation with an increased immune response, a known beneficial effect of regular physical exercise.

As with all aspects of rehabilitation, a primary goal of bladder training while an individual is maximal individual independence and self-care. Wyndaele and De Taeye (1990) conducted a prospective control trial (n=73) in which the incidence of UTIs was examined following introduction of an initiative to promote self-catheterization among those with paraplegia on an SCI unit. Prior to this, catheterization was conducted by a specialized catheter health care team using a non-touch technique. Neither UTI rates nor the proportion of people achieving a state of bladder balance or those encountering complications of urethral trauma were significantly different between these two approaches. Interestingly, the introduction of individual self-catheterization also seemed to be a factor in the individuals being ready for home visits much sooner in their rehabilitation stay.

Less information exists on the continued use of IC for individuals as they move into the community and live with SCI for a prolonged period of time. A prospective controlled trial was conducted by Yadav et al. (1993) comparing UTI incidence rates between those using a clean IC technique during individual rehabilitation with another group of individuals continuing to use the same bladder management method and living in the community for 1-12 years. Similar rates of UTI (termed acceptably low by the authors) were found in both samples although there were differences in the types of bacteria causing UTIs between the individuals with SCI in the rehabilitation unit versus in the community.

Regardless of the approach to bladder management, and even if IC is used, the rate of UTI in the SCI population is still elevated relative to a population with neurologically normal functioning bladders. This is thought to be partly due to the residual volume of urine that may persist in the bladder following IC. Jensen et al. (1995) conducted a study in individual rehabilitation (n=12), correlating UTI incidence over the rehabilitation period with the average residual urine volume after

IC. Correlations between UTIs and residual volumes were low and suggested little relationship or as the authors point out it may have been that residual volumes would have had to be reduced to negligible values to be responsible for a lower incidence of UTI compared to the mean values of 40 ± 11 mL for hyperactive bladder or 19 ± 7 mL for hypoactive bladder observed in this study.

Conclusion

There is level 1a evidence (from one meta-analysis of five RCTs; Li et al. 2013) that the use of hydrophilic catheters versus non-coated catheters is effective in reducing the incidence and occurrence of UTI and hematuria.

The RCT conducted by Bonfill et al (2017) provided level 1b evidence that indwelling silver alloy coated catheters did not reduce the incidence of UTI when compared to standard catheter use.

There is level 1b evidence (from one RCT: Lavado et al. 2013) that regular, moderate aerobic physical activity significantly increases peak oxygen consumption and also significantly reduces the number of individuals with positive urinary cultures.

There is level 2 evidence (from two RCTs; Moore et al. 2006; Peta-Fingerhut et al. 1997) that there is no difference frequency of UTI between sterile and clean approaches to intermittent catheterization during inindividual rehabilitation; however, using a sterile method is significantly more costly.

There is level 4 evidence (from one prospective controlled trial; Wyndaele & De Taeye 1990) that there is no difference in UTI rates between intermittent catheterization conducted by the individuals themselves or by a specialized team during inindividual rehabilitation.

There is level 4 evidence (from one prospective controlled trial; Yadav et al. 1993) that similar rates of UTI may be seen for those using clean intermittent catheterization during inindividual rehabilitation as compared to those using similar technique over a much longer time when living in the community.

There is level 4 evidence (from one pre-post study; Jensen et al. 1995) that differences in residual urine volume ranging from 0-153 ml were not associated with differences in UTI during inindividual rehabilitation.

There is level 4 evidence (from one retrospective case series; Mukai et al. 2016) that reports significantly higher rates of febrile UTIs in more severely injured males that use CIC.

Level 4 evidence (from one case series study, Krebs et al. 2016) suggests that transurethral indwelling catheter use results in the highest rate of symptomatic UTIs compared to lower rates from using intermittent catheters and receiving botulinum toxin injections into the detrusor.

Sterile and clean approaches to intermittent catheterization seem equally effective in minimizing UTIs in inindividual rehabilitation.

Similar rates of UTI may be seen with intermittent catheterization as conducted by the individuals themselves or by a specialized team during inindividual rehabilitation.

Similar rates of UTI may be seen with intermittent catheterization, whether conducted in the short-term during inindividual rehabilitation or in the long-term while living in the community.

UTIs were not associated with differences in residual urine volumes after intermittent catheterization.

Catheter reuse may be linked to increased frequency of UTIs.

More severely injured males who use CIC may have higher rates of febrile UTIs.

Transurethral indwelling catheter use may be associated with the highest rate of symptomatic UTIs when compared to rates.

6.3.2 Specially Covered Intermittent Catheters for Preventing UTI

Different coatings have been applied to catheters to minimize various complications associated with catheterization and neurogenic bladder and Table 25 outlines studies investigating the effect of hydrophilic catheters on UTI prevention.

Table 24 Intermittent Catheterization using Specially Coated Catheters for Preventing UTI

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
Cardenas et al. 2011 USA RCT PEDro=5 N=224	<p>Population: Treatment group: mean age: 37.2 yr; males=177, females=47, ASIA scale A=62%, B=18%, C=11%, D=11%; time post-injury=32 d. Control: mean age: 35.1 yr; male=82%, female=18%; ASIA scale: A=68%, B=10% C=19%; D=3%; time post-injury=29 d.</p> <p>Intervention: Intermittent catheterization with hydrophilic coated catheter</p> <p>Outcome Measures: Symptoms of urinary tract infection (UTI), treatment of antibiotics to prevent UTI, urolithiasis.</p>	<ol style="list-style-type: none"> 1. The time of first symptomatic UTI is significantly delayed in the treatment group ($p=0.038$). The decrease in daily risk of developing first UTI in the treatment group is 33%. 2. The incidence of UTI in treatment was reduced by 21% of treatment group. There is a significant difference presence of microhematuria ($p<0.0001$) between the two groups. 3. Overall there is a significant higher satisfaction rate reported by caregivers and participants in the treatment group ($p=0.007$). However, nurses reported no significant differences in overall

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		satisfaction of the 2 catheters group
Cardenas & Hoffman 2009 USA RCT PEDro=5 N=56	<p>Population: Treatment Group: Mean age: 42.3 yr; Gender: males=17, females=5; Level of injury: Tetraplegia=5, Paraplegia=17; Severity of Injury: AIS C4-C8 A=2, C4-C8 B-D=3, T6-L5: grade A=13, T6-L5: grade B-D=4; Control Group: Mean age: 40.1 yr; Gender: males=12, females=11; Level of injury: Tetraplegia=12, Paraplegia=11; Severity of injury: AIS C4-C8: grade A=8, C4-C8: grade B-D=4, T6-L5: grade A=5, T6-L5: grade B-D=6</p> <p>Intervention: Individuals were randomly assigned to either the hydrophilic catheter or the noncoated catheter control group. Urine from these individuals was collected once a mo for first 3 mo and then at 6, 9 and 12 mo mark.</p> <p>Outcome Measures: Urinary tract infection (UTI).</p>	<ol style="list-style-type: none"> At least 1 symptomatic UTI was seen over the course of 1 yr for 12 individuals in the hydrophilic catheter group and 14 of the control group. The hydrophilic catheter group had a mean of 1.18 UTIs, while the control group had 1. No significant difference was seen between the two groups in the number of symptomatic UTIs and type of symptoms. There was a significant number of symptomatic UTIs treated in the group using hydrophilic catheters ($p=0.02$). Females were more likely to develop UTIs regardless of catheter type.
De Ridder et al. 2005 Spain RCT PEDro=5 N=123	<p>Population: SCI using hydrophilic versus polyvinyl chloride catheter (PVC): Mean age: 37.5 yr versus 36.7 yr; Severity of injury: AIS A-D.</p> <p>Intervention: "SpeediCath®" hydrophilic catheters versus conventional uncoated PVC catheter for intermittent catheterization (IC).</p> <p>Outcome Measures: Occurrence of symptomatic urinary tract infections (UTIs), hematuria, strictures, convenience of use, satisfaction with catheter, dropout rate. Data collected over a 12 mo period.</p>	<ol style="list-style-type: none"> Lower incidence of UTIs of those using SpeediCath hydrophilic versus PVC ($p=0.02$). No difference in number of bleeding episodes or occurrence of hematuria, leukocyturia and bacteriuria between 2 catheters. More individuals expressed greater satisfaction with various aspects of the hydrophilic catheter, although these differences were not significant. 54% dropout rate (slightly more so in hydrophilic group) partially due to the fact that many subjects no longer needed to catheterize when bladder function was retained within the 1 yr period.
Vapnek et al. 2003 USA RCT PEDro=6 N _{initial} =62; N _{final} =49	<p>Population: Complete Available Data: Male SCI individuals: Hydrophilic Catheter Group: Mean age: 39.8 yr; Level of injury: paraplegia=25, tetraplegia=4; Polyvinyl chloride catheter (PVC) group: Mean age: 39.6 yr; Level of injury: paraplegia=26, tetraplegia=1.</p> <p>Intervention: SCI individuals were randomly placed in either the</p>	<p>Urinary tract infections:</p> <ol style="list-style-type: none"> Baseline: - mean incidence of monthly UTI's was higher for the hydrophilic catheter (HC) group than for the PVC/control group (0.45 ± 0.62 and 0.20 ± 0.26 per individual respectively ($p>0.3$)) Study Conclusion: - still no significant difference between HC and PVC group for mean #

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	<p>hydrophilic coated plastic LoFric catheters or standard polyvinyl chloride catheter (PVC) group.</p> <p>Outcome Measures: Urinary tract infections (UTIs), degree of microscopic hematuria and pyuria, incidence of adverse events were all assessed at baseline and every 3 mo for 1 yr.</p>	<p>of UTI's/mo (0.13 ± 0.18 and 0.14 ± 0.21 per individual resp. ($p > 0.3$))</p> <p>3. \downarrow in UTI rate per mo was significantly higher for HC group than for PVC group (0.44 to 0.14 or -0.3 versus 0.20 to 0.14 or -0.06 per individual), and was statistically significant in the HC group ($p = 0.012$ versus 0.24)</p> <p>Microscopic Hematuria:</p> <p>1. Baseline: - dipstick analysis showed some degree of hematuria in 8 of the 30 individuals from the HC group and 11 of the 31 from the PVC group (no statistically significance difference)</p> <p>2. During study - HC group showed a significantly \downarrow incidence of microhematuria ($p = 0.027$) (mean code per urinalysis for HC versus PVC (0.31 ± 0.46 and 0.65 ± 0.69 respectively)</p> <p>Microscopic Pyuria:</p> <p>1. Baseline: - number of individuals were similar from both groups (HC – 19 of 30 versus PVC – 22 of 31 respectively.)</p> <p>2. Follow-up – no differences</p> <p>Adverse Events:</p> <p>1. HC group – 1 gross hematuria, 1 epididymitis, 1 infected penile prosthesis requiring hospitalization and surgical removal (neurogenic bladder, unrelated to intermittent catheterization).</p> <p>2. PVC group – 1 gross hematuria, 1 epididymitis, 1 bladder stone surgically removed (neurogenic bladder, unrelated to intermittent catheterization).</p>
<p>Giannantoni et al. 2001 Italy RCT PEDro=9 N=18</p>	<p>Population: SCI: Mean age: 38.2 yr; Level of injury: C5-Cauda Equina; Severity of injury: AIS A-D; Time post-injury=18-60 d.</p> <p>Intervention: Comparison of "Instacath®" pre-lubricated nonhydrophilic catheter versus conventional uncoated polyvinyl</p>	<p>1. Lower incidence of UTIs ($p = 0.03$) and asymptomatic bacteriuria ($p = 0.0244$) of those using pre-lubricated catheters versus PVC.</p> <p>2. More epithelial cells found on conventional versus pre-lubricated catheter ($p = 0.01$)</p>

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
	chloride (PVC) Nelaton catheter for intermittent catheterization (IC) (crossover design). Outcome Measures: Symptomatic urinary tract infection (UTI) incidence of urethral complications (ultrasound, Cystourethrography (CUG)), urinalysis, visual analog scale of individual satisfaction. Collected at the start and end of 7 wk study period.	indicative of possible microtrauma. 3. 2 people had urethral bleeding with conventional catheter, 0 with pre-lubricated. 4. Pre-lubricated catheters had significantly higher satisfaction scores for 4 of 5 items on the scale. 5. 3 subjects requiring assistance with the conventional catheter became independent with the pre-lubricated catheter (order effect unreported) 6. No subject had impaired renal function of upper & lower tract abnormalities with either catheter.

Discussion

Another approach used to reduce the incidence of UTI associated with catheterization in individuals with neurogenic bladder involves the application of coatings to the catheter (Giannantoni et al. 2001; Vapnek et al. 2003; De Ridder et al. 2005; Cardenas & Hoffman 2009; Cardenas et al. 2011). For example, Giannantoni et al. (2001) employed a double-blind, crossover RCT design (n=18) to examine the difference between a pre-lubricated, nonhydrophilic Instantcath catheter as compared to a conventional polyvinyl chloride (PVC) silicon-coated Nelaton catheter with respect to the occurrence of UTIs and urethral trauma. The subjects were randomized to 1 of 2 groups which tried each catheter for a period of 7 weeks in an A-B, B-A design. Both incidence of UTIs ($p=0.3$) and presence of asymptomatic bacteriuria ($p=0.024$) were significantly reduced for the pre-lubricated catheter versus the conventional PVC catheter. Perhaps most interesting, three subjects requiring assistance with the conventional catheter became independent with the pre-lubricated catheter, although it was not reported if these individuals were in the group using the conventional catheter initially or lastly. The existence of an order effect (or not) for any of the measures was not reported. In terms of general satisfaction with use, subjects rated the pre-lubricated catheter significantly higher than the conventional catheter with respect to comfort, ease of inserting and extracting, and handling.

A similar finding of reduced incidence of UTIs ($p=0.02$) was reported by De Ridder et al. (2005), but in this case the reduction was associated with a hydrophilic catheter as compared to the conventional PVC catheter. This multi-centre investigation also employed an RCT design (N=123) but had several methodological problems that likely constrained the potential utility of the results. Most significant was a high drop-out rate (54%) with slightly more individuals not completing the study from the hydrophilic catheter group. A probable cause for many of these drop-outs was the

lengthy treatment period of 1 year during which many individuals were likely to improve bladder function such that intermittent catheterization was no longer required. There were no other significant differences noted between the two groups including the number of bleeding episodes or occurrence of hematuria, leukocyturia and bacteriuria. More individuals expressed greater satisfaction with various aspects of the hydrophilic catheter, although these differences were also not significant. A reduced incidence of hematuria and a significant decrease in UTI incidence was also reported by Vapnek et al. (2003), when hydrophilic versus non-hydrophilic catheter use was compared in a 12-month study of 62 individuals (n=49 completed).

Reduced numbers of treated UTIs were reported by Cardenas and Hoffman (2009) with the use of hydrophilic catheters versus standard nonhydrophilic catheters even though no difference was reported between the 2 groups of self-IC SCI individuals for number of symptomatic UTIs. Furthermore, lubrication was more beneficial for men since women on self-IC were more likely to develop UTIs regardless of catheter type. Although this study may have been underpowered, it is important to note that the drop out rate was just under 20% as compared to almost 54% in the DeRidder et al. (2005) study with only 57/123 subjects remaining at the end of year 1. Cardenas and Hoffman (2009) also included women which allowed for potential gender differentiation in the effect of hydrophilic catheter use. Although females accounted for 29% of the participants, a sample size of should invoke caution when interpreting the data.

Later, Cardenas et al. (2011) showed that time to the first antibiotic-treated symptomatic UTI in acute SCI individuals (less than 3 months injured for inclusion) could be delayed by opting for a hydrophilic coated catheter as compared to an uncoated catheter. However, effects disappeared when the first months after institutional discharge were included in the analysis. Participants and/ or caregivers reported significantly higher satisfaction ($P=0.007$) with the hydrophilic coated catheter versus uncoated; however, no differences were found in a similar evaluation by nursing staff. This is the largest RCT to date on this topic.

Conclusion

There is level 1b evidence (from one RCT; Giannantoni et al. 2001) that, compared to conventional poly vinyl chloride catheters, pre-lubricated non-hydrophilic catheters are associated with fewer UTIs and reduced urethral bleeding.

There is level 2 evidence (from one RCT; De Ridder et al. 2005) that, compared to conventional poly vinyl catheters, hydrophilic catheters may be associated with fewer UTIs, but not necessarily urethral bleeding.

There is level 2 evidence (from two RCTs; Cardenas & Hoffman 2009; Cardenas et al. 2011) that use of hydrophilic versus non-hydrophilic catheters are associated with fewer symptomatic UTIs treated with antibiotics even though the number of symptomatic UTIs are similar between groups.

A reduced incidence of UTIs or reduced antibiotic treatment of symptomatic UTIs have been associated with pre-lubricated or hydrophilic catheters as compared to standard non-hydrophilic catheters.
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6.3.3 Other Issues Associated with Bladder Management and UTI Prevention

Table 25 summarizes studies that compare IC to other bladder management methods or use aids to augment the use of a particular bladder management method with the goal of preventing UTIs.

Table 25 Other Issues Associated with Bladder Management and UTI Prevention

Author Year Country Score Research Design Total Sample Size	Methods	Outcome
Darouiche et al. 2006 USA RCT PEDro=4 N _{initial} =127 N _{final} =118	<p>Population: Hospital in individuals with neurogenic bladders requiring an indwelling or suprapubic bladder; Experimental group: Mean age: 55 yr; Gender: males=53, females=7; Level of injury: cervical=29, thoracolumbar=24, multiple sclerosis=7</p> <p>Control group: Mean age: 56 yr; Gender: males=51, females=7; Level of injury: cervical=29, thoracolumbar=26, multiple sclerosis=3</p> <p>Intervention: Experimental group: indwelling bladder catheters secured by the Statlock device; Control group: catheter secured by tape, velcro strap, cath-secure, or nothing.</p> <p>Outcome Measures: Rate of symptomatic urinary tract infections (UTIs), catheter dislodgement, urethral meatal erosion.</p>	<ol style="list-style-type: none"> 1. Trend for lower UTI incidence in the Statlock group versus the control group (13.3% versus 24.1%, p=0.16). 2. Trend for lower incidence of symptomatic UTI per 1000 device days in the Statlock group versus the control group (p=0.16). 3. No significant difference in the rates of catheter dislodgement and urethral meatal erosion between the two methods of securing catheter.
Joshi & Darouiche 1996 USA Prospective Controlled Trial N _{initial} =41 N _{final} =29	<p>Population: SCI in individuals with UTI: Mean age: 45 yr; Gender: males=29, females=0; Severity of injury: AIS: A.</p> <p>Intervention: Comparison of intermittent catheterization (IC)=10, Suprapubic catheter=10, Indwelling foley catheter =9 during a 7-d course of an appropriate antibiotic.</p> <p>Outcome Measures: Pyuria (white blood cells x10⁷/L) sampled</p>	<ol style="list-style-type: none"> 1. IC group had lowest residual pyuria at mid and endpoint (p<0.05) versus other 2 bladder management methods. 2. Pyuria was significantly reduced with antibiotic for all management groups (p<0.005). 3. Multiple organisms isolated in 62% of urine cultures.

Author Year Country Score Research Design Total Sample Size	Methods	Outcome
	at initial, mid and endpoint of 7 d antibiotic treatment.	
Gilmore et al. 1992 USA Prospective Controlled Trial N=119	<p>Population: SCI admitted for SCI in individual rehabilitation: Mean age: 28 yr; Gender: males=119, females=0; Level of injury: paraplegia=49, tetraplegia=70.</p> <p>Intervention: External urinary collection system (EUCS): Group 1-continuous EUCS, Group 2-EUCS during day only, Group 3-no EUCS.</p> <p>Outcome Measures: Number of Pseudomonas and Klebsiella in swab cultures of urethra, perineum, rectum; significant bacteriuria (10,000 bacteria/ml urine). Each collected every 2 wk during individual stay.</p>	<ol style="list-style-type: none"> 1. EUCS being on or off did not influence rate of bacteriuria. 2. Reduced Pseudomonas and Klebsiella in urethra, perineum or rectum only if no EUCS ($p<0.05$). 3. Removal of the EUCS at night reduced urethral colonization with Pseudomonas only ($p=0.03$).
Nwadiaro et al. 2007 Nigeria Case Control N=125	<p>Population: Traumatic SCI; Mean age: 30 yr; Gender: males=117, females=8; Level of injury: cervico-thoracic=53, thoraco-lumbar=72; Severity of injury: complete=125, incomplete=0.</p> <p>Intervention: Retrospective comparison of indwelling urethral catheterization (UC) versus suprapubic cystostomy (SPC).</p> <p>Outcome Measures: Prevalence of urinary tract infection (UTI), individual satisfaction with management and complications collected from hospital admission to 1 yr post-admission.</p>	<ol style="list-style-type: none"> 1. Prevalence of UTI was significantly less in the SPC group versus the UC group ($p<0.05$). 2. Individual satisfaction was significantly higher in the SPC group rather than the UC group ($p<0.05$). 3. SPC resulted in significantly less mortality at 1 yr post admission than UC ($p<0.05$).
Lloyd et al. 1986 USA Case Control N=204/203	<p>Population: SCI admitted to acute SCI care: Mean age: 29 yr; Time post-injury= within 36 hr.</p> <p>Intervention: Comparison of initial bladder management A) Intermittent catheterization (IC) at acute centre=21, B) suprapubic catheter followed by IC=21, C) indwelling catheter followed by IC at mean of 36 d=106, D) suspected long-term use of indwelling catheter=23, E) IC at community hospital=33.</p> <p>Outcome Measures: Urinary tract infections (UTIs), episodes of chills and fevers, excretor urogram (IVP) graded by 2 MDs for pyelocaliectasis, renal plasma flow assessed at 1 yr follow-up.</p>	<ol style="list-style-type: none"> 1. No statistically significant differences between groups at 1 yr post injury for any of: <ul style="list-style-type: none"> • rate of UTIs • number of chills and fevers • upper tract changes • genitourinary complications • frequency of urological procedures

Author Year Country Score Research Design Total Sample Size	Methods	Outcome
Afsar et al. 2013 Turkey Case Series N=164	<p>Population: Mean age: 40.7 yr (range 23-65 yr); Gender: males=102, females=62; Level of injury: Tetraplegia=43, Paraplegia=87, Conus-Cauda Equina Syndrome=34; Time post-injury: 51.5 d (range 5-292).</p> <p>Intervention: Retrospective review of bladder management and emptying methods.</p> <p>Outcome Measures: Prevalence of urinary tract infection (UTI).</p>	<ol style="list-style-type: none"> 1. The number of UTIs was highest in individuals using indwelling catheters.
Sugimura et al. 2008 New Zealand Case Series N=149	<p>Population: Gender: males=124, females=25; Level of injury: tetraplegia=96, paraplegia=68</p> <p>Intervention: SCI individuals managed with SPC were retrospectively reviewed for complications.</p> <p>Outcome Measures: Urinary tract infections (UTIs), complications, renal scarring, urethral incontinence.</p>	<ol style="list-style-type: none"> 1. 73 individuals experienced no complications 2. 43 experienced UTIs. 3. The most common lower tract complication was bladder stones (22%). 4. Renal complication was seen in 20 out of 149 individuals. 5. Only 9 of individuals experienced renal scarring. 6. 11 individuals experienced urethral incontinence
Ku et al. 2005 Case Series N=179	<p>Population: Mean age: 25.2 yr; Gender: males=179, females=0; Severity of injury: complete=41, incomplete=138.</p> <p>Intervention: Comparison of various bladder management methods including: urethral catheter, intermittent catheterization, suprapubic cystostomy, Crede maneuver or reflex voiding, condom catheter.</p> <p>Outcome Measures: Adverse events.</p>	<ol style="list-style-type: none"> 1. No significant difference was found in incidence of pyelonephritis or renal stones across bladder management methods. 2. Overall, 61 individuals presented with pyelonephritis, 44 had renal stones, upper tract deterioration was seen in 58. 3. Risk of pyelonephritis was 2.8 times higher in individuals with vesicoureteral reflux. 4. Upper tract deterioration (abnormal kidney appearance or function) was more common in individuals using indwelling (urethral or suprapubic) catheters.

Discussion

In addition to intermittent catheterization, the effects of other bladder management methods have been investigated with respect to their impact in preventing UTIs. In particular, intermittent catheterization has been compared to indwelling catheterization. Joshi and Darouiche (1996) reported that the response to an antibiotic, as indicated by reduced pyuria, was improved and can be assessed earlier in individuals who utilize intermittent catheterization over those whose bladder

drainage is reliant on suprapubic or indwelling foley catheters. All individuals (n=29) experienced relief from appropriate antibiotic therapy after 3-4 days, but the level of residual pyuria was lowest at mid-therapy and after therapy completion in those individuals using intermittent catheterization.

In another comparison study, Nwadiaro et al. (2007) conducted a retrospective comparison of indwelling urethral catheterization and suprapubic cystostomy on UTI prevalence in a predominately illiterate and impoverished population where intermittent catheterization was a less preferred option. Prevalence of UTI was significantly less in the group having a suprapubic versus indwelling urethral catheter ($p<0.05$). In addition, there was significantly less mortality with the SPC ($p<0.05$) at one-year post admission with UTI-related septicaemia the number one cause of death in these individuals. Sugimura et al. (2008) also examined the incidence of complications in individuals using SPC, and reported a 29% incidence of UTI's, though there was no comparison group in this study. In a study by Ku et al. (2005), no bladder management technique was found to be superior in protecting against pyelonephritis (simple UTI was not tracked as an outcome); however, the presence of vesicoureteral reflux led to a 2.8 fold higher risk of pylonephritis than those without reflux. Reflux is most often associated with high pressure urine storage due to low compliance or high pressure voiding due to sphincter spasticity and obstruction. Thus, actual bladder pathophysiology may have the largest effect on clinically significant infections with the caveat that in this study, the group with urethral catheterization did experience more total upper tract deterioration than other bladder management groups.

Lloyd et al. (1986) conducted a case control investigation reviewing a group of 204 SCI individuals grouped according to urological management techniques as follows: a) intermittent catheterization within 36h of injury, b) suprapubic trocar drainage within 36 h of injury, c) urethral catheter drainage for >36h prior to intermittent catheterization, d) indwelling urethral catheter drainage throughout and after discharge from hospital and e) intermittent catheterization placed in community hospital. Overall, these authors found that the method of initial bladder management does not affect the incidence of UTI, genitourinary complications or frequency of urological procedures at 1 year after injury. The only exception was group D who had a greater rate of UTIs as a result of the prolonged placement of indwelling urethral catheter drainage throughout and after discharge from hospitalization. It should be noted that individual variations in bladder management methods following the initial method and up to the one-year follow-up were not accounted for in this investigation representing a potential major confound. As noted in several of these comparative investigations, complications occur most frequently in those with urethral catheterization. Despite this, many individuals resort to using urethral catheterization for convenience or necessity, if hand dexterity is insufficient, or caregivers unavailable or unaffordable. Some investigators have suggested an approach to minimizing UTI when urethral catheterization is determined to be the most viable management approach. Darouiche et al. (2006) conducted a multicentre RCT of hospital in individuals (n=118) in which the effect of securing indwelling catheters with a device called the Statlock as compared to traditional means of catheter securement (i.e., tape, velcro strap, cath-secure, or

nothing) was assessed. In addition to SCI, 10 subjects had multiple sclerosis. In this trial, there was a statistically non-significant trend for a lower rate of symptomatic UTI ($p=0.16$) and also a lower incidence of symptomatic UTI per 1000 device days ($p=0.16$) for those using this Statlock device versus the control group.

Condom catheters also can be a source of bacterial colonization, especially of the perineum, which has been suggested by Sanderson and Weissler (1990a) to be significantly correlated with bacteriuria in SCI individuals. By discontinuing night time use of an external condom drainage system in a prospective controlled trial involving SCI rehabilitation individuals ($n=119$), *Pseudomonas* colonization of the urethra was found to be significantly reduced where *Klebsiella* colonization was not significantly affected ($p<0.05$; Gilmore et al. 1992). Further, a third group of individuals did not use a condom drainage system at any time and colonization rates for both *Pseudomonas* and *Klebsiella* were significantly lower in this group at all sites tested (urethra, perineum and rectum) as compared to those using the external drainage system ($p<0.05$). However, the prevalence of bacteriuria caused by either gram-negative bacilli, was not reduced with either night-time or continuous disuse of an external condom drainage system.

Conclusions

There is level 2 evidence (from one prospective controlled trial, one case control study, and one case series study; Joshi & Darouiche 1996; Nwadiaro et al. 2007; Afsar et al. 2013) that intermittent catheterization may lead to a lower rate of UTI as compared to other bladder management techniques such as use of indwelling or suprapubic catheter.

There is level 3 evidence (from one case control study; Nwadiaro et al. 2007) that bladder management with a suprapubic as opposed to indwelling catheter may lead to a lower rate of UTI and reduced mortality in a poor, illiterate population where intermittent catheterization may not be viable as an approach to bladder management.

There is level 2 evidence (from one RCT; Darouiche et al. 2006) that use of a Statlock device to secure indwelling and suprapubic catheters may lead to a lower rate of UTI.

There is level 2 evidence (from one prospective controlled trial; Gilmore et al. 1992) that removal of external condom drainage collection systems at night or for 24 hours/day might reduce perineal, urethral or rectal bacterial levels but have no effect on bacteriuria.

There is level 4 evidence (from one case series; Ku et al. 2005) that no bladder management method is advantageous in preventing pyelonephritis (though indwelling urethral catheterization does have the highest incidence of upper tract deterioration). However, the presence of reflux results in a 2.8 fold higher incidence of pyelonephritis.

Intermittent catheterization is associated with a lower rate of UTI as compared to use of indwelling or suprapubic catheter.

The Statlock device to secure indwelling and suprapubic catheters may lead to a lower rate of UTI.

Removal of external condom drainage collection systems at night or for 24 hours/day may reduce perineal, urethral or rectal bacterial levels but has no effect on bacteriuria.

The presence of vesicoureteral reflux likely has a greater impact on development of significant infections than the choice of bladder management.

6.4 Pharmacological and Other Biological Methods of UTI Prevention

There are a variety of approaches that involve pharmaceuticals and other biological agents for UTI prevention in persons with SCI, as described in several reviews on this topic (Biering-Sorensen 2002; Garcia Leoni & Esclarin De Ruz 2003). These include pharmacological approaches such as bacterial interference or antibiotic prophylaxis, the use of other biological agents such as antiseptic cleansing agents, or the use of nutraceuticals such as cranberry in varying forms (e.g., liquid, capsule).

6.4.1 Bacterial Interference for Prevention of UTIs

Bacterial interference has been touted as a promising approach to UTI prevention for the future (Biering-Sorensen 2002). In this approach, a group of bacteria that do not cause UTIs are introduced into the bladder which acts to limit the ability of other pathogens to effectively colonize the bladder and cause a symptomatic UTI.

Table 26 Bacterial Interference for Prevention of UTIs

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
Darouiche et al. 2011 USA RCT PEDro=9 N=27	<p>Population: Male SCI: Mean age: 52 yr (range 29-85 yr); Injury level: Tetraplegia =14, paraplegia=12; Bladder management type: Indwelling transurethral catheter=7, indwelling suprapubic catheter=6, intermittent catheterization=13, external condom=1.</p> <p>Intervention: Individuals were randomly allocated to either bacterial interference (E.coli HU2117) (n=17) or a placebo (n=10) for prevention of urinary tract infections (UTI).</p>	<ol style="list-style-type: none"> 5/17 (29%) of the experimental group and 7/10 (70%) of the control group developed >1 UTI during the 1-yr follow-up (p=0.049). The average number of episodes of UTI/individual per yr was also lower and significantly different in the experimental versus control groups (p=0.02).

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
	Outcome Measures: Number of UTI episodes.	
Darouiche et al. 2005 USA RCT PEDro=8 N=27	<p>Population: SCI of ≥ 1 yr with ≥ 2 UTIs/yr; Experimental group: Mean age: 52 yr; Level of injury: paraplegia=11, tetraplegia=10; Control group: Mean age: 52 yr; Level of injury: paraplegic=2, tetraplegic=4.</p> <p>Intervention: Randomly assignment (3:1 ratio) and double-blinding to bladder inoculation with either E.coli 83972 versus sterile normal saline. 2 bladder instillations/d for 3 consecutive d.</p> <p>Outcome Measures: Prevalence of urinary tract infections (UTI), risks of UTI. Urine samples were analyzed at 1 wk after bladder inoculation then monthly for 1 yr.</p>	<ol style="list-style-type: none"> 13 individuals with E coli and all of the individuals with saline developed at least 1 episode of UTI during the 1 yr follow-up ($p=0.07$). The number of UTI episodes that occurred were significantly lower ($p=0.036$) with E coli versus saline. Colonized individuals were significantly less likely than non-colonized individuals to develop at least 1 episode of UTI during the 1 yr follow up ($p=0.01$). Kaplan-Meier estimates of risk of UTI showed bladder colonization was protective against infection ($p=0.002$). 13 individuals of the experimental group became colonized with E.coli 83972 for >1 mo and 4 individuals remained colonized throughout the 12 mo, while 9 lost the inoculation after an average of 3.5 mo.
Trautner et al. 2007 USA Pre-Post N=12	<p>Population: Adult SCI individuals, who had a SCI >1 yr, whom required an indwelling catheter for drainage and had at least 1 clinically recognized urinary tract infection (UTI) in the past.</p> <p>Intervention: Insertion of a urinary catheter incubated with E.coli HU2117.</p> <p>Outcome Measures: Colony success (absence of proteus (uropathogen) and duration of catheter insertion).</p>	<ol style="list-style-type: none"> No individual experienced UTI symptoms attributable to colonization with E.coliHU2117. Proteus absence was significantly related to a longer duration of E.coliHU2117 colonization ($p=0.04$). Catheters left in place for longer periods of time resulted in a longer duration of colonization ($p=0.002$).
Hull et al. 2000 USA Pre-Post N=21	<p>Population: SCI with a history of symptomatic UTI in the past year: Mean age: 29-55 yr; Gender: males=18, females=3; Severity of injury: AIS A=10, B=6, C=3, D=2; Time post-injury: 5-24 mo.</p> <p>Intervention: Individuals were treated with antibiotics for 5 to 7 d. After 48 to 72 h, individuals were inoculated 3 times a d for 3 d with E.coli 83972. Protocol was repeated up to 3 times if individuals did not</p>	<ol style="list-style-type: none"> No symptomatic UTIs were seen in subjects while colonized with E.coli 83972. Successful colonization was achieved in 13 of 21 individuals. Mean duration of colonization was 12.3 mo. UTIs seen in 4 individuals not successfully colonized and in 5/7 who lost colonization over a mean 3.4 mo follow-up. There was a significant correlation between elevated

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
	show colonization. After 3 cycles no attempts were made to colonize. Outcome Measures: Successful colonization, duration of colonization, self-reported urinary tract infection (UTI), treatment for UTI, quality of life (QoL) reported at variable follow-up over ~1 yr.	voiding pressure and likelihood of successful colonization (p=0.02). 6. Mean QoL of subjects who remained colonized increased from 1.8 before colonization to 4.6 after (out of 5).
Prasad et al. 2009 USA Pre-Post N=13	Population: Mean age: 56 yr; Gender: males=13, females=0. Intervention: SCI individuals with history of urinary tract infections (UTIs) were given a catheter coated with E. Coli 83972 which was left in situ for three d, then removed and the individual was followed. Outcome Measures: Colonization, UTIs, adverse events.	1. Overall 8 participants became colonized with the bacteria; only 3 were due to a single inoculation. 2. Success rate of inoculation after preinsertion antibiotics was greater than that without preinsertion antibiotics (55% versus 33%); however, this did not reach significance. 3. UTI rate for participants that became colonized decreased from 2.29 per at baseline to 1.98 one yr post insertion of catheters. (no significance given) 4. Adverse events reported included fever, chills, groin pain, dysreflexia and hematuria.

Discussion

To date, the specific approach employed in studies in persons with SCI has been to colonize the bladder with either E. coli 83972 (Hull et al. 2000; Darouiche et al. 2005; Prasad et al. 2009) or E. coli HU2117 (Darouiche et al. 2011; Traunter et al. 2007). Most notably, Darouiche et al. (2005) conducted a prospective, randomized, placebo-controlled, double-blind trial (n=27) in which they randomized persons with SCI of greater than 1 years duration and with a history of symptomatic UTIs to receive bladder inoculation of either E. coli 83972 or sterile normal saline at a 3:1 ratio. This was preceded by a one-week course of empirically selected antibiotics as it had been noted that successful colonization is more likely achieved with a sterile bladder (Hull et al. 2000). Individuals were monitored over the following year with monthly urine cultures. The number of UTIs experienced by those with successful E. coli 83972 colonization was significantly fewer UTIs than those with saline inoculation or unsuccessful E. coli inoculation (1.6 versus 3.5 episodes/year, p=0.036). The period during which the bladder remained colonized by E. coli 83972 was variable among study participants with only 13 of 21 individuals being successfully colonized for at least 1 month, 4 of these remaining colonized for the entire 1 year study period and 9 losing E. coli after an average of 3.5 months. It should be noted that statistical comparisons were made between those with successful colonization (n=13) versus

those inoculated with saline (n=6) combined with those not successfully inoculated (n=8). Only 1 of the 13 participants successfully inoculated developed a UTI while E. coli 83972 was in the bladder and this was associated with another organism (P. aeruginosa). No adverse events were obtained with the E. coli 83972 inoculations although 1 person in the saline group developed autonomic dysreflexia which subsided post-inoculation. Using a less robust pre-post study design, Prasad et al. (2009) also reported that preinoculation antibiotics improved inoculation rates and that rates of UTI declined during the period of colonization.

A longer period of colonization was achieved in a pre-post study conducted by Hull et al. (2000) in which 21 individuals with longstanding SCI (>18 months) and a history of symptomatic UTI over the preceding year were inoculated with E. coli 83972 following a course of appropriate antibiotics for 5-7 days. Persistent colonization of greater than 1 month was achieved in 13 study participants with mean colonization duration of 12.3 months (range 2-40 months). No participant sustained a UTI while colonized with E. coli even though these same individuals had a mean of 3.1 UTIs over the previous year. UTIs were noted in 4 of 7 persons not successfully colonized and at a rate of 3.5 UTIs/year for the months following loss of colonization in those where E. coli 83972 was no longer found in the bladder. The overall results from these three studies point to a strong effectiveness associated with this approach while the bladder remains colonized but that more work is required to enhance the rate of successful inoculation and to examine methods for sustaining the period of colonization.

An additional strain, E.coli HU2117, when colonized has demonstrated efficacy in preventing symptomatic UTIs from other uropathogens. Traunter et al. (2007) reported that in a group of adult SCI individuals, who had been injured for one year or longer, colonization of E.coli HU2117 lead to decreases in the uropathogen Proteus. Further, a RCT conducted by Darouiche et al. (2011) reported that mean number of UTIs per individual was significantly less for those treated with E.coli HU2117 bacterial interference compared to individuals receiving a placebo inoculation.

Conclusions

There is level 1b evidence (from one RCT and two pre-post studies; Darouiche et al. 2005; Hull et al. 2000; Prasad et al. 2009) that bacterial interference in the form of E. coli 83972 bladder inoculation may prevent UTIs.

There is level 1b evidence (from one RCT and one pre-post; Darouiche et al. 2011; Trautner et al. 2007) that bacterial interference in the form of E.coli HU2117 bladder inoculation may prevent UTIs.

E. coli 83972 & HU2117 bladder inoculation & may prevent UTIs.
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6.4.2 Antibiotic Prophylaxis of UTIs

Several investigations have been conducted which explore the effectiveness of a prophylactic antibiotic approach, although cost and conflicting results, along with issues of adverse events and increasing likelihood of enhancing resistant organisms, have led reviewers to not recommend this approach for routine use (Garcia Leoni & Esclarin De Ruz 2003; Morton et al. 2002). Although researchers and clinicians have reservations about this approach, an obvious and important variable is the specific antibiotic that is used for prophylaxis. For the most part, investigations in SCI individuals have involved different dosages and regimens of orally administered ciprofloxacin or co-trimoxazole (trimethoprim-sulfamethoxazole; TMX-SMX) as prophylactic measures.

Table 27 Antibiotic Prophylaxis of UTIs

Author Year Country Score Research Design Total Sample Size	Methods	Outcome
Morton et al. 2002 USA Systematic Review N=15 studies	<p>Population: <i>Acute studies=8 (individuals with SCI<90 days ago; n=510):</i> Treatments: trimethoprim, sulfamethoxazole, neomycin, polymyxin B, nitrofurantoin, methenamine hippurate, methenamine madelate, hemiacidrin, ascorbic acid.</p> <p><i>Nonacute studies=7 (individuals with SCI>90 days ago (n=356):</i> Treatments: nitrofurantoin, methenamine, mandelate, ammonium chloride, sulfamethoxazole, trimethoprim, ciprofloxacin, ascorbic acid.</p> <p>Intervention: Literature search of Medline (1966- January 1998), Embase (1974-January 1998), and cinahl (1982-July 1998).</p> <p>Outcome Measures: Symptomatic Urinary tract infections (SUTI), asymptomatic bacteriuria count.</p>	<ol style="list-style-type: none"> 1. Antimicrobial prophylaxis did not significantly decrease SUTIs in either acute or nonacute individuals ($p>0.05$). 2. Antimicrobial prophylaxis reduced asymptomatic bacteriuria in acute individuals ($p<0.05$), and nonacute individuals ($p=0.06$) but the reduction was not significant in either.
Darouiche et al. 1994 USA RCT PEDro=9 N=40	<p>Population: SCI Individuals: Treatment group: Mean age: 52.9 yr; Gender: males=18, females=0; Placebo group: Mean age: 46.9 yr; Gender: males=22, females=0.</p> <p>Intervention: Double blind comparison of 500mg of ciprofloxacin bid versus placebo bid for 3 d prior to urodynamic testing.</p> <p>Outcome Measures: Incidence of urinary tract infection (UTI) (culture), bacteriuria, pyuria, adverse events collected prior and 3-5 d post urodynamic testing.</p>	<ol style="list-style-type: none"> 1. 3 individuals in the placebo group and none the individuals in the treatment group developed symptomatic UTI but this was not significant ($p=0.24$). 2. No adverse effects were reported.
Biering-Sorensen et al. 1994 Denmark	<p>Population: SCI with neurogenic bladder: Mean age: 38 yr; Gender: males=18, females=3.</p>	<ol style="list-style-type: none"> 1. Ciprofloxacin versus placebo prophylaxis (6 mo): number of

Author Year Country Score Research Design Total Sample Size	Methods	Outcome
PEDro=8 RCT N=21	Intervention: Cross-over comparison of 6 mo ciprofloxacin (100mg/night) versus placebo prophylaxis. Outcome Measures: Number of urinary tract infections (UTIs), urine and fecal cultures, side effects collected over 6 mo periods.	UTIs greatly reduced with 5 versus 59 ($p<0.00005$) 2. 1 instance of ciprofloxacin resistant <i>E. coli</i> found in the feces of 1 cipro individual 3. No severe side effects.
Gribble & Puterman 1993 Canada RCT PEDro=8 N=129	Population: Acute (<30 d) SCI: Mean age: 38 yr; Gender: males=112, females=17. Intervention: Efficacy of trimethoprim-sulfamethoxazole (TMP-SMX; TMP 40 mg, SMX 200mg) for UTI prophylaxis in acute SCI, during the first 4 mo of intermittent catheterization (IC). Breakthrough bacteriuria treated with conventional antimicrobial therapy and prophylaxis was continued. Outcome Measures: Clinical: weekly rectal and urethral swab and urine cultures collected for 4 mo or until hospital discharge.	1. TMP-SMX more efficacious than placebo (P) prophylaxis: <ul style="list-style-type: none"> Lower incidence/freq/relapse of bacteriuria and symptomatic UTI in males ($p<0.003/0.0001/0.0001$ and 0.0003). Similar trends in women. 2. Other results: <ul style="list-style-type: none"> Adverse events similar between groups ≥ 1 TMP-SMX-resistant bacteriuria in all P subjects by yr 3. Rectal/urethral swab TMP-SMX-resistant organisms- both grps. TMP-SMX UTI prophylaxis effective in acute SCI/IC but emergent TMP-SMX-resistance limits usefulness.
Sandock et al. 1995 USA Prospective Controlled Trial N=43	Population: SCI individuals; Treatment group: Mean age: 46 yr; Gender: males=20; Level of injury: lumbar=2, paraplegic=5, tetraplegia=13; Mean time post-injury=9.2 yr; Control group: Mean age: 58.3 yr; Gender: males=23; Level of injury: lumbar=3, paraplegic=8, tetraplegic=12; Mean time post-injury=14.9 yr. Intervention: Comparison of 400mg trimethoprim-sulfamethoxazole (TMP-SMX) daily versus no treatment over a minimum of 3 mo. Outcome Measures: Incidence of asymptomatic bacteria, prevalence of urinary tract infection UTI, types of bacteria present. Urine cultures weekly.	1. No significant difference was found between the control and treatment groups in: <ul style="list-style-type: none"> Incidence of asymptomatic bacteriuria. Percent of cultures with asymptomatic bacteriuria ($p>0.1$). Incidence of symptomatic UTIs per week ($p>0.5$). Percentage of TMP-SMX resistant UTIs ($p>0.5$). Types of bacteria present. 2. The control group was significantly lower than the treatment group in: <ul style="list-style-type: none"> Percent of cultures with TMP-SMX resistant asymptomatic bacteriuria ($p<0.05$).
	Population: SCI individuals with intermittent catheterization: Age range 20-66 yr; Gender: males=11, females=3.	1. TMP-SMX versus non-prophylaxis prophylaxis subjects:

Author Year Country Score Research Design Total Sample Size	Methods	Outcome
Reid et al. 1994a Canada Prospective Controlled Trial N=14	<p>Intervention: Comparison of co-trimoxazole (TMP-SMX 160/800 mg bid) versus no prophylaxis. Symptomatic urinary tract infections (UTIs) were treated with appropriate antibiotic and a separate analysis was done on effect of fluoroquinolones (ciprofloxacin, ofloxacin and norfloxacin) on bladder biofilm bacteria.</p> <p>Outcome Measures: Infection rate, extent of biofilm formation, level of bacterial adhesion; urine samples collected for culture and sonication for 8 wk.</p>	<ul style="list-style-type: none"> • 54% versus 68% infection rate (not significant; no p value reported) • <i>E coli</i> replaced by <i>E faecalis</i> as dominant uropathogen with TMP/SMX use. • 39±42 versus 44±49 adherent bacteria/bladder cell (not significant; no p value reported) <p>2. Laboratory results for treatment effect of fluoroquinolones versus TMP-SMX prophylaxis on biofilms:</p> <ul style="list-style-type: none"> • Reduced adhesion counts in favour of Fluoroquinolone versus TMP-SMX (63% versus 44%, no p value). • 92%, 71%, 56% biofilm reduction with ciprofloxacin, ofloxacin & norfloxacin.
Chew et al. 2018 USA Case Control N=421	<p>Population: Long-term nitrofurantoin (LTN): Mean age=60.5±12.4yr; Gender: males=208, females=17; Etiology: SCI=225; Time since injury=24.4±14.2yr Control (CG): Mean age=61.1±12.2yr; Gender: males=187, females=9; Etiology: SCI=196; Time since injury=22.0±13.9yr. Inclusion criteria: recurrent (≥3) positive urine cultures and at least one occurrence of UTI or asymptomatic bacteriuria.</p> <p>Intervention: Medical records of SCI individuals who received long-term nitrofurantoin (≥90 d) for treatment of UTI and SCI individuals who did not receive nitrofurantoin (controls) were reviewed. Clinical outcomes of asymptomatic bacteriuria and UTI occurring during the study year (2012-2013) were extracted.</p> <p>Outcome Measures: UTI frequency; number of days between positive urine cultures; frequency of isolates in urine; presence of nitrofurantoin-resistant isolates; presence of multidrug-resistant organism isolates; number of outindividual encounters; hospitalization.</p>	<ol style="list-style-type: none"> 1. There were no significant differences in the frequency or types of UTI symptoms when comparing LTN to CG ($p>0.05$). 2. CG had a higher proportion of positive urine cultures compared to LTN ($p<0.001$). 3. CG had significantly fewer nitrofurantoin-resistant isolates ($p<0.001$). However, there was no significant difference in the number of multidrug-resistant organism isolates between CG and LTN ($p>0.05$). 4. Average number of days between positive urine cultures was significantly shorter in the CG group compared to LTN ($p<0.001$). 5. There was no significant difference in the frequency of isolates between CG and LTN ($p>0.05$). 6. LTN had significantly fewer outindividual encounters, and hospitalizations compared to CG ($p<0.001$).
Cox et al. 2017 USA Pre-Post	<p>Population: Median age=37.5yr (18-75); Gender: males=13; females=9; Etiology: SCI (n=14, 63.6%); Multiple</p>	<ol style="list-style-type: none"> 1. The incidence of symptomatic UTI decreased significantly ($p<0.004$).

Author Year Country Score Research Design Total Sample Size	Methods	Outcome
N=22	<p>Sclerosis=3; Myelodysplasia=2; Transverse Myelitis=2; Other=1, Median time since injury=14yr.</p> <p>Intervention: 480 mg of gentamicin was diluted in 1 L of water. Each individual received a gravity instilled dose of 30-60 mL (dependent on bladder capacity) of solution instilled into the bladder after drainage of urine was complete at the individual's last evening catheterization. Instillations were left indwelling until the next catheterization.</p> <p>Outcome Measures: Symptomatic UTI median; Courses of oral antibiotics; Courses of IM or IV antibiotics; Days of antibiotic therapy; ED/hospital visits for UTI; Telephone encounters for UTI; Multidrug-resistant organisms; Gentamicin resistant organisms</p>	<ol style="list-style-type: none"> 2. Individuals underwent fewer course of treatment with oral antibiotics after gentamicin instillations ($p<0.01$). 3. There was a significant decrease in the number of individuals who used oral antibiotic prophylaxis ($p=0.03$). 4. There was a significant decrease in the proportion of multidrug-resistant organisms in urine culture ($p=0.04$). 5. The number of telephone encounters for UTI decreased significantly ($p=0.03$).
Poirier et al 2016 France Pre-Post N=50	<p>Population: SCI, NBD; Mean age: 51 yr; Gender: males=30, females=20; Level of injury: paraplegia=33, tetraplegia=6, MS=4, other=6, missing data=1; Mean time post-injury: 19.4 yr.</p> <p>Intervention: Alternate weekly administration of oral antibiotics, which have been proven effective in treating UTIs.</p> <p>Outcome Measures: UTI frequency (per year), antibiotic use post regimen, presence of multidrug resistant bacteria (MDRB) in rectal swabs.</p>	<ol style="list-style-type: none"> 1. The number of UTIs per year significantly decreased with oral antibiotic cycling ($p<0.001$). 2. The number of antibiotic treatments per year ($p<0.001$) and the number of hospitalizations per year ($p=0.001$) also significantly decreased with cycling treatment. Additional antibiotic treatment length was also significantly shorter ($p<0.001$) if individuals were already on antibiotic cycling treatment. 3. MDRB presence significantly decreased in individuals after starting antibiotic cycling ($p<0.001$).
Chong et al. 2015 USA Pre-Post N=60	<p>Population: Mean age: 55.75 yr; Gender: males=59, females=1; ASIA classification: A=34, B=11, C=9, D=6; Short-term treatment=35, Long-term treatment=25.</p> <p>Intervention: Individuals either received 1-day of pre-procedural antibiotic treatment or 3-5 days of pre-procedural antibiotic treatment before a urological procedure.</p> <p>Outcome Measures: Quality of life (EQ-5D), physical exam data (vital signs), antibiotic usage (type,</p>	<ol style="list-style-type: none"> 1. There were no significant differences in EQ-5D scores between the short-term and long-term treatment groups. The long-course group reported significantly higher anxiety levels pre-procedurally when reporting anxiety/depression ($p=0.010$) and "extremely anxious" ($p=0.010$) compared to the short treatment group. 2. There were no significant differences in vital signs

Author Year Country Score Research Design Total Sample Size	Methods	Outcome
	frequency), post-procedural day 1 white blood cell count (WBC), complications (UTIs).	between or within groups, pre or post procedure. Additionally, the WBC was similar in both groups. 3. Five adverse events occurred, 2 participants from the long-course group and 3 from the short-term group. One participant from each group was found to have urosepsis and was admitted to the intensive care unit for treatment.
Salomon et al. 2009 France Pre-Post N=6	Population: Mean age: 34 yr; Gender: males=0, females (pregnant)=6; paraplegic=4, tetraplegic=2. Intervention: Weekly oral cyclic antibiotic (WOCA) program. Outcome: Urinary tract infection (UTI) rate, birth weight, obstetric and neonatal characteristics.	1. Significant reduction in UTI rate. Only 2 individuals had a UTI compared to before the treatment with 6 UTI per yr per individual ($p<0.001$). 2. No complications were observed during the delivery. 3. All newborns were born healthy with a mean weight of 3180g.
Salomon et al. 2006 France Pre-Post N=38	Population: SCI with neurogenic bladder and undergoing intermittent catheterization; Mean age: 45.9 yr; Gender: males=22, females=16; daily catheterizations=6. Intervention: Weekly oral cyclic antibiotic (WOCA); Wk 1-one antibiotic+wk 2 another antibiotic (over 2 yr). Antibiotic choice based on urine culture results: amoxicillin 3000mg; trimethoprim/sulfamethoxazole 320-1600mg; fosfomycin trometamol 6000mg; nitrofurantoin 300mg; cefixime 40mg. Outcome Measures: Number of urinary tract infections (UTIs) with weekly cultures for first 3 mo and monthly thereafter over 2 yr.	Before/after WOCA programme: <ul style="list-style-type: none"> Reduced symptomatic UTIs/pt/yr from 9.4 to 1.8, $p<0.01$ Reduced febrile UTI/pt/yr from 0.75 to 0.31, $p<0.04$ Reduced hospitalization days from 4 to 1.2 d/individual, $p<0.01$. Decreased antibiotic consumption correlated with decreased incidence of UTIs over the course of the study.
Previnaire et al. 2017 France Post-Test N=57	Population: Mean age=40.9±16.8; Gender: males=43; females=14; Etiology: SCI=57; Mean time since Injury: 18.4±49.1 mo; Inclusion criteria: individuals using IC; presence of UTI compatible with cystitis; prescription of a 5-day narrow spectrum antibiotic for either symptomatic or asymptomatic bacteremia. Intervention: Individuals were divided into 4 groups: Group 1	1. There was a 99% eradication rate and 100% clinical cure rate for subjects treated for UTI. 2. There was no significant difference in the UTI-free period after treatment for asymptomatic bacteriuria compared with treatment for UTI ($p>0.05$). 3. There was no significant difference in UTI rates after treatment of UTI or

Author Year Country Score Research Design Total Sample Size	Methods	Outcome
	<p>(recurrence of a treated UTI); Group 2 (occurrence of UTI after treatment for asymptomatic bacteriuria); Group 3 (treatment for asymptomatic bacteriuria after UTI); Group 4 (consecutive treatments for asymptomatic bacteriuria). Common 5-day narrow spectrum antibiotic treatments included: Third-generation cephalosporin; Trimethoprim-sulfamethoxazole; Fluoroquinolone; Nitrofurantoin. Outcome measures were assessed at 3, 6, 9wk follow-ups.</p> <p>Outcome Measures: occurrence of UTI; Duration of UTI-free urine; clinical cure at end of therapy for UTI; relapse and reinfection rates.</p>	<p>asymptomatic bacteriuria ($p>0.05$).</p> <p>4. There was no significant difference in UTI rates between those who underwent non-urological procedures and those who underwent invasive urological exams ($p>0.05$).</p> <p>5. There was no significant difference in UTI-free periods between Group 1 and Group 2 ($p>0.05$).</p>

Discussion

An RCT comparing low-dose, long-term treatment with ciprofloxacin (100 mg nightly) versus placebo concluded that ciprofloxacin prophylaxis for up to 39 months resulted in a marked reduction from the pre-study infection rate ($p<0.00005$, corrected) with no severe side effects and only 1 instance of ciprofloxacin resistant *E. coli* found in the feces of one individual (Biering-Sorensen et al. 1994). Another RCT involved a three-day course of ciprofloxacin (500 mg twice daily) or suitable placebo as a pre-cursor to urodynamic investigation (Darouiche et al. 1994), which has been associated with subsequent development of UTI (Pannek & Nehiba 2007). Of those receiving ciprofloxacin, none had a symptomatic UTI at the study follow-up visit (3-5 days post urodynamic testing), whereas 3 of 22 study participants (14%) in the placebo group developed a symptomatic UTI. This finding was statistically non-significant ($p=0.24$), but the trend for reduced UTI incidence and the fact that no subjects in the treatment group developed a UTI suggests that a study with greater power may demonstrate the benefit of pre-urodynamic testing prophylaxis more conclusively.

Nitrofurantoin is commonly used to treat acute, uncomplicated UTI or *E. coli* and Enterobacteriaceae origin. In the population of veterans with SCI, nitrofurantoin is often used for long-term UTI prophylaxis. Using a matched pairs design, Chew et al 2018 reported less frequent UTIs and a significantly greater mean number of days between positive urine cultures as compared to controls (<0.0001). Pairs included “cases” and “controls”, matched within a facility, where cases received ≥ 90 days per study year of continuous daily nitrofurantoin. Matched controls did not receive long-term nitrofurantoin but had a history of at least ≥ 3 positive urine cultures with at least one UTI or asymptomatic bacteriuria per study year. Although the nitrofurantoin group were more likely to have isolates resistant to nitrofurantoin ($P \leq$

0.00001), the frequency of multi-drug resistant organisms isolated from the urine was not significantly different. Therefore, the Chew investigative team concluded support for the long-term prescription of nitrofurantoin to reduce UTIs in veterans with SCI.

Although oral prophylaxis is thought to delay the onset of bacteriuria, a rare result is the decrease in occurrence of symptomatic UTI. Furthermore, oral administration is often accompanied by side effects in multiple body systems (oral, pulmonary, skin, genitourinary, and bowel). Cox et al (2017) investigated the ability of gentamicin bladder instillations to reduce the rate of symptomatic UTIs in neurogenic bladder individuals (63% of the study population had a SCI) using intermittent self-catheterization and who suffered recurrent UTIs. Reported results pre and post gentamicin instillation included a 75% decrease in symptomatic UTI episodes ($p=0.004$), a reduction in the need for oral antibiotics (27.3 to 10%; $p=0.16$), and a decrease in antibiotic resistance (58.3 to 47.1%; $p=0.04$). However, it should be noted that these results may not be generalizable given the observational and retrospective study design.

Conflicting results have been obtained across separate controlled trials conducted in individuals undergoing acute SCI in individual rehabilitation of sustained (i.e., >3 months) prophylaxis with TMP-SMX. Gribble and Puterman (1993) reported that oral administration of a TMP-SMX (40 mg and 200 mg, respectively) formulation once daily was found to significantly reduce frequency and relapse rates of bacteriuria ($p=0.0001$) and symptomatic UTI ($p=0.0003$) in persons with recent SCI using intermittent catheterization for bladder management ($n=129$). Conversely, Sandock et al. (1995) reported on an investigation of individuals at least 6 months post-injury within an individual SCI rehabilitation program in which the standard of care was to prescribe TMP-SMX liberally as a prophylaxis. This practice was stopped for the purpose of conducting a prospective controlled trial in 1 of 2 units and it was noted that there was no significant difference in the number of symptomatic UTIs between those stopping versus those continuing suppressive therapy (0.043 versus 0.035 UTIs/week; $p>0.5$). In addition, there was a significant decrease in the emergence of TMP-SMX resistant asymptomatic bacteriuria in the individuals who stopped suppressing therapy (78.8% versus 94.1%; $p<0.05$). This latter finding was also consistent with that noted by Gribble and Puterman (1993) who noted this, along with TMP-SMX related adverse events, as serious limitations of TMP-SMX prophylaxis therapy. Reid et al. (1994b) also showed an inability of a higher dose of TMP-SMX (160 mg and 800 mg, respectively) to reduce rates of symptomatic UTI among individuals using intermittent catheterization for bladder management.

Given the conflicting findings noted above and in other individual groups, a novel approach to UTI prevention in SCI individuals was undertaken by Salomon et al. (2006). After a prospective, pre-post study with 2-year follow-up, they concluded that a weekly oral cyclic antibiotic (WOCA) program was beneficial in preventing UTI in SCI individuals, decreasing antibiotic consumption and decreasing the number and length of hospitalizations, without severe adverse events or the emergence of multi-drug resistant bacteria (MDRB). The WOCA regimen involved alternating between two antibiotics, administered once per week over at least two years. The specific

antibiotics selected as prophylaxis were customized to the individual, chosen based on allergy and antimicrobial susceptibility. The most frequent combination of antibiotics utilized were TMP-SMX and cefixime (30%) followed by cefixime and nitrofurantoin (25%). The combination of antibiotics was modified in 40% of the individuals once, 20% twice and 10% on three occasions during the follow-up. Salomon et al. (2009) expanded on earlier work specifically to employ a WOCA program in pregnant women with SCI. In this study, UTI rate during pregnancy (which is commonly elevated) was significantly reduced, no complications were observed during delivery, and all newborns were a healthy weight (Salomon et al. 2009). This level 4 evidence for the effectiveness of WOCA in SCI UTI prevention, treatment and cost, and would serve well as guidance in design of a randomized, double-blind, placebo-controlled study to confirm these results. Poirier et al (2016) confirmed the conclusion that WOCA is effective in preventing UTI without MDRB emergence.

Regardless of the antibiotic used, the optimal duration of therapy for UTI is not well understood. Establishing the shortest duration that is clinically effective and safe was the goal of Previnaire et al 2017. For mild UTIs, bacteria eradication was evident in 56 of 57 (99%) cases on day 4 of antibiotic treatment and 100% clinical cure was achieved in all individuals by day 5 (end of treatment). Despite the short 5 day course of treatment, short-term and long-term UTI recurrence (16 and 38%, respectively), was reported to be strikingly similar to another study using a 14 day course of treatment (Dow et al 2004).

Urological procedures are known to have the potential to initiate bacteriuria, surgical site infections, pyelonephritis, and septicemia (Grabe 2004). Therefore, for endoscopic urological procedures in people with SCI, who are already at higher risk for UTIs, pre-procedural antibiotics are a reasonable consideration. In an effort to compare safety, efficacy, quality-of-life impact and costs, single dose vs longer courses of pre-procedural antibiotics was compared for use prior to elective endoscopic urological procedures in spinal cord injured individuals with asymptomatic bacteriuria (Chong et al 2015). The Chong investigative team (2015) reported that a single dose of pre-procedural antibiotics was sufficient to protect individuals with SCI and asymptomatic bacteriuria in preparation for most endoscopic urological procedures.

Conclusion

There is level 1b evidence (from one RCT; Biering Sorensen et al. 1994) that low-dose, long-term ciprofloxacin may prevent symptomatic UTI.

There is level 1b evidence (from one RCT; Gribble & Puterman 1993) that TMP-SMX as prophylaxis may reduce symptomatic UTI rates although conflicting findings were obtained from two prospective controlled trials (Sandock et al. 1995; Reid et al. 1994b). The potential for emergence of drug resistant bacteria and TMP-SMX related adverse events further limit the potential use of TMP-SMX for prophylaxis.

The Chew 2018 investigative team presented level 4 (matched pairs design) evidence in support of long-term prescription of nitrofurantoin to reduce UTIs in veterans with SCI.

There is level 4 evidence (Previnaire et al 2017; N=57 retrospective study) supporting the use of a 5 day course of antibiotic to achieve day 4 bacterial eradication and day 5 clinical cure.

Level 5 evidence is provided by Cox et al 2017 to suggest that gentamicin instillation into the neurogenic bladder could result in the reduction of, episodes of symptomatic UTI, need for oral antibiotics, and antibiotic resistance.

There is level 4 evidence (from two pre-post studies; Salomon et al. 2006; Poirier et al. 2016) that suggests weekly oral cyclic antibiotic use, customized to individual allergy and antimicrobial susceptibility, may be effective for UTI prevention in SCI individuals, and UTI reduction in pregnant individuals.

Ciprofloxacin may be indicated for UTI prophylaxis in SCI but further research is needed to support its use.

Long-term use of TMP-SMX is not recommended for sustained use as a suppressive therapy for UTI prevention.

A weekly oral cyclic antibiotic, customized to the individual, may be beneficial in preventing UTI in SCI.

6.4.3 Antiseptic and Related Approaches for Preventing UTIs

Table 29 Antiseptic and Related Approaches for Preventing UTIs

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
Lee et al. 2007 Australia RCT PEDro=7 N=305	<p>Population: SCI with Neurogenic bladder and stable management: Mean age: 43.5 yr; Gender: males=253, females=52; Level of injury: paraplegia=137, tetraplegia=168; Severity of injury: complete=149, incomplete=156</p> <p>Intervention: Double-blinded comparison of methenamine hippurate (MH, 2g) with cranberry (1600mg), MH (2g) with cranberry placebo, cranberry (1600mg) with MH placebo or MH placebo with cranberry placebo).</p>	<ol style="list-style-type: none"> 1. The Kaplan-Meier curves for MH and Cranberry compared to placebo showed no evidence of a treatment effect. 2. The unadjusted analysis confirms that there was no statistically significant effect of MH tablets (HR 0.94, 95% confidence interval 0.68-1.32) or cranberry tables (HR 0.93, 95% CI 0.66-1.29). 3. The only significant predictor of a future UTI was found to be the number of UTIs in the preceding 6 mo.

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
	Outcome Measures: Time to symptomatic urinary tract infection (UTI) (culture), predictors of UTI, adverse events collected for up to 6 mo.	<ol style="list-style-type: none"> Common adverse effects included diarrhea or constipation. There was no difference in adverse event rates between the groups.
Waites et al. 2006 USA RCT PEDro=6 N _{initial} =89; N _{final} =52	Population: SCI or other neurological disease with indwelling or suprapubic catheter with bacteriuria and pyuria: Mean age: 45.8 yr; Gender: males=49, females=40; Mean time post-injury=11.2 yr. Intervention: Comparison of twice daily bladder irrigation with normal saline versus 0.25% acetic acid versus neomycin-polymyxin (N-P) GU irrigant for treatment of bacteriuria for 8 weeks. Outcome Measures: Numbers and types of bacteria (culture and susceptibility), urinary pH, urinary leukocytes, generation of antimicrobial-resistant organisms collected at baseline, 2, 4, and 8 wk.	<ol style="list-style-type: none"> No difference among 3 irrigation solutions for bacteriuria. Overall, no difference in bacteriuria for any 7 of 8 species ($p>0.1$) other than <i>Enterococcus spp.</i> which increased significantly from week 0 to 8 ($p=0.0006$) and between solutions was significant for N-P group only ($p=0.02$). Mean urinary pH for all 3 groups increased from mean of 6.6 to 7.0–7.2 range ($p=0.01$) at wk 8. No significant increase in urinary leukocytes in any group ($p\geq 0.6$), MRSA ($p\geq 0.37$) or gram-negative resistance to common UTI antimicrobials ($p\geq 0.11$).
Castello et al. 1996 Spain RCT PEDro=4 N _{initial} =38; N _{final} =13	Population: SCI: Mean age: 27.83 yr; Gender: males=9, females=4; Level of injury: paraplegia=12, tetraplegia=1. Intervention: Ascorbic acid versus placebo (lactose) for urinary tract infection (UTI) prophylaxis for an unspecified duration. Outcome Measures: Urine pH, culture.	<ol style="list-style-type: none"> No significant difference in baseline or post-treatment urine pH for ascorbic acid or placebo, or number of individuals developing UTI between groups.
Sanderson & Weissler 1990b UK RCT PEDro=4 N=19	Population: SCI rehabilitation individuals: Gender: males=16, females=3. Intervention: Individuals washed daily in chlorhexide versus unmedicated soap for 8 wk with crossover. Individuals receiving antibiotics for either urinary tract infections (UTIs) or skin infections were analysed separately as 3 rd and 4 th groups depending on their initial treatment (chlorhexide versus soap). Outcome Measures: Bacteriuria assessed by urine culture, perineal colonization (swab), bedsheet, pillow case and environmental	<ol style="list-style-type: none"> Bacteriuria reduced by washing with chlorhexidine versus soap. ($p<0.01$). Bacteriuria less for those on antibiotics and using chlorhexidine ($0.05<p<0.01$). Proportion of negative cultures progressively rose for those on soap alone, to those on chlorhexidine alone, to those on antibiotics with soap, to those on antibiotics with chlorhexidine. Antibiotics usage resulted in significant increase in perineal swabs negative for coliforms ($p<0.01$).

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
	swab samples collected each week day.	
Pearman et al. 1988 Australia RCT PEDro=3 N _{initial} =18; N _{final} =18	<p>Population: SCI in individual: Age range 18-49 yr; Gender: males=15, females=3.</p> <p>Intervention: Trisdine bladder instillation following intermittent catheterisation versus kanamycin and colistin bladder instillation.</p> <p>Outcome Measures: Episodes of bacteriuria, number of catheterizations.</p>	<ol style="list-style-type: none"> 1. No significant difference (chi square, no p value given) in number of episodes of bacteriuria between Trisdine versus kanamycin-colistin bladder instillations; 2. 0.56% (9 of 1609) versus 0.53% (9 of 1704) of instillations were associated with episodes of bacteriuria for Trisdine versus kanamycin-colistin respectively.
Krebs et al. 1984 USA RCT PEDro=4 N=40	<p>Population: Individual SCI (≤ 6 mo post-injury) with intermittent catheterization; Gender: males=40, females=0; Level of injury: T6 & above=27, T7 & below=13.</p> <p>Intervention: Instillation of 45 ml, 5% hemiacidrin solution at each catheterization and 2 mg methanamine mandelate orally 4 times daily versus no bacterial prophylaxis.</p> <p>Outcome Measures: Urinary pH determination culture, rate of urinary tract infections (UTIs), antibiotic susceptibility collected weekly during length of hospital stay.</p>	<ol style="list-style-type: none"> 1. Urine pH lower in methenamine and hemiacidrin group ($p < 0.01$). 2. Control group had double the number of positive cultures ($p < 0.001$). 3. UTI rates were higher in controls ($p < 0.02$). 4. Higher rate of symptomatic UTI in controls (chi-square 3.84, $p < 0.05$).
Wikstrom et al. 2018 Sweden Pre-Post N=19	<p>Population: Mean age=43.7yr, Gender: males=19, females=2; Etiology: SCI (n=21, 100%); Inclusion criteria: SCI; IC as primary as chief method of bladder management; history of recurrent symptomatic UTI; with asymptomatic bacteriuria</p> <p>Intervention: Bladder irrigation with 120 mL of 0.2% chlorohexidine solution was performed 2x/d (morning and evening) for up to 7d. The instilled solution was drained using IC after 15min of being in the bladder.</p> <p>Outcome Measures: Bacteriuria levels below cut-off value; return of bacteriuria to above cut-off levels; adverse events.</p>	<ol style="list-style-type: none"> 1. There was a significant reduction in bacteriuria above the set cut-off after post-treatment ($p < 0.005$). 2. Eight of 14 subjects had a subsequent return of bacteriuria levels above the set cut-off one day post-treatment. 3. Seven adverse events were reported by six subjects: urine leakage; cramping sensation in bladder; increased urine leakage; diarrhea, symptomatic UTI post-treatment.
Shigemura et al 2015 Japan	<p>Population: SCI, NBD; Type of injury: SCI=38,</p>	<ol style="list-style-type: none"> 1. Eighteen MDRPs were detected in 8 mo of surveillance. The

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
Pre-Post N=41	encephalomyelitis=1, spinal tumor=1, aneurysm=1. Intervention: Researchers recommended preventative measures to limit the spread and development of multidrug-resistant <i>Pseudomonas aeruginosa</i> (MDRP) outbreaks. Outbreak trends were monitored over an 8 mo period. Outcome Measures: Spread of MDRPs within individual population, catheterization use.	isolation of MDRPs significantly decreased from the 1st quarter to the last (p=0.02), even though urinary tract device use significantly increased (p<0.001). 2. Rates of hand washing, thoroughness and checking of standard precautions, the use of common shelves for personal antiseptic solutions were the measures recommended seen to improve the rates of MDRPs in individuals.
Jia et al. 2013 China Pre-Post N=41	Population: Mean age: 36 yr; Gender: males=41, females=0; Severity of injury: C2-6 =9, T1-6=8, T7-12=19, L1=5. Intervention: Individuals were administered a 300 U injection of botulinum toxin A. Outcome Measures: Number of UTIs.	1. The mean number of UTIs significantly decreased post-injection (p=0.023). 2. The decrease of UTI was significant in the detrusor over-activity individuals (p=0.015), while the decrease was not significant in norm-active detrusor individuals (p=0.319).
Game et al. 2008 France Pre-Post N=30	Population: Mean age: 39.4 yr; Gender: males=18, females=12; Etiology of neurogenic detrusor over activity: Multiple sclerosis=15, SCI=14, Myelitis=1. Intervention: Individuals were administered an injection of 300 U OnaBTx into the detrusor muscle. Outcome Measures: Frequency of urinary tract infections (UTI).	1. The mean number of UTIs was significantly different from pre-injection compared to post-injection (p=0.003); just 3 individuals still acquired UTIs post injection.
Schlager et al. 2005 USA Pre-Post N=7	Population: Neurogenic bladder caused by myelomeningocele=5, and traumatic SCI=2, and using clean intermittent catheterization: Age range 18-29 yr; Gender: males=3, females=4; Level of Injury: L2 & 4, T6, 8 & 12(x2); Time post-injury>2 yr. Intervention: Phosphorus supplement (Neutra-phos®) as urine-acidifying agent. Wk 2 and 3, individual drank a phosphorus supplement 3 times/d over 4 wk study period. Outcome Measures: Urinalysis (Urine pH) measured 3 times/d (1 st morning, afternoon, evening) for 4 wk; urine sample (cultured) 2 times/wk over 4 wk.	1. No significant change in urine pH during the 2-wk period when individual was on phosphorus supplement (vs when off supplement). 2. Urine acidification not achieved with phosphate supplement. 3. Frequency of bacteriuria in an individual individual was similar on and off supplementation.

Discussion

Good hygiene practices are imperative to UTI prevention. Therefore, it is a natural extension to expect that antiseptic agents applied either directly to the bladder or to potential vectors of indirect transference might be effective in UTI prevention. Accordingly, Sanderson and Weissler (1990a) found that perineal colonization of SCI individuals was significantly correlated with bacteriuria and may be associated with contamination of the environment and indirectly the hands of individuals and staff. This group further examined the effect of chlorhexidine antiseptics on bacteriuria, perineal colonization and environmental contamination in spinally injured individuals requiring intermittent catheterization (Sanderson & Weissler 1990b). In male individuals not receiving antibiotics, daily body washing in chlorhexidine and application of chlorhexidine cream to the penis after every catheterization significantly reduced bacteriuria to 60% from 74% in individuals who only washed with standard soap; however, the effect was not as strong as that delivered by treatment with appropriate antibiotics. Chlorhexidine antiseptics alone did not affect perineal coliform colonization or contamination of the environment although there was a trend for this effect ($p < 0.1$). In essence, this antiseptic effect acted to amplify the bacteria-reducing effects of antibiotics.

Acidifying urinary pH for the prevention of UTIs is based on the established fact that pH reduction to ≤ 5.0 will inhibit growth of urinary *E. coli* (Shohl & Janney 1917), a prevalent pathogen in the urinary tract. An RCT conducted by Waites et al. (2006) on individuals with indwelling or SPC with existing bacteriuria and pyuria ($n=89$) examined the effects of sterile saline, acetic acid and neomycin-polymyxin solution bladder irrigants on the degree of bacteriuria/pyuria, or development of antimicrobial resistance; the authors found no significant difference between groups. Moreover, the twice daily bladder irrigation for 8 weeks resulted in a significant increase in urinary pH ($p=0.01$) for all groups to a range that was more favourable for the growth of *E. coli* (i.e., pH 6.0-7.0). Similarly, 2 weeks of phosphate supplementation (Schlager et al. 2005) or 2 g daily ascorbic acid (Castello et al. 1996) for unspecified duration in SCI neurogenic bladder managed with IC or indwelling catheter have proved ineffective in acidifying urine or altering UTI rates.

Feasibility of treatment is a valid issue for consideration as evidenced by the study conducted by Pearman et al. (1988). These investigators compared the use of trisdine with kanamycin-colistin, a medicated bladder instillation previously demonstrated to be effective to prevent bacteriuria and UTI in SCI (Pearman 1979). In this trial ($n=18$), they found no difference between incidence of bacteriuria in catheterized individuals yet concluded that trisdine was preferred based on its stability at room temperature, association with a reduced likelihood for antibiotic-resistant bacteria and reduced cost compared to kanamycin-colistin. Although the latter are important factors for treatment choice, this study presents no evidence for preferential beneficial effects based on incidence of bacteriuria.

Twice daily bladder irrigation with chlorhexidine was reported, by Wikstrom et al 2018, to be effective in reducing bacteriuria in some people with SCI suffering from recurrent UTIs. It is important to note that the bacteria count chosen to define

treatment success ($<10^3$ CFU/ml) was arbitrary and effectiveness in reducing the risk of symptomatic infections is unknown. Nevertheless, the Wikstrom team concluded that chlorhexidine bladder irrigation did reduce bacterial counts and was practically feasible as an add-on to IC for the short-term. Further study is required to determine whether reduction of asymptomatic bacteriuria actually leads to a reduced frequency of UTIs.

Another solution shown to have some promise in UTI prevention was studied as a combination therapy, both with antiseptic properties. Krebs et al. (1984) investigated the potential of a 5% hemiacidrin solution instilled as an intravesicular acidifying agent at each intermittent catheterization combined with oral administration of methenamine mandelate (2 mg four times daily) in persons undergoing SCI individual rehabilitation. As compared to individuals undergoing no bacterial prophylaxis, the pH of urine was significantly reduced ($p<0.01$) and there was a lower rate of symptomatic UTI ($p<0.05$) and less bacteriuria as indicated by a reduced number of positive cultures ($p<0.001$). The role of hemiacidrin solution alone in these findings remains uncertain.

In contrast to these findings, as part of a double-blind, placebo-controlled RCT ($n=305$), Lee et al. (2007) found oral methenamine hippurate (another formulation of methenamine as an antiseptic) was generally ineffective in preventing symptomatic UTIs. In this well-conducted large sample trial, active and placebo formulations (oral tablet) of both methenamine hippurate and a cranberry preparation were compared as to the occurrence of asymptomatic UTI (up to 6 months) as a primary end-point. There were no statistically significant effects with either treatment alone or in combination as compared to placebo.

These various conflicting results suggest the specific antiseptic agent, alone or in combination with others, and its mode of administration might be important in determining clinical effectiveness and that the practice of antiseptic bladder instillation along with other methods of delivery, dismissed as ineffective by some or in general practice by others (Pearman et al. 1988; Castello et al. 1996; Schlager et al. 2005; Lee et al. 2007), requires further study.

Botulinum toxin therapy has been discussed extensively in this chapter as it relates to improving urodynamic parameters. It has also been studied for the use of reducing UTIs post SCI in two pre-post studies. Both Jia et al. (2013) and Game et al. (2008) reported that after treatment with 300 U botulinum toxin A into the detrusor, individuals had significantly fewer UTIs at follow-up. Further, Jia et al. (2013) reported that the reduction of UTIs was significant only in individuals with detrusor overactivity but not in those without normally active detrusors.

The high prevalence of prophylactic and emergent antibiotic treatment of bladder management related infections has increased catheter-associated urinary tract infections (CAUTI) in spinal cord injury individuals (Dedeic-Ljubovic et al. 2009). Regular rectal swab surveillance, disposable aprons and glove use, and strictly monitored cleaning procedures (materials, instruments, infected individuals and environmental) are among the necessary activities to prevent multi-drug resistant P.

aeruginosa (MDRP). Shigemura et al. (2015), in a small (n=41) pre-post study of measures and costs associated with preventing MDRP revealed how modest expenses associated with strict surveillance was able to reduce an MDRP outbreak by 50% over 8 months (i.e. 12 cases over a 4 month outbreak was reduced to 6 cases over the next 4 months).

ConclusionS

There is level 2 evidence (from one RCT; Sanderson & Weissler 1990a) that daily body washing with chlorhexidine and application of chlorhexidine cream to the penis after every catheterization versus using standard soap reduces bacteriuria and perineal colonization.

There is level 1b evidence (from one RCT; Waites et al. 2006) that bladder irrigation with neomycin/polymyxin or acetic acid is not effective for UTI prevention.

There is level 2 evidence (from one RCT; Castello et al. 1996) that bladder irrigation with ascorbic acid is not effective for UTI prevention.

Level 4 evidence (from one pre-post study, Wikstrom et al 2018) suggests that bladder irrigation with chlorhexidine reduces asymptomatic bacteriuria. This evidence cannot be extended to UTI reduction.

There is level 4 evidence (from one pre-post study; Schlager et al. 2005) that phosphate supplementation is not effective for UTI prevention.

There is level 2 evidence that bladder irrigation with trisdine (RCT; Pearman et al. 1988), kanamycin-colistin (RCT; Pearman et al. 1988) or a 5% hemiacidrin solution combined with oral methenamine mandelate (2 mg four times daily; RCT; Krebs et al. 1984) may be effective for UTI prevention.

There is level 1b evidence (from one RCT; Lee et al. 2007) that oral methenamine hippurate, either alone or in combination with cranberry, is not effective for UTI prevention.

There is level 4 evidence (from two pre-post studies; Jia et al. 2013; Game et al. 2008) that 300 U botulinum toxin type A may reduce UTIs among individuals with neurodestrusor overactivity post SCI.

There is level 4 evidence (from one pre-post study; Shigemura et al. 2015) that suggests strict surveillance methods (associated with modest costs) may be able to reduce the number of multidrug resistant P aeruginosa cases.

Daily body washing with chlorhexidine and application of chlorhexidine cream to the penis after every catheterization instead of using standard soap may reduce bacteriuria and perineal colonization.

The antiseptic agents delivered via bladder irrigation (5% hemiacidrin solution combined with oral methenamine mandelate; trisdine, kanamycin colistin) may be effective for UTI prevention, whereas others are not (i.e., neomycin/polymyxin, acetic acid, ascorbic acid and phosphate supplementation).

Oral methenamine hippurate, either alone or in combination with cranberry, is not effective for UTI prevention.

6.4.4 Alternative Approaches for UTI Prevention

Table 30 Alternative Approaches for Preventing UTIs

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
Hess et al. 2008 USA PEDro=9 RCT N=47	<p>Population: Mean age: 53 yr; Gender: males=47, females=0; Level of injury: tetraplegia=23, paraplegia=24; Severity of injury: AIS A=27, B=10, C=10</p> <p>Intervention: SCI individuals with neurogenic bladder were divided into two groups. Each group was randomly selected to receive either 6 mo of cranberry extract tablet 500 mg BID, or placebo and then the alternate for the next 6 mo. Bladder management methods: condom catheter=35, intermittent catheterization (IC)=8, and indwelling catheter=4.</p> <p>Outcome Measures: Incidence of urinary tract infection (UTI) ($>10^4$ organisms, one+new symptoms, evidence of tissue invasion – hematuria or pyuria; urine pH.</p>	<ol style="list-style-type: none"> 1. No significant difference was seen between the two groups in the incidence of bacteriuria; however UTI were fewer in the period of cranberry treatment (7 UTI/6 mo) versus placebo (21 UTI/6 mo) ($p=0.01$). 2. 34% of individuals in the placebo period experienced at least one UTI; while only 13% experienced at least one UTI in the cranberry tablet consumption period ($p=0.03$). 3. Urine pH was not significantly different between the two periods. 4. The 22 participants with a high glomerular filtration rate (GFR) reported no incidence of UTIs during the cranberry period, while 9 had 11 UTIs during the placebo period.
Lee et al. 2007 Australia RCT PEDro=7 N=305	<p>Population: SCI with Neurogenic bladder and stable management: Mean age: 43.5 yr; Gender: males=253, females=52; Level of injury: tetraplegia=168; Severity of injury: complete=150</p> <p>Intervention: Double-blinded comparison of methenamine hippurate (MH, 2g) with cranberry (1600mg), MH (2g) with cranberry placebo, cranberry (1600mg) with</p>	<ol style="list-style-type: none"> 1. The Kaplan-Meier curves for MH and Cranberry compared to placebo showed no evidence of a treatment effect. 2. The unadjusted analysis confirms that there was no statistically significant effect of MH tablets (HR 0.94, 95% confidence interval 0.68-1.32) or cranberry tablets (HR 0.93, 95% CI 0.66-1.29).

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
	MH placebo or MH placebo with cranberry placebo). Outcome Measures: Time to symptomatic urinary tract infection (UTI) (culture), predictors of UTIs, adverse events collected for up to 6 mo.	3. The only significant predictor of a future UTI was found to be the number of UTIs in the preceding 6 mo. 4. Common adverse effects included diarrhea or constipation. 5. There was no difference in adverse event rates between the groups.
Linsemeyer et al. 2004 USA RCT PEDro=6 N _{initial} =37; N _{final} =21	Population: SCI with neurogenic bladder: Gender: males=16, females=5; Level of injury: C4-L1; Number of UTIs=0 to 2. Intervention: Randomized, crossover: placebo or cranberry tablets (400 mg) 3 times daily for 4 weeks. Outcome Measures: Urinary bacterial counts, white blood cell counts, combination of both counts.	1. No statistically significant findings for the effect of cranberry tablets versus placebo: <ul style="list-style-type: none"> • Urinary bacterial count (p=0.96), • White blood cell count (p<0.27) or • Urinary bacterial + white blood cell count combination (p<0.27).
Waites et al. 2004 USA RCT PEDro=5 N _{initial} =74; N _{final} =48	Population: SCI with neurogenic bladder: Age range 20-73 yr; Gender: males=42, females=6; Severity of injury: complete=40, incomplete=6; Time post-injury=1-30 yr. Intervention: Randomized to cranberry versus placebo capsules. Outcome Measures: Bacterial counts and urinalysis.	1. No significant differences between groups: <ul style="list-style-type: none"> • Bacterial colony counts, bladder management method, or within groups over time (p=0.758). • Urinary leukocyte counts /mL urine, bladder management method, or within groups over time (p=0.929). • pH of urine, or within groups over time (p=0.659). • For each outcome, no interaction between groups, bladder management method, and time (p>0.05). 2. pH higher for external collection versus intermittent catheter (p=0.046) for all time periods for both groups combined.
Pannek et al. 2018a Switzerland Prospective Controlled Trial N _{Initial} =46 N _{Final} =35	Population: Homeopathy (HT): Median age=23.9yr (3.6 – 49.9); Gender: males=16, females=9; Etiology: SCI=25; Median time since injury=13.8yr (1.4 - 45.0). Control (CG): Median age=47yr (37 – 73); Gender: males=7, females=3; Etiology: SCI=10; Median time since injury=22.0±13.9yr. Intervention: Participants were allocated to either HT or CG. CG consisted of the standard of practice at the authors' institution which consisted of urine	1. HT was more effective for prophylaxis of UTI compared to CG (p<0.001). 2. HT showed a significant decrease in the number of UTIs per year at the end of the study compared to the pre-study rate (p<0.001). 3. There was no significant difference in UTI rate when comparing pre- and post-study for the CG (p>0.05).

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
	acidification with either L-methionine, 3x500 mg, or one teaspoon of cider vinegar in 1 glass of water with cranberry extracts 3x daily. Participants in the HT group received one of 6 different homeopathic remedies; Staphysagria, Nux-vomica, Lycopodium clavatum, Hypericum, Sulphur, and Acidum nitricum. Outcomes measures were assessed at baseline and 1x/mo, for 4 yr. Outcome Measures: UTIs per yr.	
Pannek et al. 2018b Switzerland Prospective Controlled Trial N _{Initial} =46 N _{Final} =35	Population: Homeopathy (HT): Median age=23.9yr (3.6 – 49.9); Gender: males=16, females=9; Etiology: SCI=25; Median time since injury=13.8yr (1.4 - 45.0). Control (CG): Median age=47yr (37 – 73); Gender: males=7, females=3; Etiology: SCI=10; Median time since injury=22.0±13.9yr. Intervention: <i>Sub-analysis of Pannek et al. 2018a.</i> Data was organized relative to UTI treatment to assess antibiotic vs non-antibiotic treatment success rate. Antibiotic treatment methods included; Ciprofloxacin, Nitrofurantoin, Norfloxacin, other. Non-antibiotic treatment methods included; homeopathy (Staphysagria, Lycopodium clavatum, Hypericum, Nux vomica, Sulphur, Acidum nitricum), Bladder tea, bladder irrigation with saline, cranberry products, increased fluid intake. Outcome Measures: Treatment success rate.	1. There was no difference antibiotic and non-antibiotic success rates (p>0.05).
Reid et al. 2001 Canada Pre-Post N=15	Population: SCI: Age range 21-78 yr; Gender: males=10, females=4, not determined=1. Intervention: 250 mL water and cranberry juice with meals successively, each for 7 d treatment arms separated by 2 days. Outcome Measures: Biofilm load, bacterial adhesion collected at 0, 7 and 15 days, gram negative counts.	Cranberry juice versus water significantly reduces: 1. Biofilm load (p=0.028); and compared to baseline (p=0.013). 2. Bacterial Adhesion counts (p<0.033). 3. Gram positive counts (p=0.022). 4. Gram negative counts (p=0.054).
Pannek et al. 2014 Switzerland Case Series N=8	Population: Neurogenic lower urinary tract dysfunction; Mean age: 38.75 yr; Gender: males; Level of injury: cervical=3, thoracic=5;	1. At a median follow-up of 15 mo, 5 participants did not experience new UTIs, and UTI

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
	<p>Severity of injury: complete=4, incomplete=4.</p> <p>Intervention: In addition to standard urologic prophylaxis consisting of 4 mo antibiotic treatment (Nitrofuracin or Trimethoprim) and urine acidification with L-Methionine and Cranberry tablets (twice/day), individuals underwent homeopathic case taking by experienced homeopaths.</p> <p>Outcomes: Description of cases, UTI frequency, adverse events, reduction of standard treatment.</p>	<p>frequency was reduced in 3 participants.</p> <ol style="list-style-type: none"> 2. Standard prophylactic treatment could be reduced in 4 participants. 3. No side effects or adverse drug reactions were observed. 4. Bladder management and standard prophylactic measured remained unchanged for all participants.

Discussion

Cranberry (in various forms) is in widespread use for UTI prevention and many clinicians recommend it for this purpose. This remains the case despite uncertainty as to its effectiveness, especially in persons requiring ongoing catheterization as reported in a Cochrane systematic review (Jepson & Craig 2008). However, Hess et al. (2008) conducted a cross-over study in which subjects were given either cranberry tablets or placebo for 6 months, and then crossed to the opposite arm. The authors showed a significant reduction in UTI incidence for those on cranberry treatment. These authors chose a robust definition of UTI (see above) and they presumed the treatment effect arose from an effect on cell wall adherence to the uroepithelial cell wall, an effect that they proposed takes over one month to develop. As such, without sufficient longer-term post-treatment followup, shorter-term studies may fail to note benefit from cranberry treatment (see Linsemeyer et al. 2004). While Reid et al. (2001) employed a study with follow-up only up to 15 days post-treatment, significant results were noted in biofilm load and bacterial adhesion (though this study was not designed to determine effect on significant UTI). These hypotheses help build our understanding of the potential mechanisms of action cranberry may have in preventing UTI.

As noted in the section on antiseptic agents above, Lee et al. (2007) conducted a well-designed double-blind, placebo-controlled RCT (n=305) that examined the effectiveness of cranberry tablets (1600 mg) for UTI prevention alone or in combination with oral methenamine hippurate (2 g). Neither treatment alone or in combination was effective in preventing symptomatic UTIs as assessed over a 6 month study period. This rigorous study incorporated intention-to-treat and multiple analysis methods including survival analysis and multivariate analysis using Cox proportional hazards regression and investigated outcomes associated with both symptomatic UTIs (primary) and bacteriuria (secondary). These results were confirmed by two additional RCTs. Linsenmeyer et al. (2004) found that cranberry

tablets (400 mg) were not effective in changing bacterial or white blood cell counts of 21 participants who underwent a 9-week placebo-controlled, crossover trial. Similar results were obtained by Waites et al. (2004) in community residing persons with SCI of greater than 1 years duration (n=48) which showed no difference between cranberry extract or placebo taken for 6 months in reducing bacteriuria or pyuria nor for reducing symptomatic UTI rates. In contrast to these findings, a pre-post study (n=15) conducted by Reid et al. (2001) showed that cranberry juice intake significantly reduced the adhesion of bacteria to bladder cells whereas water intake did not significantly reduce the bacterial adhesion or biofilm presence in individuals with SCI. These conflicting conclusions may be influenced by the variation in “dose” and formulation of cranberry product (i.e., tablet versus juice) and the outcome measures used across the various studies. Notably, this study (Reid et al. 2001) was not designed or intended to assess the effect of cranberry on asymptomatic UTI.

Hess et al. (2008) noted that subjects in the Waites et al. (2004) study may have been non-compliant given that study medication was mailed to subjects, that the UTI definition may not have been as robust, and that there was an imbalance in bladder management methods between groups. It is important to be note that the studies by Hess et al. (2008), Linsenmeyer et al. (2004), and Waites et al. (2004) all lacked intent-to-treat statistical analyses which reduces the quality of these investigations. The lack of consistency between results underscores the need for yet further efforts to convincingly prove or disprove the potential value of cranberry prophylaxis.

Individuals who have had less than optimal results from traditional treatments for neurogenic lower urinary tract dysfunction will sometimes seek alternative options such a homeopathy. In a series of 8 cases, individuals who received standard antibiotic prophylaxis and urine acidification also received homeopathic care and were reported to have reduced prophylactic treatments in half of the participants and reduced UTI frequency in 3/8 participants while bladder management remained unchanged in all participants.

In a first study to prospectively consider the efficacy of homeopathic treatment for UTI prevention in SCI, Pannek et al 2018a concluded that adjunctive homeopathic treatments decrease UTI in SCI. Although the decrease was reported as significant ($P<0.001$ from medical history and $P=0.008$ from completed questionnaires), it is important to note that complete recruitment was not achieved for the study. Due to participants not wanting to be randomized to the control group, only 10 controls were recruited for comparison to 25 homeopathy participants. As well, since homeopathy is individualized, 12 different homeopathic remedies were included in the study analysis. Because the homeopathic group had statistically fewer UTIs accompanied by a high satisfaction with the homeopathic treatments, the Pannek team suggested that classical homeopathy be considered for people with SCI who have recurrent UTIs.

Pannek et al 2018b reported that 67.8% of individuals were free of symptoms after choosing homeopathic treatment as compared to 78.8% of individuals choosing first-line antibiotic treatments for UTI in SCI. Although the latter was based on 104 episodes of UTIs treated with antibiotics, the smaller homeopathic group only

contributed 59 UTIs treated with homeopathic remedies. The Pannek team felt that non-antibiotic therapy was feasible as a first-line treatment option even in complicated UTI provided the individual was febrile. This conclusion was further supported by the reduced risk for serious complications as a result of homeopathic treatments.

Conclusion

There is conflicting level 1a evidence (from four RCTs; Lee et al. 2007; Linsenmeyer et al. 2004; Waites et al. 2004; Hess et al. 2008) to support the effectiveness of cranberry in preventing UTI in individuals with neurogenic bladder due to SCI.

There is level 2 evidence (from two prospective studies; Pannek et al 2018a and 2018b) suggesting that homeopathy might be a treatment consideration for people with SCI who suffer from recurrent UTIs.

There is level 4 evidence (from one case series; Pannek et al. 2014) that suggests adjunctive homeopathic care may be able to reduce standard antibiotic prophylaxis and UTI frequency in some individuals.

<p>It is uncertain if cranberry is effective in preventing UTIs in persons with SCI.</p> <p>Adjunctive homeopathic care may reduce standard antibiotic prophylaxis and UTI frequency.</p>

SCI individuals with neurogenic bladder typically receive education while initially in rehabilitation to assist with bladder management and maintain a healthy bladder. This may continue as their bladder function changes following rehabilitation discharge.

Table 31 Individual Studies of Educational Interventions

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
Cardenas et al. 2004 USA RCT PEDro=5 N _{initial} =68; N _{final} =56	<p>Population: Age range 20-77 yr; Gender: males=42, females=14; Level of injury: C1-S4/5; Severity of injury: AIS A-D; Bladder Management: IC=33, Condom catheter=11, Indwelling catheter=11, Spontaneous management=1; Time post-injury=5-48 yr.</p> <p>Intervention: Specialized educational program for the prevention of urinary tract infections (UTIs) versus no program.</p>	<ol style="list-style-type: none"> No significant difference between the groups for National Institute on Disability Rehabilitation Research (NIDRR) defined UTI. Significant changes in favour of treatment: <ol style="list-style-type: none"> Fewer Urinary Colony Counts (p=0.009). Fewer symptom reports (p=0.097). Fewer episodes treated with antibiotics (p=0.232).

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
	Outcome Measures: Episodes of symptomatic UTI, bacterial colony counts, number of antibiotic treatments for UTI, UTI related symptoms, health belief questionnaire, multidimensional health locus of control, self-efficacy.	3. Increase in the perception of the severity of the UTI ($p=0.042$). 4. Higher locus of control ($p=0.066$). 5. Lower self-efficacy ($p=0.033$).
Hagglund et al. 2005 USA Prospective Controlled Trial N=60	Population: Mean age: 39 yr; Gender: males=44, females=16; Receiving personal assistance=8 yr. Intervention: Based on geographic residence subjects were assigned to either i) treatment group: 6hr training group workshop delivered by a SCI specialist physician addressing commonly occurring secondary conditions, prevention and treatment including an 8 min video specific to urinary tract infections (UTIs) followed by discussion or ii) control group with no education session. Outcome Measures: Number of d/visits to hospital/ER and presence of UTIs via interview at baseline and 6 mo later.	1. Within treatment group significant reduction in UTI ($p\leq 0.03$) between baseline and 6 mo. 2. Significantly fewer UTIs at 6 mo ($p\leq 0.02$) in the treatment versus control group for both those reporting and not reporting a UTI at baseline. 3. Those reporting a UTI at baseline were significantly more likely to report one at 6 mo ($p=0.04$).
Anderson et al. 1983 USA Case Control N=75	Population: SCI individuals. Intervention: Urinary tract care education program (individual and staff training), 5 classes and one manual. Outcome Measures: Functional Impairment Scale for Bacteriuria, urinary tract infections (UTIs), UTI symptoms, time lost due to UTI assessed 6 mo after discharge.	1. Treatment versus Control following education: <ul style="list-style-type: none"> No impairment: 71 versus 32%. Symptomatic: 24 versus 57% No time lost: 71 versus 50% Time lost: 5 versus 23% 2. Recognition of symptoms: no difference
Barber et al. 1999 USA Pre-Post N=17	Population: SCI outpatients. Intervention: Intensive counselling by clinic nurse with respect to proper clean intermittent catheterization (IC) technique, daily external catheter application and care, appropriate hygiene. If subjects continued to exceed 2 or more urinary tract infections (UTIs) in the following 6 mo they were started on either nitrofurantoin or methenamine mandelate with ascorbic acid or given more instruction on proper techniques. Outcome Measures: Compliance with regime, number of UTIs collected over 1000 d prospectively.	1. Compliance found to be a problem in individuals in both medication regimes after 1 yr of treatment. 2. 11/17 responders although 8 of these required multiple counselling sessions. 3. 4/17 were placed on prophylactic methenamine mandelate and ascorbic acid with various treatment periods; 2/4 developed 1 UTI 4. 3/17 were placed on prophylactic nitrofurantoin for 1 to 2 3/4 yr; none developed UTIs

Discussion

Health care providers have an excellent opportunity to provide proper bladder management education during individual rehabilitation to significantly affect the quality of bladder management after discharge with the goal of assisting clients in maintaining a healthy bladder and preventing UTIs. Anderson et al. (1983) reported on a case-control study where individuals completed a special urinary tract care education program consisting of classes, reading material, written examinations, and demonstration of acquired skills. With this approach 71% of individuals were asymptomatic of UTI at 6 month follow-up. Only 32% of individuals had no symptoms when a group of individuals, tested 4 years earlier in 1975, did not undergo the education program. Furthermore, as a result of the education program only 5% of the educated group lost time from their usual daily activities compared to 23% of the non-educated group losing time. However, both groups registered the same incidence of confirmed or suspected UTI (62-63%). Therefore, the benefit translated into early detection and definitive action resulting in less impairment and less lost time due to the UTI. This study was assessed as comprising Level 4 evidence due to inadequate control of potential confounds between the education and non-education group, among other limitations.

Once discharged, some SCI individuals experience unacceptable recurrence of UTIs. Cardenas et al. (2004) examined the effectiveness of an educational program in an RCT of 56 community-dwelling SCI individuals with a self-reported history of UTIs. The educational intervention included written material, a self-administered test, a review by nurse and physician, and a follow-up telephone call. The control group did not receive the intervention and final interventional data was compared to an equivalent baseline period. A significant decrease in urine bacterial colony count (but not in UTI incidence) and increased Multidimensional Health Locus of Control scale score reflected the beneficial effects of UTI educational intervention in improving bladder health and the individual's perception of control over their own health behaviour. These results were amplified by Hagglund et al. (2005) and Barber et al. (1999), who each examined participants with longstanding SCI and conducted their investigations in conjunction with outindividual rehabilitation follow-up services. Positive benefits of reduced UTI occurrences were seen following a 6 hour physician-mediated educational workshop conducted as part of a prospective controlled trial with 6 month follow-up periods (n=60) (Hagglund et al. 2005). Of note, Hagglund et al. (2005) directed their educational intervention at the consumer-personal assistant dyad.

Barber et al. (1999) identified 17 high risk individuals (i.e., ≥ 2 UTI/6months) over 1000 consecutive outindividual SCI clinic days. These authors found that 11 (65%) of these individuals were able to reduce their number of UTIs to be reclassified as not high-risk with intensive counseling on proper bladder management technique and hygiene, although 8 required multiple counseling sessions to realize an effective reduction of number of UTIs. The remaining individuals in this series required pharmaceutical prophylaxis for UTI prevention although there were some issues with compliance when treatment was extended over 1 year. The authors suggested

that education intervention by a clinic nurse is a simple, cost-effective means of decreasing the risk of UTIs in at-risk SCI individuals, although the sample size was small and the study was neither randomized nor controlled.

The four aforementioned articles were assessed collectively in a systematic review by Mays et al. (2014). While the authors reported that there is limited positive evidence for educational programs directed towards reducing UTIs, they also note that “As there is no downside to this simple, inexpensive intervention, the data are still supportive of nurses providing education on urinary care and management with their individuals” (p. 9).

Conclusion

There is level 2 evidence (from one RCT; Cardenas et al. 2004) that a single educational session conducted by SCI specialist health professionals with accompanying written materials and a single follow-up telephone call can result in reduced urine bacterial colony counts in community-dwelling individuals with prior history of SCI.

There is level 2 evidence (from one RCT, and two pre-post study; Hagglund et al. 2005; Barber et al. 1999; Anderson et al. 1983) that there are beneficial effects of education mediated by SCI specialist health professionals on reducing UTI risk in community-dwelling individuals with SCI using various approaches (e.g., one-on-one or group workshops, demonstrations, practice of techniques and written materials).

There is no evidence assessing the relative effectiveness of different educational approaches for reducing UTI risk.

A variety of bladder management education programs are effective in reducing UTI risk in community-dwelling persons with SCI, although limited information exists as to which is the most effective approach.

6.6 Pharmacological Treatment of UTIs

UTIs in persons with SCI with neurogenic bladder are termed “complicated UTIs” which refers to the presence of a UTI in a functionally, metabolically, or anatomically abnormal urinary tract or that are caused by pathogens that are resistant to antibiotics (Stamm & Hooton 1993). Complicated UTIs may be caused by a much wider variety of pathogens in persons with SCI and are often polymicrobial. It is generally recommended that persons with SCI be treated for bacteriuria only if they have symptoms, as many individuals especially with indwelling or SPC typically have asymptomatic bacteriuria (Biering-Sorensen et al. 2001). Once symptomatic UTI is confirmed, the first line of empirical treatment is via antibiotics and the most common antibiotics chosen for UTI treatment include fluorquinolones (e.g., ciprofloxacin), TMP-SMX, amoxicillin, nitrofurantoin and ampicillin. Fluorquinolones are often chosen because of their effectiveness over a wide spectrum of bacterial

strains (Waites et al. 1991; Garcia Leoni & Esclarin De Ruz 2003). Although much experience with treating UTIs in SCI has been gleaned from other indications, there are several studies that are reviewed below which have investigated a variety of antibiotic agents in this population.

Table 32 Antibiotics in Treatment of UTIs

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
Darouiche et al. 2014 United States RCT PEDro=6 N _{initial} =61; N _{final} =55	<p>Population: Mean age: 59.9 yr; Gender: males=52, females=3.</p> <p>Intervention: Spinal cord injury individuals with lower urinary tract infection (UTI) associated with an indwelling transurethral or suprapubic catheter were randomized to 5-day course of antibiotics with catheter exchange (treatment group) (n=28) or the standard 10-day antibiotic treatment (control group) (n=27).</p> <p>Outcome Measures: Clinical cure, microbiologic response, resolution of pyuria, individual survival, adverse events.</p>	<ol style="list-style-type: none"> 1. At end of therapy (EOT), all participants in both groups achieved clinical cure, with the experimental group noninferior to the control group (p<0.001). 2. At EOT, the experimental group was not found to be significantly noninferior to the control group in terms of microbiologic response or resolution of pyuria. 3. There were 24 participants with adverse events within 180 days EOT. Compared to the control group, the experimental group had a significantly higher risk for recurrent catheter associated urinary tract infection (p=0.043). There were no significant differences between groups in terms of new urinary tract infection, <i>C difficile</i> colitis, or death.
Dow et al. 2004 USA RCT PEDro=10 N _{initial} =60; N _{final} =52	<p>Population: SCI with bacteriuria: Mean age: 39 yr; Gender: males=51, females=9; Time post-injury=7.1 yr; Bladder management: intermittent catheterization=50, condom drainage=10</p> <p>Intervention: Comparison of oral ciprofloxacin (250mg) bid for 14 d versus oral ciprofloxacin (250mg) bid for 3 d followed by 11 d of placebo.</p> <p>Outcome Measures: Urinalysis with leukocyte count, urine culture and surveillance cultures (defined microbiological cure); and type and duration of symptoms (defined clinical cure). All were taken before and at 3-5, 12-16, 19-23 d (defined as short term follow-up) and at 45-51 d (defined as long-term follow-up).</p>	<ol style="list-style-type: none"> 1. Higher microbiological cure rates for 14 d versus 3 d treatment at long-term (p=0.02) but not short-term (p=0.29) follow-up. 2. No difference in clinical cure rate between 14 d versus 3 d treatment at long-term (p=1.0) or short-term (p=0.6) follow-up. 3. Lower rates of clinical & microbiological relapse at short (p=0.001) & long term (p=0.01) follow-up for the 14 d treatment. 4. Trend for higher treatment failure rate for 14 d treatment at short (p=0.07) & long term (p=0.07) follow-up largely due to greater number of cipro-resistant isolates in this treatment arm (especially <i>E. faecalis</i>).

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
Reid et al. 2000 Canada RCT PEDro=8 N=42	<p>Population: SCI with symptomatic UTI; Age range 18-75 yr; Gender: males=28, females=14.</p> <p>Intervention: Comparison of ofloxacin (300 mg bid) versus trimethoprim-sulphamethoxazole (TMP-SMX; TMP=160 mg, SMX=800 mg; twice daily) or another antibiotic if resistant to TMP-SMX for 7 d.</p> <p>Outcome Measures: Bacteriuria (culture), biofilm presence (number of bacteria/epithelial cell) collected on day 1, 4 or 7.</p>	<ol style="list-style-type: none"> 1. Clinical cure rate in favour of Ofloxacin versus TMP-SMX or other antibiotic at day 4 ($p=0.003$) and day 7 ($p=0.015$). 2. Biofilm clearance rate was better with Ofloxacin versus TMP-SMX or other antibiotic at day 4 ($p=0.005$); and day 7 ($p=0.014$); 3. Both treatments effective at reducing bacterial biofilms at day 4 and 7 ($p<0.001$).
Sapico et al. 1980 USA RCT PEDro=6 N=29	<p>Population: SCI with asymptomatic UTI; Age range 21- 32 yr; Bladder Hyperreflexia=22, Bladder Hypotonic=7</p> <p>Intervention: Comparison of standard and low-dose tobramycin (1 mg/kg and 0.5 mg/kg IM every 8 hr) and amikacin (500 mg and 250 mg bid) for 5 d.</p> <p>Outcome Measures: UTI rate (culture) classified as persistence, relapse or reinfection with other bacteria; Urine and serum antibiotic levels. Cultures conducted prior and 2 and 4 d after treatment completion.</p>	<ol style="list-style-type: none"> 1. No significant differences ($p>0.05$ between dose strengths or tobramycin and amikacin. 2. Overall there was a low cure rate of 48% with significant relapse (31%) and reinfection (21%) rates. 3. High urine antibiotic concentrations were found in all subjects. 4. Authors suggested tobramycin and amikacin not recommended for use in SCI.
Dinh et al. 2016 France Cohort N=94	<p>Population: Neurogenic bladder; Mean age: 38.4 yr; Gender: males=80, females=32; Level of injury: paraplegia=65, tetraplegia=20; Injury etiology: spinal cord injury=85, multiple sclerosis=16, brain injury=11.</p> <p>Intervention: Individuals with febrile urinary tract infection (UTI) were divided into three groups according to the duration of antibiotic treatment: less than 10 days (group 1), between 10 and 15 days (group 2), more than 15 days (group 3).</p> <p>Outcome Measures: Cure rate (persistent UTI or UTI-related death was considered failure), bacteriuria.</p>	<ol style="list-style-type: none"> 1. At 1 mo after treatment, there was no significant difference in the cure rate of the three groups (1=71.4%, 2=54.2%, 3=57.1%). 2. There was no significant difference in the bacteriuria rate of the three groups. 3. Regardless of group, there was no significant difference in cure rate between mono (44%) and dual (40%) therapy.
Lee et al. 2014b Taiwan Cohort N=73675	<p>Population: Trimethoprim: Mean age: 48.3 yr; Gender: males=10076, females=44720; Injury etiology: spinal cord injury=298. Ciprofloxacin: Mean age: 51.8 yr; males=1116,</p>	<ol style="list-style-type: none"> 1. Within the 30 day observation period for spinal cord injury participants, there was no significant difference in risk of

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
	<p>females=3068; Injury etiology: spinal cord injury=48. Levofloxacin: Mean age: 55.3 yr; Gender: males=967, females=2175; Injury etiology: spinal cord injury=32. Ofloxacin: Mean age: 47.9 yr; Gender: males=1165, females=4819; Injury etiology: spinal cord injury=29. Norfloxacin: Mean age: 51.4 yr; Gender: males=766, females=4803; Injury etiology: spinal cord injury=31.</p> <p>Intervention: Out individuals with urinary tract infections (UTI) were divided into 5 groups depending on which UTI-related antibiotic regimen was received.</p> <p>Outcome Measures: Treatment failure (as defined by presence of further hospitalization/emergency visit consistent with the initially identified UTI).</p>	<p>treatment failure between any of the 5 groups.</p> <p>2. Other results of this study were not spinal cord injury-specific.</p>
<p>Waites et al. 1991 USA Pre-Post N_{initial}=78; N_{final}=69</p>	<p>Population: SCI with UTI susceptible to norfloxacin: Age range 18-69 yr; Gender: males=66, females=3; Severity of injury: complete=58, incomplete=11; Time post-injury: <6 mo=5, ≥ 6mths=64.</p> <p>Intervention: Oral norfloxacin 400 mg bid for 14 d after initial bacteriologic confirmation of urinary tract infection (UTI).</p> <p>Outcome Measures: Bacterial strain/species identification, culture results collected at 2-4 d after initiating and 5-7 d and 8-12 wk after completing treatment.</p>	<ol style="list-style-type: none"> 58/79 negative for UTI mid-treatment at day 2-4. 5 to 7 d after administration of norfloxacin, infection was eradicated in 42 cases while 37 cases had evidence of infection ($\geq 10^5$ cfu/mL). 8-12 wk after administration, 27/32 were infected after previous eradication (either reinfection or relapse). Of 20 species initially identified, 14 were completely eradicated and remaining 6 had >50% eradication. Of 120 strains identified during or after treatment, 20 were resistant to norfloxacin. Clinical cure in 67% symptomatic UTIs Side effects in 8% of individuals.
<p>Linsenmeyer et al. 1999 USA Case Series N=10</p>	<p>Population: SCI with indwelling catheter and asymptomatic bacteriuria resistant to oral antibiotics: Gender: males=7, females=3.</p> <p>Intervention: Bladder irrigation with 30 cc of neomycin/polymyxin solution 3 x with each session (3 session/d for 5 d).</p>	<ol style="list-style-type: none"> 9 of 12 bladder irrigation trials across 10 individuals led to changed resistance (resistant → susceptible) allowing use of an oral antibiotic. The remaining 3 bladder irrigations were not successful. No change in white blood cells with irrigation ($p>0.05$). No change in bacterial colony count with irrigation ($p>0.05$).

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
	Outcome Measures: Urine culture (type, count and sensitivity) collected pre and post irrigation.	

Summarized Level 5 Evidence Studies:

Pannek et al. (2015) suggest that Phytotherapy, focusing on cranberry extracts to treat UTI has yielded conflicting results (Lee et al. 2007; Linsenmeyer et al. 2004; Waites et al. 2004; Hess et al. 2008).

Discussion

The range of effective antibiotic treatment duration can vary widely depending on the specific microorganism causing the infection, the antibiotic used and the individuals' UTI history. Dow et al. (2004) conducted an RCT (n=60) to compare a 14 day versus 3 day course of ciprofloxacin treatment in SCI individuals with UTI symptoms or microbially documented bacteriuria and concluded that a 14 day Ciprofloxacin treatment results in improved clinical and microbiological outcomes. Microbiological relapse rates were significantly lower for those individuals treated for 14 versus 3 days. Although this study advocates for the use of a 14 versus 3-day course of ciprofloxacin in SCI UTI, as the author notes, it does not address the optimal treatment period which may be 5, 7 or 10 days, nor does it examine the question of whether a higher dose might have been more effective with the shorter therapy. An RCT comparing 5- to 10-day courses of appropriate antibiotic choice accompanied by a catheter change during the 5-day course yielded clinical cures in both groups (Darouiche et al. 2014). However, for these catheter-associated UTIs (CAUTI), the 5-day course was less effective for the microbiologic response, resolution of pyuria and recurrence prevention. Therefore, the authors concluded that the 5-day course, even when combined with catheter exchange, was not an adequate alternative to the 10-day course of antibiotics to treat CAUTI. Muddying the waters somewhat is a non-randomized cohort study reporting no difference in improving clinical signs of UTI regardless of the antibiotic treatment (<10 days, 10-15 days, > 15 days, mono or dual therapy). However, this study (Dinh et al, 2016) did not report on microbiological change and included individuals using a wide variety of voiding practices. Dihn et al. (2016) does concur with Darouiche et al. (2014) since both groups suggest no difference in clinical cure rate regardless of duration of antibiotic treatment.

Ofloxacin is a fluoroquinolone antibiotic shown to be promising in its ability to penetrate and eradicate bacterial biofilms in the bladder in vitro and in SCI individuals (Reid et al. 1994a; Reid et al. 1994b, Lee et al. 2014b)). Bacterial biofilms are colonies of microorganisms along with their extracellular products that may form on surfaces as a structured community that enables the pathogens to resist antibiotics and persist in the urinary tract thereby potentially causing recurrent UTI. Reid et al. (2000) employed a randomized, double blind design (n=42) to assess the relative

effectiveness of a 7-day course of ofloxacin as compared to TMP-SMX or other more appropriate antibiotics as detected by culture sensitivity. Study participants had symptomatic UTI and clinical cure rates, defined as individuals becoming asymptomatic with sterile urine, assessed at day 4 and day 7. Clinical cure rate was significantly greater for Ofloxacin as compared to TMP-SMX or other antibiotic at day 4 (90% versus 48%; $p=0.003$) and day 7 (90% versus 57%; $p=0.015$). In addition, both treatments were effective at reducing bacterial biofilms at day 4 and 7 ($p<0.001$), although the biofilm eradication rate was significantly higher with Ofloxacin versus TMP-SMX or other antibiotic at day 4 (62% versus 24%; $p=0.005$); and day 7 (67% versus 35%; $p=0.014$). This finding was supported by an earlier study (Reid et al. 1994a) noting that fluoroquinolone therapy was more effective at reducing bladder cell adhesion counts in 63% of asymptomatic SCI UTIs versus 44% of SCI subjects treated with TMP-SMX. Lee et al. (2014) also concluded that ofloxacin and norfloxacin might have better outcomes when compared with TMP-SMX for the treatment of outindividual UTIs, noting the limitation of regional differences in antibiotic resistance patterns.

Reid et al. (2000) suggested that a 3-day regimen in the treatment of SCI UTI could be sufficient based on significant biofilm eradication detected in bladder epithelial cells in individuals treated with Ofloxacin compared to TMP-SMX. Shorter courses of antibiotic treatment are currently considered by clinicians and individuals who are concerned with side effects, cost and antimicrobial resistance due to longer term use. The difference in effective treatment duration, compared to the findings of Dow et al. (2004), is due, in part, to the difference in anti-microbial used. However, further study comparing the two antimicrobials (and others) and differing treatment durations are needed.

Gram-negative bacteria such as *Pseudomonas*, *Acinetobacter*, *Enterobacter* and mycobacteria are susceptible to aminoglycosides such as tobramycin and amikacin which may be chosen for complicated UTI treatment. Due to their toxicity and inconvenient route of administration (i.e. intramuscular injection), their use is limited. To investigate the effectiveness of a lower dose of these aminoglycosides, Sapico et al. (1980) compared infection, persistence and reinfection rates of SCI UTI against a standard dose. It was found that there was an overall low rate of success and no difference between the dose strengths or between tobramycin and amikacin even though high antibiotic concentrations were found in the urine of all subjects; this suggests that alternative antimicrobial agents may be better to consider for use in this population.

Although Waites et al. (1991) showed norfloxacin, another fluoroquinolone, to be 73% effective in eradicating UTIs by mid-treatment, the rate of reinfection was 84% after 8 to 12 weeks post initial eradication. Furthermore, 16% of strains isolated after eradication became resistant to norfloxacin. This trial, employing a pre-post study design ($n=78$) with a 14 day course of treatment, enrolled participants with symptomatic UTI and the equivocal results point to the utility of controlled study designs when assessing antibiotic effectiveness. The authors concluded that norfloxacin is a reasonable treatment choice for SCI UTI but the subsequent and

problematic emergence of resistance must be monitored (as with other antimicrobials).

In addition to decisions on selecting the most appropriate antibiotic, the clinician is sometimes faced with additional treatment option challenges when multi-drug resistant bacteria or the individual's allergy to the appropriate antibiotic are encountered. Although conflicting results have been obtained with the use of antiseptic agents as part of a prophylactic strategy to lower urine pH and thereby assist in the prevention of UTIs, Linsenmeyer et al. (1999) used a case series review (n=10) to investigate the use of medicated bladder irrigation as a method to alter the existing antimicrobial resistance. They found that intermittent neomycin/polymyxin bladder irrigation was effective in altering the resistance of the offending bladder organism(s) to allow for appropriate antibiotic treatment, therefore proving preliminary evidence advocating for a short course treatment of neomycin/polymyxin irrigant to alter existing antimicrobial resistance.

Since side effects from traditional treatments discussed above are not uncommon, a subset of individuals turn to complementary and alternative medicine (CAM). Although individuals with SCI are among those with chronic diseases that use CAM the least, the most common reason for CAM use is UTI (and pain) and the most common form of CAM chosen is acupuncture and homeopathy (Panneck et al. 2015). There exist some positive indications for adjunctive homeopathy related UTI improvements (Pannek et al. 2014). Pannek et al. (2015, 2016) reported that 12/13 (92.3%) individuals regarded homeopathy as an effective treatment for UTI. There was an overall satisfaction rate of 90.5% for adjunctive CAM effectiveness for complications secondary to SCI.

Conclusions

There is level 1a evidence (from two RCTs; Dow et al. 2004; Darouiche et al. 2014) that supports the use of longer (10 or 14 day) versus shorter (5 with catheter change to 3 day) courses of antibiotic to improve clinical and microbiological outcomes in the treatment of catheter associated UTIs in persons with SCI.

There is level 1b evidence (from one RCT; Reid et al. 2000; supported by level 2 evidence from one cohort study, Lee et al 2014) that Ofloxacin treatment is more effective than trimethoprim-sulfamethoxazole in treating UTI.

There is level 1b evidence (from one RCT; Sapico et al. 1980) that there is a low success with aminoglycosides for the treatment of UTI post SCI.

There is level 4 evidence (from one pre-post study; Waites et al. 1991) that norfloxacin may be a reasonable treatment for UTI post SCI but subsequent resistance must be monitored.

There is level 4 evidence (from one case series study; Linsenmeyer et al. 1999) that intermittent neomycin/polymyxin bladder irrigation is effective in altering the resistance of the offending bladder organism(s) to allow for appropriate antibiotic treatment.

Optimum antimicrobial treatment duration and dosage is uncertain due to the lack of comparative trials in persons with SCI.

Antibiotics administered over longer durations (10-14 days versus 3 days) is likely to result in improved clinical and microbiological SCI UTI treatment outcome including recurrence prevention.

Ofloxacin treatment is likely to result in significant SCI UTI cure rate, more so than trimethoprim-sulfamethoxazole.

Norfloxacin may be a reasonable treatment choice for UTI in SCI but subsequent resistance must be monitored.

Aminoglycosides have a low success rate in the treatment of SCI UTI.

Intermittent neomycin/polymyxin bladder irrigation may be effective in altering the resistance of the offending bladder organism(s) to allow for appropriate antibiotic treatment.

7.0 Summary

There is level 1a evidence (from three RCTs; Stohrer et al. 1999; Stohrer et al. 2007; Stohrer et al. 2013) that supports the use of propiverine in the treatment of detrusor hyperreflexia resulting in significantly improved bladder capacity, with one of these trials showing equivalent results to oxybutinin but fewer side effects, notably dry mouth.

There is level 1b evidence (from a single RCT; Stohrer et al. 2013) that demonstrated superiority for continence and tolerability when propiverine extended-release is compared to immediate release formulations.

There is level 4 evidence (from a single case series; Krebs et al. 2013) suggesting that solifenancin id (10 or 5 mg) is effective in improving bladder capacity, detrusor compliance, reflex volume and maximum detrusor pressure in individuals with neurogenic detrusor overactivity secondary to SCI.

There is level 1b evidence (from a single RCT, Ethans et al. 2004) that supports the use of tolterodine versus placebo to significantly increase intermittent catheterization volumes and decrease incontinence in neurogenic detrusor overactivity.

There is level 2 evidence (from a prospective controlled trial; Ethans et al. 2004) that tolterodine and oxybutynin are equally efficacious in SCI individuals with neurogenic detrusor overactivity except that tolterodine results in less dry mouth.

There is level 1b evidence (from an RCT; Chen et al. 2015) that CIC frequency and total leakage volume per day decreased while catheterization volume increased equivocally with Oxybutynin administration or percutaneous tibial nerve stimulation (PTNS) where problematic side effects of Oxybutynin were not reported in the PTNS group.

There is level 4 evidence (from pre-post studies; O'Leary et al. 2003; Kennelly et al. 2009; Hadiji et al 2014; Ersoz et al 2016) that supports the potential benefits of oxybutinin administration (oral, controlled-release or transdermal), with transdermal administration resulting in a reduced side effect profile.

There is level 4 evidence (from a prospective controlled trial; Amend et al. 2008) that suggests benefits such as reduced incontinence and increased bladder capacity from combination treatments of two of oxybutinin, trospium chloride or tolterodine, even in individuals with unsatisfactory outcomes following a trial with one of these medications.

There is level 1a evidence (from two RCTs; Stohrer et al. 1991; Madersbacher et al. 1995) that support the use of trospium chloride to increase bladder capacity and compliance, and decrease bladder pressure with very few side effects in SCI individuals with neurogenic bladder.

There is level 1a evidence (from several RCTs: Abdel-Meguid et al (2010); Kruhut et al 2012; Hui et al 2016; Huang et al 2016; Ginsberg) that supports the use of onabotulinum toxin A injections into the detrusor muscle to provide targeted treatment for neurogenic detrusor overactivity resistant to oral anticholinergic treatments in SCI; these studies reveal decreased incontinence, improved bladder capacity, decreased detrusor pressure, improved quality of life, amongst other findings. Numerous level 3 and 4 studies confirm the efficacy and safety.

Dosages of 200U and 300U onaBTX are non-superior for symptom and QoL improvement secondary to NDO as supported by level 2 evidence represented by 2 less rigorous RCTs (Schurch et al 2007; Chen et al 2014). There are higher retention rates with 300U, thus 200U is the recommended dosing (Ginsbger et al. 2012).

Intradetrusor botulinum toxin is supported by level 2 evidence for its superiority in fewer complications and better quality of life compared to augmentation cystoplasty even though the latter was better at decreasing incontinence and improving cystometric capacity.

There is level 4 evidence that onaBTX may improve NDO in individuals that are refractory to antimuscarinics (Chen & Kuo 2015; Al Taweel et al 2015) or anticholigergics (Alvarez et al 2014).

Level 4 evidence is available for onaBTX administration as the basis for reducing (Soler et al 2016) or discontinuing (Fougere et al 2016; Soler et al 2016) autonomic dysreflexia while improving NDO symptoms.

There is level 4 evidence (from one pre-post and one case series study (Klaphajone et al. 2005; Caremel et al. 2011) that detrusor contractility may be decreased through repeated BTX-A injection.

There is level 1a evidence (from four RCTs and three level 4 studies; Silva et al. 2005; deSeze et al. 2004; Kim et al. 2003; deSeze et al. 1998) that the use of vanillanoid compounds such as capsaicin or resiniferatoxin increases maximum bladder capacity, and decreases urinary frequency, leakages, and pressure in neurogenic detrusor overactivity of spinal origin.

There is level 4 evidence (from one post test study; Dasgupta et al. 1998) that intravesical capsaicin instillation in bladders of individuals with SCI does not increase the rate of common bladder cancers after 5 years of use.

There is level 1a evidence (from two RCTs; Lazzeri et al. 2003; Lazzeri et al. 2006) that supports the use of nociceptin/orphanin phenylalanine glutamine, a nociceptin orphan peptide receptor agonist for the treatment of neurogenic bladder in SCI.

There is level 2 evidence (from one RCT; George et al. 2007) advocating for propantheline and oxybutynin intravesical instillation as adjuvant therapy, with propantheline being superior in more cystometric parameters, for neuropathic bladder managed with clean intermittent catheterization.

There is level 4 evidence (from a pre-post study; George et al. 2007) that supports the use of capsaicin intravesical instillation to improve leak volume and frequency. However, this study also revealed that capsaicin intravesical instillation worsened residual volume and cystometric capacity, and can induce hyperreflexia in individuals with SCI and neuropathic bladder.

There is level 4 evidence (from three pre-post studies; Vaidyanathan et al. 1998; Szollar & Lee 1996; Parsad & Vaidyannathan 1993) that intermittent catheterization combined with intravesical oxybutynin instillation is effective in the treatment of neuropathic bladder in individuals with SCI.

There is level 4 evidence (from three pre-post studies; Haferkamp et al. 2000; Pannek et al. 2000; Ersoz et al. 2010) that suggest intravesical instillation of oxybutynin is an effective adjuvant therapy for individuals with SCI managing their neuropathic bladder with catheterization and oral oxybutynin.

There is level 4 evidence (from one pre-post study; Singh & Thomas 1995) that intravesical oxybutynin instillation is not effective in male, SCI individuals with an implanted Brindley anterior root stimulator.

There is level 1b evidence (from one RCT and one pre-post study; Gacci et al. 2007; Taie et al. 2010) that phosphodiesterase-5 inhibitors may be beneficial in improving bladder function post SCI.

There is level 1b evidence (from one RCT; Steers et al. 1992) that intrathecal baclofen may be beneficial for bladder function improvement in individuals with SCI when oral pharmacological interventions are insufficient.

There is level 4 evidence (from one case series; Chartier-Kastler et al. 2000a) that the use of intrathecal clonidine improves detrusor overactivity in individuals with SCI when a combination of oral treatment and sterile intermittent catheterization is insufficient.

There is level 4 evidence (from one retrospective chart analysis; Wollner & Pannek 2016b) that supports the use of Mirabegron to improve the symptoms of NDO.

There is level 4 evidence (from six pre-post, one post-test, one cohort, three case series, and one case control; Gobeaux et al. 2012; Chen & Kuo 2009; Chartier-Kastler et al. 2000b; Anquetil et al 2016; Krebs et al. 2016; Perrouin-Verbe et al. 2016; Gurung et al. 2012; Quek & Ginsberg 2003; Nomura et al. 2002; Reyblat et al. 2009) that surgical augmentation of the bladder (ileocystoplasty) may result in improved continence in persons with SCI who previously did not respond well to

conservative, medical or interventional purposes for neurogenic bladder dysfunction.

There is level 3 evidence (from one case control; Reyblat et al. 2009) that extraperitoneal versus intraperitoneal augmentation enterocystoplasty produces equivocal postoperative continence with easier early postoperative recovery.

There is level 1b evidence (from one RCT; Costa et al. 1993) that moxislyte decreases maximum urethral closure pressure by 47.6% at 10 minutes after an optimum dose of 0.75 mg/kg in individuals with SCI.

There is level 4 evidence (from one pre-post study; Abrams et al. 2003) that tamsulosin may improve bladder neck relaxation and subsequent urine flow in SCI individuals.

There is level 4 evidence (from one pre-post and one case series study; Perlash 1995; Chancellor et al. 1993a) that supports terazosin as an alternative treatment for bladder neck dysfunction in SCI individuals provided that side effects and drug tolerance are monitored.

There is level 4 evidence (from one case series study; Al-Ali et al. 1999) that indicates some potential for phenoxybenzamine as an adjunct treatment for neurogenic bladder following SCI, when tapping or crede is insufficient to achieve residual urine volume of <100mL.

There is level 4 evidence (from one case series study; Linsenmeyer et al. 2002) that 6 months of alpha-1 blocker therapy may improve upper tract stasis secondary to SCI in men by decreasing the duration of involuntary bladder contractions.

There is level 1 evidence (from one RCT and several controlled and uncontrolled trials; DeSeze et al. 2002) that botulinum toxin injected into the external urinary sphincter may be effective in improving outcomes associated with bladder emptying in persons with neurogenic bladder due to SCI.

There is level 4 evidence (from one case series; Soler et al 2016) that the presence of detrusor contraction and normal bladder neck activity may be strong predictors of good outcome for urethral injection of botulinum toxin to treat DSD.

There is level 4 evidence (from one pre-post study; Reitz et al. 2004) that isosorbide dinitrate may be effective in reducing eternal urethral pressure and dyssynergic contraction.

There is level 4 evidence (from one pre-post study; Griljava et al. 2010) that 4-aminopyridine, at sufficient dosage, may be effective in restoring sensation and/or control of the bladder sphincter.

There is level 1b evidence (from one RCT; Gu et al 2015) that electroacupuncture in combination with CIC results in reduced residual volume and CIC frequency while increasing voided volume.

There is level 4 evidence (from one case series study; El Masri et al. 2012) that severity of injury and urinary sensation could be predictive parameters of future voiding function.

There is level 4 evidence (from one case series study; Gohbara et al. 2013) that supervised, sequential conservative bladder management options result in favourable urological complication rates.

There is level 4 evidence (from two case series studies; Ord et al. 2003; Weld & Dmochowski 2000) that indwelling urethral catheterization is associated with a higher rate of acute urological complications than intermittent catheterization.

There is level 4 evidence (from one case series study; Weld & Dmochowski 2000) that prolonged indwelling catheterization, whether suprapubic or urethral, may result in a higher long-term rate of urological and renal complications than intermittent catheterization, condom catheterization or triggered spontaneous voiding.

There is level 4 evidence (from two case series studies; Ord et al. 2003; Weld & Dmochowski 2000) that intermittent catheterization, whether performed acutely or chronically, has the lowest complication rate.

There is level 4 evidence (from two case series studies; Yavuser et al. 2000; Green 2004) that those who use intermittent catheterization at discharge from rehabilitation may have difficulty continuing, especially those with tetraplegia and complete injuries. Females also have more difficulty than males in maintaining compliance with IC procedures.

There is level 4 evidence (from one case series; Bothig et al. 2012) supporting significantly fewer urological complications and higher quality of life for high-tetraplegic respirator-dependent individuals who use suprapubic catheters (versus intermittent catheterization) for bladder management.

There is level 4 evidence (from 1 case series; Bartel et al 2014, n=2825) that supra pubic catheter use is most highly associated with bladder stone occurrence while transurethral catheters are most highly associated bladder stone recurrence.

There is level 1b evidence (from one RCT; Polliack et al. 2005) that using a portable ultrasound device reduces the frequency and cost of intermittent catheterizations.

Level 2 evidence (from 1 cohort study; Kriz and Relichova 2014) reflects the higher likelihood of IC independence based on the individual's neurological level of lesion, with lower cervical lesions (e.g. C7) being more favourable than higher cervical lesions (e.g. C4).

There is level 4 evidence (from many non-randomized controls) that urethral complications and epididymo-orchitis occurs more frequently in those using IC programs for bladder emptying, but the advantages of improved upper tract outcome over those with indwelling catheters outweigh these disadvantages.

There is level 4 evidence (from 1 pre-post study; Wilde et al. 2016) showing that an IC self-management educational program may lead to modest improvement in IC self-management.

There is level 1b evidence (from one RCT; Giannantoni et al. 2001) that, compared to conventional poly vinyl chloride catheters, pre-lubricated non-hydrophilic catheters are associated with fewer UTIs and reduced urethral bleeding.

There is level 2 evidence (from one RCT; De Ridder et al. 2005) that, compared to conventional poly vinyl catheters, hydrophilic catheters may be associated with fewer UTIs, but not necessarily urethral bleeding.

There is level 2 evidence (from one RCT; Sarica et al. 2010) that, compared to hydrophilic or conventional poly vinyl catheters, pre-lubricated non-hydrophilic catheters are associated with reduced pyuria and greater individual satisfaction.

There is level 1b evidence (from two RCTs; Giannantoni et al. 2001; Sarica et al. 2010) that, compared to hydrophilic or conventional poly vinyl catheters, pre-lubricated non-hydrophilic catheters are associated with reduced urethral microtrauma.

There is level 1b evidence (from one crossover RCT; Denys et al. 2012) that compared to standard catheters, no-touch catheters may promote greater confidence and security to individuals performing intermittent catheterization post SCI.

There is level 1a evidence (from three crossover RCTs; Chartier-Kastler et al. 2011, 2013; Biering-Sorensen et al. 2007) that, compared to standard catheters, compact catheters may be more discrete for carrying and disposing and therefore provide greater satisfaction to individuals performing intermittent catheterizations post SCI.

There is level 1b evidence (from two cross-over RCTs; Domurath et al. 2011; Biering-Sorensen et al. 2007) that compact catheters (30 cm) and standard

catheters (40 cm) provide comparable bladder performance with equitable residual urine volume.

There is level 1b evidence (from 1 RCT; Elmend et al. 2018) that pelvic floor muscle training (PFMT) combined with intravaginal electrical stimulation is no more effective than PFMT alone for urinary incontinence.

There is level 1b evidence (from 1 RCT; Shendy et al. 2015) supports the use of TENS biofeedback bladder training to improve bladder function.

There is level 1b evidence (from 1 RCT; Xia et al. 2014) is the basis for electroacupuncture assistive bladder training to improve bladder function.

There is level 4 evidence (from one case series study; Greenstein et al. 1992) that triggering mechanisms such as the Valsalva or Crede maneuvers may assist some individuals with neurogenic bladder in emptying their bladders without catheterization; however, high intra-vesical voiding pressures can occur which can lead to renal complications.

There is level 4 evidence (from one pre-post study; McGee et al. 2017) that co-stimulation of multiple afferent reflex pathways was found to enhance activation of spinal circuits and improve bladder emptying in SCI when stimulation of a single pathway is not sufficient.

There is level 4 evidence (from four cases series studies, one observational study, and one pre-post study) that despite an associated significant incidence of urological and renal complications, acute and chronic indwelling catheterization may be a reasonable choice for bladder management for people with poor hand function, lack of caregiver assistance, severe lower limb spasticity, urethral disease, and persistent incontinence with intermittent catheterization.

There is level 4 evidence (from one cohort and one case series study; Groah et al. 2002; El Masri et al. 2014) that those with indwelling catheters are at higher risk for bladder cancer compared to those with non-indwelling catheter management programs.

There is level 4 evidence (from 1 case series; El Masri et al. 2014) that recurrent catheter blockage is associated predominantly with SPC use and symptomatic UTIs with IUC use.

There is level 4 evidence (from one Newman & Price 1985) that condom drainage may be associated with urinary tract infection and upper tract deterioration.

There is level 4 evidence (from one case series; Perlash et al. 1992) that penile implants may allow easier use of condom catheters, thereby reducing incontinence and improving sexual function.

There is level 4 evidence (from one case series and one pre-post study; Hakenberg et al. 2001; Sylora et al. 1997) that most individuals who receive catheterizable stomas become newly continent and can self-catheterize. It appears possible that this surgical intervention could protect upper tract function. Larger studies are needed to better evaluate true incidence of complications, and long-term bladder and renal outcome.

There is level 4 evidence (from two case series studies; Chartier-Kastler et al. 2002; Kato et al. 2002) that most individuals undergoing cutaneous ileal conduit (ileo-ureterostomy) diversion became newly continent and were more satisfied than with their previous bladder management method. Long-term follow-up demonstrated the presence of a high incidence of urological or renal complications.

There is level 4 evidence (from one pre-post study; Perrouin-Verbe et al 2016) that continent cutaneous urinary diversion (CCUD) with augmentation enterocystoplasty results in increased urethral continence and QoL despite complications of the catheter tube and bladder enlargement that would benefit from annual monitoring.

There is level 4 evidence (from six pre-post studies, five case series, and one observational study) that ongoing use of sacral anterior root stimulation (accompanied in most cases by posterior sacral rhizotomy) is an effective method of bladder emptying resulting in reduced incontinence for the majority of those implanted. This is associated with increased bladder capacity and reduced post-void residual volume.

There is level 1b evidence (from one RCT; Fergany et al. 2017) that PEMFT may improve bladder capacity and urinary flow more than TENS when stimulating the sacral roots.

There is level 4 evidence (from four pre-post studies and two case series study) that sacral anterior root stimulation (accompanied in most cases by posterior sacral rhizotomy) may be associated with reducing UTIs and autonomic dysreflexia.

There is level 4 evidence (from one pre-post study and one case series study; Madersbacher et al. 1982; Radziszewski et al. 2009) that direct bladder stimulation may result in reduced incontinence, increased bladder capacity and reduced residual volumes (with two year efficacy data from one study group) but requires further study as to its potential for larger scale clinical use.

There is level 4 evidence (from various single studies) that other forms of neuroanatomically-related stimulation (e.g., electrical conditioning stimulation to posterior sacral, thoracolumbar, anal, pudendal, dorsal penile or clitoral nerve or surface magnetic sacral stimulation) may result in increased bladder capacity but require further study as to their potential clinical use. These non- or

minimally invasive techniques are preferred by individuals over more invasive methods such as use of the Brindley device, with or without rhizotomy.

There is level 2 evidence (from a one prospective controlled trial; Sievert et al. 2010) that reports early sacral neuromodulation may improve management of lower urinary tract dysfunction. Further investigation is required to confirm the results and substantiate the hypothesis of resultant plastic changes of the brain.

There is level 4 evidence (from one case series study; Katz et al. 1991) that epidural dorsal spinal cord stimulation at T1 or T11 originally intended for reducing muscle spasticity may have little effect on bladder function.

There is level 4 evidence (from one pre-post study; Wheeler et al. 1986) that a program of functional electrical stimulation exercise involving the quadriceps muscle originally intended for enhancing muscle function and reducing muscle spasticity has only marginal (if any) effects on bladder function.

There is level 2 evidence (from one prospective controlled trial; El-Azab et al. 2014) in support of tension-free vaginal tape (TVT) and pubovaginal slings as both effective for neurogenic stress urinary incontinence, with TVT associated with 50% of individuals not needing de novo CIC post-surgery.

There is level 4 evidence (from one case series study; Vainrib et al. 2014) that 1-3 successive BNI/ES procedures are required to achieve 50-85.7% success rate, respectively, in neurogenic detrusor overactivity.

There is level 4 evidence (from one case series study; Perlash 2007) that sphincterotomy is effective in reducing episodes of autonomic dysreflexia associated with inadequate voiding.

There is level 4 evidence (from one case series study; Pan et al. 2009) that sphincterotomy, as a staged intervention, can provide long-term satisfactory bladder function.

There is level 2 evidence (from a one RCT and several level 4 studies; Chancellor et al. 1999) that both sphincterotomy and implantation of a sphincteric stent are effective in reducing incontinence, with little need for subsequent catheterization, and both treatments are associated with reduced detrusor pressure and reduced post-void residual volume but not with changes in bladder capacity. The only significant difference in these two treatments was the reduced initial hospitalization associated with the stent, given the lesser degree of invasiveness.

There is level 4 evidence (from one pre-post study and one case series study; Chancellor et al. 1993c; Seoane-Rodriguez et al. 2007) that implantation of a sphincteric stent may result in reduced incidence of UTIs and bladder-related autonomic dysreflexia over the short-term although several studies have

demonstrated the potential for various complications and subsequent need for re-insertion or another approach over the long-term.

There is level 4 evidence (from one pre-post study; Juma et al. 1995) that over the long-term, previous sphincterotomy may contribute to a high incidence of various upper and lower tract urological complications.

There is level 4 evidence (from one case series study; Game et al. 2008) that advocates for placement of a temporary stent early after injury as a reversible option that allows individuals to choose from the range of permanent stent placement to less invasive bladder management methods such as intermittent catheterization.

There is level 4 evidence (from one pre-post study; Chancellor et al. 1993b) that transurethral balloon dilation of the external sphincter may permit removal of indwelling catheters in place of condom drainage, and also may result in reduced detrusor pressure and post-void residual volume but not with changes in bladder capacity.

There is level 4 evidence (from one case series study and one pre-post study; Patki et al. 2006; Bersch et al. 2009) that implantation of an artificial urinary sphincter may be useful in the treatment of incontinence in SCI but further study is required.

There is level 4 evidence (from one pre-post study; Ke & Kuo 2010) that transurethral incision of the bladder neck may be useful in bladder neck and voiding dysfunction.

There is level 4 evidence (from one case series study; Pannek et al. 2012) that sub-urethral transobturator tape implantation is not effective in managing neurogenic stress incontinence in females living with SCI.

There is level 4 evidence (from one case series study; Losco et al. 2015) that mid-urethral transobturator tape implantation is effective in managing neurogenic stress incontinence in females living with SCI.

There is level 1a evidence (from three RCTs; Cheng et al. 1998; Xia et al. 2014; Gu et al 2015) that supports using electroacupuncture to significantly improve bladder function, when combined with conventional methods of bladder management.

There is level 2 evidence (from one prospective controlled trial; Hubshcer et al. 2018) that the use of locomotor training may increase bladder capacity, voiding efficiency and detrusor contraction time, as well as significant decreases in voiding pressure post-training.

There is level 4 evidence (from one pre-post study and one case series study; Zahariou et al. 2007; Chancellor et al. 1994) that intranasal DDVAP may reduce

nocturnal urine production with fewer night-time emissions and also may reduce the need for more frequent catheterizations in persons with SCI with neurogenic bladder that is otherwise unresponsive to conventional therapy.

There is level 4 evidence (from one pre-post study; Agarwal et al. 2018) that Rectus abdominis detrusor myoplasty (RADM) appears to be a promising option in a individual with acontractile/ hypocontractile bladder to restore the bladder function.

There is level 4 evidence (from one pre-post study; Takahashi et al. 2018) that Mean maximum bladder pressure (MBP) is preserved at a low level following external sphincterotomy (ES), however neurogenic detrusor overactivity (NDO) gradually decreases over time over the years after ES, which would be one of the causes of failure of ES.

There is level 4 evidence (from three pre-post studies; Lin et al. 2009; Lin et al. 2008; Lin & Hou 2013) that nerve crossover surgery (anastomosis of T11 or S1 to S2-S3 spinal nerve roots) may result in improved bladder function in chronic SCI.

The balance of level 4 evidence (from three pre-post studies; Xiao et al. 2003 (positive results), Rasmussen et al. 2015 (negative results); Sievert et al. 2016 (negative results)) suggests that the Xiao procedure (L5-S3 ventral root anastomosis to establish a new reflex pathway) is ineffective for improving bladder function).

There is level 2 evidence (from one cohort study; Lee et al. 2014a, n=27,2005) that reported a lower rate of bladder and prostate cancer in people with SCI vs people without SCI.

There is level 2 evidence (from one cohort study; Eyre et al. 2015) that reports higher complication rates for combined bladder stone procedures vs stone punch alone.

There is level 4 evidence (from one case series study; Bartel et al. 2014) suggesting that bladder stone development occurs with suprapubic, transurethral, intermittent catheter use in descending frequency with reflex micturition have the lowest occurrence.

There is level 3 evidence (from one case control study; Virseda et al. 2014) suggesting the eradication of NDO before proceeding with endoscopic application of bulking agents to treat VUR with a higher success rate.

There is level 4 evidence (from one case series study; Escalrin de Ruz et al. 2000) that individuals with SCI who are completely dependent (FIM<74) or who have vesicourethral reflux are at highest risk for UTI.

There is level 4 evidence (from one case series study; Massa et al. 2009) that the presence of cloudy urine or a positive urine dipstick test are better predictors of

UTI compared with the individual's own subjective impression of their own signs and symptoms.

There is conflicting level 4 evidence (from two pre-post studies; Hoffman et al. 2004; Faarvang et al. 2000) concerning whether dipstick testing for nitrates or leukocyte esterase is recommended to guide treatment decision-making.

There is level 1b evidence (from one RCT; Darouiche et al. 1997) that both limited and full microbial investigation result in adequate clinical response to UTI treatment with antibiotics. Therefore the cost savings attributed to a limited microbial investigation favours this practice in the investigation of UTI although more rigorous investigation of the individual outcomes and attributed costs is needed.

There is level 1b evidence (from one RCT; Horton et al. 1998) that refrigeration (up to 24 hours) of urine samples prior to sample processing does not significantly alter urinalysis or urine culture results in SCI individuals.

There is level 2 evidence (from one prospective controlled trial study; Shah et al. 2005) that fewer false positive tests showing bacteriuria occur if indwelling or suprapubic catheters are changed prior to collection for urine culture analysis. There is level 1a evidence (from one meta-analysis of five RCTs; Li et al. 2013) that the use of hydrophilic catheters versus non-coated catheters is effective in reducing the incidence and occurrence of UTI and hematuria.

The RCT conducted by Bonfill et al (2017) provided level 1b evidence that indwelling silver alloy coated catheters did not reduce the incidence of UTI when compared to standard catheter use.

There is level 1b evidence (from one RCT: Lavado et al. 2013) that regular, moderate aerobic physical activity significantly increases peak oxygen consumption and also significantly reduces the number of individuals with positive urinary cultures.

There is level 2 evidence (from two RCTs; Moore et al. 2006; Peta-Fingerhut et al. 1997) that there is no difference frequency of UTI between sterile and clean approaches to intermittent catheterization during inindividual rehabilitation; however, using a sterile method is significantly more costly.

There is level 4 evidence (from one prospective controlled trial; Wyndaele & De Taeye 1990) that there is no difference in UTI rates between intermittent catheterization conducted by the individuals themselves or by a specialized team during inindividual rehabilitation.

There is level 4 evidence (from one prospective controlled trial; Yadav et al. 1993) that similar rates of UTI may be seen for those using clean intermittent catheterization during inindividual rehabilitation as compared to those using similar technique over a much longer time when living in the community.

There is level 4 evidence (from one pre-post study; Jensen et al. 1995) that differences in residual urine volume ranging from 0-153 ml were not associated with differences in UTI during individual rehabilitation.

There is level 4 evidence (from one retrospective case series; Mukai et al. 2016) that reports significantly higher rates of febrile UTIs in more severely injured males that use CIC.

Level 4 evidence (from one case series study, Krebs et al. 2016) suggests that transurethral indwelling catheter use results in the highest rate of symptomatic UTIs compared to lower rates from using intermittent catheters and receiving botulinum toxin injections into the detrusor.

There is level 1b evidence (from one RCT; Giannantoni et al. 2001) that, compared to conventional poly vinyl chloride catheters, pre-lubricated non-hydrophilic catheters are associated with fewer UTIs and reduced urethral bleeding.

There is level 2 evidence (from one RCT; De Ridder et al. 2005) that, compared to conventional poly vinyl catheters, hydrophilic catheters may be associated with fewer UTIs, but not necessarily urethral bleeding.

There is level 2 evidence (from two RCTs; Cardenas & Hoffman 2009; Cardenas et al. 2011) that use of hydrophilic versus non-hydrophilic catheters are associated with fewer symptomatic UTIs treated with antibiotics even though the number of symptomatic UTIs are similar between groups.

There is level 2 evidence (from one prospective controlled trial, one case control study, and one case series study; Joshi & Darouiche 1996; Nwadiaro et al. 2007; Afsar et al. 2013) that intermittent catheterization may lead to a lower rate of UTI as compared to other bladder management techniques such as use of indwelling or suprapubic catheter.

There is level 3 evidence (from one case control study; Nwadiaro et al. 2007) that bladder management with a suprapubic as opposed to indwelling catheter may lead to a lower rate of UTI and reduced mortality in a poor, illiterate population where intermittent catheterization may not be viable as an approach to bladder management.

There is level 2 evidence (from one RCT; Darouiche et al. 2006) that use of a Statlock device to secure indwelling and suprapubic catheters may lead to a lower rate of UTI.

There is level 2 evidence (from one prospective controlled trial; Gilmore et al. 1992) that removal of external condom drainage collection systems at night or for 24 hours/day might reduce perineal, urethral or rectal bacterial levels but have no effect on bacteriuria.

There is level 4 evidence (from one case series; Ku et al. 2005) that no bladder management method is advantageous in preventing pyelonephritis (though indwelling urethral catheterization does have the highest incidence of upper tract deterioration). However, the presence of reflux results in a 2.8 fold higher incidence of pyelonephritis.

There is level 1b evidence (from one RCT and two pre-post studies; Darouiche et al. 2005; Hull et al. 2000; Prasad et al. 2009) that bacterial interference in the form of E. coli 83972 bladder inoculation may prevent UTIs.

There is level 1b evidence (from one RCT and one pre-post; Darouiche et al. 2011; Trautner et al. 2007) that bacterial interference in the form of E.coli HU2117 bladder inoculation may prevent UTIs.

There is level 1b evidence (from one RCT; Biering Sorensen et al. 1994) that low-dose, long-term ciprofloxacin may prevent symptomatic UTI.

There is level 1b evidence (from one RCT; Gribble & Puterman 1993) that TMP-SMX as prophylaxis may reduce symptomatic UTI rates although conflicting findings were obtained from two prospective controlled trials (Sandock et al. 1995; Reid et al. 1994b). The potential for emergence of drug resistant bacteria and TMP-SMX related adverse events further limit the potential use of TMP-SMX for prophylaxis.

The Chew 2018 investigative team presented level 4 (matched pairs design) evidence in support of long-term prescription of nitrofurantoin to reduce UTIs in veterans with SCI.

There is level 4 evidence (Previnaire et al 2017; N=57 retrospective study) supporting the use of a 5 day course of antibiotic to achieve day 4 bacterial eradication and day 5 clinical cure.

Level 5 evidence is provided by Cox et al 2017 to suggest that gentamicin instillation into the neurogenic bladder could result in the reduction of, episodes of symptomatic UTI, need for oral antibiotics, and antibiotic resistance.

There is level 4 evidence (from two pre-post studies; Salomon et al. 2006; Poirier et al. 2016) that suggests weekly oral cyclic antibiotic use, customized to individual allergy and antimicrobial susceptibility, may be effective for UTI prevention in SCI individuals, and UTI reduction in pregnant individuals.

There is level 2 evidence (from one RCT; Sanderson & Weissler 1990a) that daily body washing with chlorhexidine and application of chlorhexidine cream to the penis after every catheterization versus using standard soap reduces bacteriuria and perineal colonization.

There is level 1b evidence (from one RCT; Waites et al. 2006) that bladder irrigation with neomycin/polymyxin or acetic acid is not effective for UTI prevention.

There is level 2 evidence (from one RCT; Castello et al. 1996) that bladder irrigation with ascorbic acid is not effective for UTI prevention.

Level 4 evidence (from one pre-post study, Wikstrom et al 2018) suggests that bladder irrigation with chlorhexidine reduces asymptomatic bacteriuria. This evidence cannot be extended to UTI reduction.

There is level 4 evidence (from one pre-post study; Schlager et al. 2005) that phosphate supplementation is not effective for UTI prevention.

There is level 2 evidence that bladder irrigation with trisdine (RCT; Pearman et al. 1988), kanamycin-colistin (RCT; Pearman et al. 1988) or a 5% hemiacidrin solution combined with oral methenamine mandelate (2 mg four times daily; RCT; Krebs et al. 1984) may be effective for UTI prevention.

There is level 1b evidence (from one RCT; Lee et al. 2007) that oral methenamine hippurate, either alone or in combination with cranberry, is not effective for UTI prevention.

There is level 4 evidence (from two pre-post studies; Jia et al. 2013; Game et al. 2008) that 300 U botulinum toxin type A may reduce UTIs among individuals with neurodestrusor overactivity post SCI.

There is level 4 evidence (from one pre-post study; Shigemura et al. 2015) that suggests strict surveillance methods (associated with modest costs) may be able to reduce the number of multidrug resistant *P aeruginosa* cases.

There is conflicting level 1a evidence (from four RCTs; Lee et al. 2007; Linsenmeyer et al. 2004; Waites et al. 2004; Hess et al. 2008) to support the effectiveness of cranberry in preventing UTI in individuals with neurogenic bladder due to SCI.

There is level 2 evidence (from two prospective studies; Pannek et al 2018a and 2018b) suggesting that homeopathy might be a treatment consideration for people with SCI who suffer from recurrent UTIs.

There is level 4 evidence (from one case series; Pannek et al. 2014) that suggests adjunctive homeopathic care may be able to reduce standard antibiotic prophylaxis and UTI frequency in some individuals.

There is level 2 evidence (from one RCT; Cardenas et al. 2004) that a single educational session conducted by SCI specialist health professionals with accompanying written materials and a single follow-up telephone call can result

in reduced urine bacterial colony counts in community-dwelling individuals with prior history of SCI.

There is level 2 evidence (from one RCT, and two pre-post study; Hagglund et al. 2005; Barber et al. 1999; Anderson et al. 1983) that there are beneficial effects of education mediated by SCI specialist health professionals on reducing UTI risk in community-dwelling individuals with SCI using various approaches (e.g., one-on-one or group workshops, demonstrations, practice of techniques and written materials).

There is no evidence assessing the relative effectiveness of different educational approaches for reducing UTI risk.

There is level 1a evidence (from two RCTs; Dow et al. 2004; Darouiche et al. 2014) that supports the use of longer (10 or 14 day) versus shorter (5 with catheter change to 3 day) courses of antibiotic to improve clinical and microbiological outcomes in the treatment of catheter associated UTIs in persons with SCI.

There is level 1b evidence (from one RCT; Reid et al. 2000; supported by level 2 evidence from one cohort study, Lee et al 2014) that Ofloxacin treatment is more effective than trimethoprim-sulfamethoxazole in treating UTI.

There is level 1b evidence (from one RCT; Sapico et al. 1980) that there is a low success with aminoglycosides for the treatment of UTI post SCI.

There is level 4 evidence (from one pre-post study; Waites et al. 1991) that norfloxacin may be a reasonable treatment for UTI post SCI but subsequent resistance must be monitored.

There is level 4 evidence (from one case series study; Linsenmeyer et al. 1999) that intermittent neomycin/polymyxin bladder irrigation is effective in altering the resistance of the offending bladder organism(s) to allow for appropriate antibiotic treatment.

Optimum antimicrobial treatment duration and dosage is uncertain due to the lack of comparative trials in persons with SCI.

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Abbreviations

AboBTx	AboBotulinum Toxin A (Dysport)
BTX-A	Botulinum Toxin A
CAP	Capsaicin
DDAVP	Desmopressin Acetate
DESD	Detrusor External Sphincter Dyssynergia
IC	Intermittent Catheterization
N/OFG	Nociceptin/Orphanin Phenylalanine Gluame
NDO	Neurogenic Detrusor Overactivity
NLUTD	Neurogenic Lower Urinary Tract Dysfunction
OnaBTX	OnaBotulinum Toxin A (Botox)
PVC	Polyvinyl Chloride Catheter
QoL	Quality of Life
RCT	Randomized Controlled Trial
RTX	Resiniferatoxin
SCI	Spinal Cord Injury
SPC	Suprapubic Catheter/ization
TMp-SMX	Trimethoprim-Sulpharmethoxazole
TCL	Trospium Chloride
UTI	Urinary Tract Infection
WOCA	Weekly Oral Cyclic Antibiotics