Drugs 2001; 61 (9): 1275-1287
0012-6667/01/0009-1275/$27.50/0

Urinary Tract Infections in Patients with Spinal Cord Lesions

Treatment and Prevention

Fin Biering-Sørensen,[1] *Per Bagi*[2] and *Niels Høiby*[3]

1 Clinic for Para- and Tetraplegia, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark
2 Urological Clinic, Surgical Department D, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark
3 Department of Medical Microbiology, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark

Contents

Abstract

Even though the mortality due to urinary tract complications has decreased dramatically during the last decades in individuals with spinal cord lesions (SCL), urinary tract infections (UTI) still cause significant morbidity in this population.

Complicated UTI are caused by a much wider variety of organisms in individuals with SCL than in the general population and are often polymicrobial. *Escherichia coli*, *Pseudomonas* spp., *Klebsiella* spp., *Proteus* spp., *Serratia* spp., *Providencia* spp., enterococci, and staphylococci are the most frequently isolated bacteria in urine specimens taken from individuals with SCL. There is no doubt

that the greatest risk for complicated UTI in these individuals is the use of an indwelling catheter. Intermittent catheterisation during the rehabilitation phase has been shown to lower the rate of UTI, and virtually eliminate many of the complications associated with indwelling catheters.

Persons with SCL should only be treated for bacteriuria if they have symptoms. Generally, it is advisable to use antibacterial agents with little or no impact on the normal flora. Single agent therapy – in accordance with antimicrobial susceptibility test – is preferred. We advise extending treatment to at least 5 days, and in those with reinfection or relapsing UTI, at least 7 to 14 days, depending on the severity of the infection.

The diagnosis of structural and/or functional risk factors is essential in order to plan an optimal treatment for UTI in individuals with SCL, which should include treatment of simultaneously occurring predisposing factors. The treatment of structural risk factors follows general urological principles, aiming for sufficient outlet from the bladder with minimal residual urine and low pressure voiding.

For prevention of UTI, general cleanliness and local hygiene should be encouraged. If the patient has a reinfection or relapsing symptomatic UTI, it is important to check for inadequately treated infection and complications, which need special attention, in particular residual urine and urinary stones. No reliable evidence exists of the effectiveness of cranberry juice and other cranberry products. Prophylactic antibacterials should only be used in patients with recurrent UTI where no underlying cause can be found and managed, and in particular if the upper urinary tract is dilated. Antibacterials should not be used for the prevention of UTI in individuals with SCL and indwelling catheters. However, the use of prophylactic antibacterials for individuals with SCL using intermittent catheterisation or other methods of bladder emptying is controversial.

Life expectancy among individuals with spinal cord lesions (SCL) remains below normal.[1-3] In particular, until the mid-1970s, renal failure and other urinary tract complications were the most frequent causes of death.[3-5] Urinary tract infection (UTI) is still one of the leading causes of morbidity in individuals with SCL.[6-10] Indeed, Maynard and Diokno[11] studied patients with acute spinal cord injury and found at least 22% to have clinical UTI during a period of 50 days. In individuals with chronic SCL, a 20% annual incidence of UTI has been reported,[12] although UTI was not clearly defined. Waites et al.[10] found an overall incidence of bacteriuria/UTI in catheter-free outpatients of 18.4 episodes per person-year at risk; whereas the rate for those associated with fever and chills was 1.82 episodes per person-year at risk. The prevalence of UTI in this study was 57.4%.

Therefore, bladder management and treatment and prevention of UTI in individuals with SCL takes up a significant amount of time for nurses, doctors and others involved with this population.

1. Bacteriuria: Urinary Tract Infection

As stated by Hull et al.[13] there is considerable controversy about the definition of UTI in individuals with SCL.[7,10,11] Various classifications have been used, based both on laboratory results, such as number of bacteria and leucocytes,[7,10,11,14-16] and clinical symptoms, such as malodorous urine, changes in continence or bladder emptying pattern, fever or chills etc.[11,16,17]

Cardenas and Hooton[7] refer to the consensus conference by the National Institute on Disability and Rehabilitation Research regarding the recommended uropathogen colony count criteria for the diagnosis of significant bacteriuria in persons with SCL: (i) $\geq 10^2$ cfu/ml (cfu = colony forming units)

for catheter specimens from individuals on intermittent catheterisation; (ii) $\geq 10^4$ cfu/ml for clean-void specimens from catheter-free males using condom collection devices; and (iii) any detectable concentration of uropathogens from indwelling catheters or suprapubic aspirates.

These criteria stress the importance of considering the bladder drainage method when evaluating bacteriuria.

Gribble et al.[15] concluded that for their group of acutely spinal cord-injured patients undergoing intermittent catheterisation, a criterion of $\geq 10^2$ cfu/ml of midcatheter urine should be used for diagnosis of bacteriuria, instead of the traditional diagnostic criterion of $\geq 10^5$ cfu/ml, because of unacceptably low sensitivity for bacteriuria documented by suprapubic aspiration. They found the best diagnostic criterion for Gram-positive bacteriuria was between $\geq 10^1$ cfu/ml and $\geq 10^2$ cfu/ml.

Bacteriuria in itself does not necessary imply that there is UTI; it may be a true infection or just colonisation. Today we don't have the methods to determine if tissue invasion has occurred or not, and so, there will always be discussion on which terms are correct. This is not least because the diagnosis of UTI in persons with SCL is complicated by the poor sensitivity and specificity of symptoms and signs. Assessment of pyuria is also complicated by the irritative effect of the catheter on the bladder wall especially in individuals with indwelling catheters in whom pyuria has low specificity as a diagnostic test for UTI.[7] The significance of pyuria in the SCL population warrants further research.

Cardenas and Hooton[7] even state that the laboratory results may be misleading and the inexperienced physician may overtreat patients or, of greater concern, fail to recognise and treat early infection.

Asymptomatic bacteriuria seems of no consequence to the integrity of the upper urinary tract when low vesical pressures are operant.[18]

Like Stover et al.[16] we intend to follow the terms and definitions which are generally accepted in the medical literature (see table I).

Table I. Terms and definitions in urinary tract infections[16]

Bacteriuria	Bacteria isolated from the urine irrespective of collection method or presence of symptoms
Asymptomatic bacteriuria	Bacteriuria without clinical symptoms
Colonisation	Bacteria without tissue invasion
Urinary tract infection (UTI)	Microbial invasion of any of the tissues of the urinary tract
Uncomplicated UTI	Community-acquired cystitis without structural or neurological abnormalities
Complicated UTI	Presence of any underlying condition making therapy less effective, that is, neurogenic bladder, large residual volumes, stones etc
Relapse	The occurrence of bacteriuria with the same organism within a defined time interval after treatment
Reinfection	Isolation of a new pathogen within a defined time interval after treatment

2. Aetiology

Generally, the development of UTI depends upon the balance between bacterial virulence and host defences. The host defences include the mechanical effect of flushing the urine, cell mediated immunity, local production of immunoglobulin in the bladder wall and the mucous lining of the bladder. When the host defences are seriously compromised then the individual is likely to be susceptible to virtually any organisms that can invade the urinary tract.[9]

The host defence implies development of antibodies to bacterial antigens during chronic or recurrent UTI. In other chronic infections (e.g. cystic fibrosis, endocarditis and leprosy) the occurrence of such antibodies may be of prognostic significance for the course of the disease in the infected patients. Similarly in individuals with SCL, recurrent UTI induce precipitating antibodies and the level may correlate to the tissue damage in the kid-

ney. This suggestion has been supported by the finding of a correlation between the level of precipitating antibodies and plasma creatinine in individuals with spina bifida.[19]

Risk factors for UTI may be divided into 3 groups: structural/physiological factors; behavioural; and demographic.[7]

Structural/physiological factors include overdistension of the bladder, vesicoureteral reflux, high-pressure voiding, large post-void residuals, presence of stones in the urinary tract, and outlet obstruction, such as detrusor-sphincter dyssynergia, urethral stricture and enlarged prostate. Therefore, the method of bladder management has great importance on the risk of UTI. At the same time, there is less evidence for the effects of inadequate fluid intake, reduced host defences, pregnancy, repeated traumatic urethral catheterisations, and pre-existing structural anomalies of the urinary tract.

Behavioural and demographic characteristics have not been so well studied, but the following may have an association with UTI: patient's knowledge of the urinary system, adjustment to disability, personal hygiene, self-esteem, work or productivity, social support systems, age, gender, residence and access to services.

In a prospective study in a cohort of catheter-free outpatients, Waites et al.[10] found that black ethnicity, poor personal hygiene, and less-than-daily condom catheter changes correlated with risk of bacteriuria/UTI. In the same study, pyuria was significantly associated with the occurrence of fever and chills, whereas bladder drainage method, age, gender, years since injury, neurological level, income, and education were not correlated with increased risk of bacteriuria/UTI. In a very recent study from the same group of 287 outpatients, significantly higher rates of multidrug-resistant bacteria were found in specimens from males, younger age group (≤45 years), and those with indwelling and condom catheters.[20]

UTI most commonly results from ascending transurethral invasion of the bladder by pathogenic organisms normally present in the gut. Ascending infection is preceded by colonisation of the introitus or periurethral area, or migration of bacteria within the urinary collection system.[9]

2.1 Aetiological Organisms

Complicated UTI are caused by a much wider variety of organisms in individuals with SCL than in the general population and are often polymicrobial, in particular in persons with indwelling catheters.[7,16] *Escherichia coli*, *Pseudomonas* spp., *Klebsiella* spp., *Proteus* spp., *Serratia* spp., *Providencia* spp., enterococci, and staphylococci are the most frequently isolated bacteria in urine specimens taken from individuals with SCL.[7,10,14,16,17,20]

3. Bladder Management

The period of spinal chock immediately after a traumatic SCL results in urinary retention, which requires either continuous or intermittent bladder catheterisation.

3.1 Indwelling Catheters

The use of an indwelling catheter, either urethral or suprapubic, is virtually always associated with bacteriuria within 2 weeks. In addition, it predisposes to urinary calculi and bladder carcinoma, and an indwelling urethral catheter further increases the risk of urethritis, periurethral abscess, prostatitis, epididymitis, orchitis, testicular abscess, and fistula.[7,16,21]

There is no doubt that the greatest risk for complicated UTI in individuals with SCL is the use of an indwelling catheter.

3.2 Intermittent Catheterisation

Intermittent catheterisation during the rehabilitation phase has been shown to lower UTI rate, and has virtually eliminated many of the complications associated with indwelling catheters.

Individuals with SCL who were catheterised by someone else were found to be much more likely to have experienced at least one episode of bacteriuria with fever at the first year follow-up than those on self-intermittent catheterisation or those using an indwelling catheter. In patients who un-

derwent external sphincterotomy, the incidence of bacteriuria with fever was significantly decreased.[22] This finding indicates that eliminating outlet obstruction may help preventing recurrent UTI in individuals using condom catheters.

In a hospital facility, sterile intermittent catheterisation is preferred over a nonsterile procedure as fewer cases of bacteriuria and UTI occur.[23]

Bennett et al.[24] found an introducer tip catheter, which bypasses the colonised 1.5cm of the distal urethra decreased UTI in hospitalised men with SCL using intermittent catheterisation.

Hydrophillic catheters for intermittent catheterisation have low friction and seem to be associated with a lesser degree of urethral inflammatory response when compared to the use of PVC catheters.[25,26] Furthermore, it seems that the hydrophillic catheter is as good or better than conventional catheters, and even strictures after early urethral trauma seem to be preventable if this catheter is used.[27]

Intermittent catheterisation is the most used method of bladder management, but with a non-negligible rate of urethral trauma in men. Percussion and the Credé manoeuvre appear to be acceptable techniques of bladder management if the patient is closely monitored.[28]

3.3 Reflex Voiding and Condom Catheters

Reflex voiding will often require an external collecting device, such as a condom catheter, for control of incontinence. Condom catheters seem to have the least risk of complicated UTI in cooperative individuals with SCL compared with indwelling as well as intermittent catheterisation.[22] Symptomatic complicated UTI may indicate that an obstructed voiding pattern is present. High pressure voiding may result in vesicoureteral reflux, which is seen in 5 to 10% of individuals with SCL. Higher grades of reflux will often be associated with recurrent symptomatic pyelonephritis and declining renal function. Segmental or global renal atrophy may occur as a result of reflux. Early detection and appropriate changes in bladder management are necessary to minimise these deleterious effects.[16]

Changing the method of urinary drainage should not be recommended without careful consideration of the impact on the person's lifestyle as well as their ability to manage a different method. Ultimately, the primary goals of management of UTI are to prevent the insidious loss of renal function and to improve the quality of life of the patient.[7]

4. Treatment

4.1 When to Treat

It should be kept in mind that dipstick screening tests (leucocyte esterase activity and nitrite production) are not recommended for detection of low colony count UTI (10^3 to 10^4 cfu/ml), since the positive predictive values are low (0% and 43%, respectively), and since not all bacteria are nitrite positive. Therefore, if only dipstick positive urine is cultured, many patients with significant bacteriuria will be missed. Although the negative predictive value is high (99% and 96%, respectively), a few patients with significant bacteriuria are missed if urine is not cultured when the dipstick test is negative.[29] Generally routine dipstick screening tests are not recommended for asymptomatic persons.

Most individuals with SCL and bacteriuria have no associated signs or symptoms. Chills and fever are often considered to be signs of acute pyelonephritis; however, these signs do not confirm an infection in the upper urinary tract.[16] Still, chills and fever may be the only symptoms in persons with SCL and pyelonephritis, bacteraemia, upper tract obstruction by calculi, renal abscesses and periphrenic abscess. Other suspicious signs and symptoms may include increased sweating, abdominal discomfort, costovertebral angle pain or tenderness, and increased muscle spasticity.[16] Cloudy and malodorous urine and changes in urine pH may be signs of UTI but can also occur with colonisation, changes of bacterial organisms and the digestion of various foods. Increased spontane-

Table II. Recommended first and second line antibacterial agents for the treatment of urinary tract infections in patients with spinal cord lesions

Route of administration	First line agents	Second line agents
Oral	Cotrimoxazole[a]	Amoxicillin/clavulanic acid
	Trimethroprim	Norfloxacin
	Mecillinam	Ofloxacin
	(Nitrofurantoin)	Ciprofloxacin
		Second generation cephalosporins
		Fosfomycin
Parenteral – intravenous	Netilmicin (also intramuscular administration)	Ceftazidine
	Ciprofloxacin	Meropenem
	Gentamicin	Piperacillin (+/- tazobactam)
	Amikacin	

a Trimethroprim/sulfamethoxazole.

ous voiding or larger residual urine volume including acute urinary retention may be seen with acute infection.[16]

Schlager et al.[30] found bacteriuria to persist for weeks in symptom-free children treated with clean intermittent catheterisation for neurogenic bladder associated with a normal upper urinary tract.

According to a study in 64 catheter-free patients, the advisability of treating asymptomatic UTI following SCL is questionable from both a medical-economic and microbiological standpoint, particularly in view of the likelihood of inducing multidrug resistance with prolonged antibacterial exposure.[31]

In a study of 50 patients using intermittent catheterisation symptomatic UTI was observed at a rate of 9.35, relapsing asymptomatic bacteriuria 35.59, and recurrent asymptomatic bacteriuria 55.80 per 1000 patient days. There was a significant difference between relapsing and recurrent asymptomatic bacteriuria with regard to occurring symptomatic UTI, as relapsing asymptomatic bacteriuria was an important factor in the development of symptomatic UTI.[8]

There seems to be a general agreement that asymptomatic bacteriuria in an individual with SCL and an indwelling catheter should not be treated. We believe that a similar attitude should prevail for persons with SCL and neurogenic bladder, that is, they should only be treated for bacteriuria if they have symptoms. These symptoms may be annoying malodorous urine, changes in the bladder management pattern including increased incontinence and residual urine, signs of autonomic dysreflexia with increased sweating, increased spasticity or spasms, discomfort or pain over the kidney or bladder, malaise, lethargy, sense of unease or fever.

4.2 Antibacterials

Symptomatic UTI in SCL individuals should be treated in accordance with the result of a culture with antimicrobial susceptibility testing. Generally, it is advisable to use antibacterials with little or no impact on the normal flora.[32] Single agent therapy is preferred.

Depending on the antimicrobial susceptibility testing we suggest that antibiotics such as cotrimoxazole (trimethroprim/sulphamethoxazole), trimethroprim, nitrofurantoin and mecillinam be used primarily in patients with SCL and symptomatic UTI. It has been claimed that amoxacillin, sulfonamides as single therapy, and nitrofurantoin are poor choices in patients with SCL because of the high prevalence of resistance to these agents among uropathogens in complicated UTI.[7] Amoxicillin plus the β-lactamase inhibitor clavulanic acid is, however, still active against many of the uropathogens. Nitrofurantoin should be avoided in ill patients because it achieves sub-optimal renal parenchymal concentrations.[7] When necessary, the more broad-spectrum fluoroquinolones (norfloxacin,

ofloxacin or ciprofloxacin) or a second generation cephalosporin, or fosfomycin can be used orally (table II).

Since most antibacterials are excreted in the urine, high dosage is not necessary. However, from a pharmacodynamic point of view, β-lactam antibacterials (time-dependent killing) should be administered to maximise the time of exposure of the bacteria to the drug, whereas aminoglycosides and fluoroquinolones (concentration-dependent killing) should be administered to maximise the peak concentration of the drug that the bacteria are exposed to. From a practical point of view, these pharmacodynamic principles are fulfilled with most UTI treatment regimens except for the single-dose treatment regimens, which have repeatedly performed significantly less effectively compared with other regimens.[33] For empirical treatment, the drugs used should be those where the prevalence of resistance among the most common UTI pathogens is less than 10 to 20%.[33]

In persons with SCL we recommend that the treatment is extended to at least 5 days, and in those with reinfection or relapsing UTI at least 7 to 14 days,[7] depending on the severity of the infection.

Where oral antibacterials cannot be administered, because of vomiting or nausea or because the bacteria are not susceptible to available oral agents, intramuscular netilmicin is a possibility. However, kidney function has to be carefully observed and serum drug concentrations monitored.

Intravenous treatment may be necessary when the patient presents with fever indicating pyelonephritis. Often ciprofloxacin, gentamicin or netilmicin are used. Among the aminoglycosides, netilmicin and amikacin have the lowest potential for nephrotoxicity.[34]

For more seriously ill, hospitalised patients, we would use ceftazidime (not for enterococci), meropenem or piperacillin (both are also active against enterococci), and the latter can be given in combination with the β-lactamase inhibitor tazobactam, if necessary (table II). Patients initially given parenteral therapy can be switched to oral treatment following clinical improvement after 28 to 72 hours (sequential therapy).

If there is any suspicion of bacteraemia, blood cultures should be obtained. Since the urinary tract is the most common focus of bacteraemia, the initial treatment should cover the bacteria present in the urine.

Pharmacodynamics of drugs may be altered in patients with SCL requiring adjustment of drug dosage.[16] Sustaining urine antibacterial concentrations is more important than blood concentrations. Changing the urine pH to enhance antibacterial activity has not proven effective.[16]

If the antibacterial treatment is sufficient, that is, the uropathogen is susceptible, there should be clinical improvement within 24 to 48 hours. If this is not the case, then the urine culture should be repeated and further investigations may be appropriate including plain abdominal film to detect urinary tract stones, or ultrasound or computerised tomography to exclude other treatable urinary tract pathology. Moreover, invasive procedures like a cystogram should be avoided until the patient has responded to the antibacterial treatment.

A Cochrane review has shown no evidence to suggest that cranberries (particularly in the form of cranberry juice) are effective for the treatment of UTI.[35] Harkins[36] even states that this treatment cannot be recommended, and it would be better to enter patients with recurrent UTI in clinical trials.

4.3 Predisposing Factors

The diagnosis of structural and/or functional risk factors is essential in patients with SCL and UTI in order to plan an optimal treatment, which, if possible, should include treatment of a simultaneously occurring predisposing factor as well as the infection. The treatment of structural risk factors follows general urological principles used in patients without SCL.

The treatment of urinary tract stones depends on the location, size, hardness and radiodensity of the stone, as well as the physical condition of the patient. The majority of bladder stones should be removed by means of transurethral lithotripsy, leav-

ing only a few patients requiring open surgery. Ureteral and kidney stones may be treated by a number of modalities including ureteroscopic stone extraction or lithotripsy, percutaneous nephrolithotripsy or extracorporeal shock wave lithotripsy. Infrequently, ureteral and kidney stones may be treated by dissolving chemical agents,[37] or open surgical stone removal may necessary.[38]

Mechanical outlet obstruction may be caused by bladder neck stricture, prostatic enlargement or urethral stricture, which should be treated endoscopically. Outflow obstruction may occasionally result in bladder diverticula formation, and even though it requires no treatment in the majority of patients, large diverticulars interfering with voiding should be excised.

The functional risk factors are consequences of disruption of the neurogenic coordination of voiding and/or storage function of the lower urinary tract, and include detrusor-sphincter dyssynergia, high pressure voiding, vesicoureteral reflux, and bladder areflexia.

The dynamic outlet resistance may be decreased pharmacologically by blocking the α-receptors in the bladder neck and proximal urethra.[39] Phenoxybenzamine was the α-adrenoceptor antagonist originally used for this purpose. However, a high number of adverse effects were common and the drug has almost been replaced by newer more selective α_1-adrenergic antagonists, such as alfuzosin, prazosin, doxazosin, terazosin and tamsulosin.[40] The results of trials of α-blockade in individuals with SCL have been somewhat conflicting. However, they seem to indicate that voiding pressures and residual volume may decrease following α-blockade.[41-43] Furthermore, it has been claimed that these drugs may decrease the pressure generated by the external striated sphincter, at least in individuals without SCL.[44] Consequently, Wein[40] concluded that a trial of such an agent is worthwhile, as the effect or non-effect will become obvious in a matter of days and the pharmacological adverse effects are reversible.

In men, increased outlet resistance caused by detrusor-sphincter dyssynergia has commonly been treated by sphincterotomy in the last decades.[45-49] The procedure has been reported to result in improved emptying function, with lower voiding pressures and residual urine in the majority of patients. However, recent publications have revealed a significant incidence of treatment failure and recurrence,[46-48] and the complications following the procedure are not negligible.[49] Thus, some centres find this procedure seldom indicated.[6]

Alternatively, the use of a permanent stent to bypass the sphincteric area has been proposed, and an increasing number of reports have dealt with this procedure during recent years.[50-52] In a long term study over 5 years, Chancellor et al.[50] found that the mean voiding pressure and residual urine declined significantly after treatment with an endoprosthesis, whereas bladder capacity remained unchanged. Hydronephrosis and autonomic dysreflexia improved or stabilised in most patients with a functioning stent. Stent explant was necessary in 15% of patients.

Chancellor et al.[51] also compared the efficacy of conventional sphincterotomy with endoprosthesis. In a randomised study they evaluated the changes in mean maximum detrusor pressure and residual volume, and found comparable results in the 2 groups. In addition, they found that duration of hospitalisation was significantly greater in the sphincterotomy group.

In some individuals with SCL, detrusor contractions are either absent or insufficient, and these patients may experience recurrent symptomatic UTI related to insufficient bladder emptying. If the individual patient cannot satisfactorily catheterise intermittently, they may benefit from implantation of a sacral anterior root stimulator.[53] This stimulates the anterior roots to S2-4 electrically via implanted electrodes, thereby inducing detrusor contraction and bladder emptying. The stimulator is activated through a radio signal from an external sender placed over the implanted stimulator, which is positioned subcutaneously in the abdomen.

Rarely, individuals with SCL experiencing insufficient bladder emptying, yet not able to perform catheterisation per urethra, may benefit from

supravesical urinary diversion.[40] Depending on the indications for performing a urinary diversion and the physical capabilities of the patient, in particular the capability to perform catheterisation of a reservoir, continent reservoir (e.g. Indiana pouch, Kock pouch) or incontinent conduit (e.g. ileal conduit) procedures should be carefully selected.[54] No matter which type of diversion is chosen, these procedures imply ureteral implantation into a bowel segment, which is excluded from the intestinal continuity. Depending on the type of diversion to be performed, the bowel may serve as a simple conduit ending in a wet ostomy, or the bowel segment is used to construct a reservoir, which is connected to a dry ostomy via a continent valve mechanism.

Furthermore, a number of predisposing factors including hydroureter/-nephrosis, residual urine, bladder distension and bladder diverticula, are mainly functional in nature, yet may also be caused or worsened by structural changes. The common denominator in relation to UTI in persons with SCL is incomplete bladder emptying, that is, residual urine. This is one of the well-known predisposing causes for UTI in individuals with neurogenic bladder,[7] as low residuals are important in preventing bacterial multiplication and may also reduce the pressure within the bladder. For individuals not using a catheter for bladder emptying it is important to secure the nearly complete emptying of the bladder with each emptying procedure.

Therefore, if reflex voiding or bladder emptying with abdominal pressure or manual expression is performed it should be checked that the bladder is empty after voiding with repeated ultrasound investigations. At least the residual should not exceed 100ml, and if possible it should be lower. If the upper urinary tract is normal and the person has no signs or symptoms of UTI one may accept larger residual urine. On the other hand, in patients with recurrent symptomatic UTI or a dilated upper urinary tract, even a small residual urine volume may be harmful and outflow obstruction should be abolished if possible or alternative bladder emptying methods used, in order to reduce or eliminate residual urine. Usually, this will imply using intermittent catheterisation or, if this is not possible, an indwelling catheter, preferably suprapubic.

5. Prevention

5.1 General

A closed drainage system, hand hygiene, and staff and patient education are recognised as important parts of care in the prevention of UTI in patients using catheters.[9] This includes the use of the correct technique. Catheterisations should only be performed when necessary and when irrigation is needed, and the intermittent method should be used. It may also be advisable to periodically re-educate the personnel, use the smallest suitable catheter, refrain from daily meatal care and change the catheter at arbitrarily fixed intervals.[9]

The importance of hand washing has repeatedly been emphasised as a primary infection control measure in preventing cross-infection. This is also true in SCL centres, because there is often widespread contamination of the environment with Gram-negative bacilli, which are often multi-resistant.[9] Thus, general cleanliness and local hygiene is encouraged.

If the individual with SCL has a reinfection or relapsing symptomatic UTI, it is important to check for inadequately treated infection and complications, which need special attention, in particular residual urine and urinary stones. Excretory urograms, cystograms (to rule out vesicoureteral reflux), or urodynamic evaluation may be indicated after successful treatment to look for correctable anatomic or functional abnormalities. All such patients should undergo a careful assessment of the catheterisation or voiding schedule, the care of any urinary appliance, the use of recommended drugs, and of catheterisation procedure. In addition, urodynamics can help determine whether changes in bladder function have occurred, which may necessitate a modification in the system of drainage.[7]

5.2 Antiseptic Agents

Topical administration of antiseptic agents, for example, chlorhexidine to the perineal area or urethra prior to catheterisation have not proven effective in preventing bacteriuria.[7,9,16] Similarly, the use of antiseptic solution in drainage bags and as bladder washouts or installations have been disappointing.[7,9,16] In addition, bladder washouts and installations are not without problems. There is an increased risk of infection from frequently breaking the closed drainage system, the problem of bacterial resistance, chemical cystitis may occur, and mechanical damage to the bladder may facilitate bacterial invasion into deeper mucosal layers. For those patients with long term indwelling catheters it is likely that the physical effects of a washout may be more important than the action of any local antiseptic especially in controlling the formation of debris.[9]

Methenamine salts (mandelate and hippurate) is hydrolysed in sufficiently acidic urine to formaldehyde and ammonia. The common urinary bacteria are susceptible to formaldehyde, and resistance does not develop. Furthermore, there is no effect on the bowel flora and it is relatively inexpensive. In 2 studies on individuals with neurogenic bladder using intermittent catheterisation, methenamine was administered orally together with a urine acidifying agent. It appeared that fewer patients had infections in the active group[55] and there was a reduction in the frequency of pyelonephritis.[56] On the other hand, a recent study in individuals with SCL showed that administration of ascorbic acid 500mg every 6 hours did not decrease the pH of the urine and there was no clinical benefit from the use.[57]

The use of alkalinising agents is likely to predispose to the formation of debris or urinary stones, and is contraindicated in patients with poor renal function.[7]

The effectiveness of acidifying and alkalinizing agents is influenced by diet and this should be kept in mind when managing the individual person.

No reliable evidence exists of the effectiveness of cranberry juice and other cranberry products. There have been a large number of dropouts/withdrawals from the trials, indicating that cranberry juice may not be acceptable over longer periods of time. Other cranberry products such as cranberry capsules may be more acceptable. On the basis of the available evidence, cranberry juice cannot be recommended for the prevention of UTI in individuals with SCL.[58]

5.3 Antibacterials

Before any urinary operative procedure, specific antibacterial therapy should be administered to minimise the risk of urosepsis. In a small, randomised, double-blind study, a 3-day oral course of ciprofloxacin beginning 2 days before urodynamic procedures seemed to decrease the incidence of UTI.[59]

For individuals with SCL and indwelling catheters there seems to be a general agreement not to use antibacterials for the prevention of UTI. This not least because of the high risk of causing bacterial resistance.[9]

The use of prophylactic antibacterials for individuals with SCL using intermittent catheterisation or other methods of bladder emptying, on the other hand, is controversial.[9]

Several studies have not found success in preventing UTI in individuals with SCL, and the risk of developing resistant isolates have been stressed.[9,11,60-62] However, similarly, many studies have provided support to the view that the prophylactic use of antibacterials may be of benefit to this population in selected situations.[9,17,63-67]

In our opinion, prophylactic antibacterials should only be used in patients with recurrent UTI where no underlying cause can be found and managed, and in particular if the upper urinary tract is dilated. We usually choose to treat for 3 months, but may treat for longer periods in patients with recurrence of UTI shortly after termination of the preventive treatment.

5.4 Indwelling Catheters

In individuals with indwelling catheters it is important to be aware that catheter-associated infec-

tions are frequently caused by biofilm-forming bacteria, which are impossible to eradicate with antibacterials.[68] Therefore, to prevent recurring UTI in patients with a permanent catheter it can sometimes be advisable to change the catheter more frequently than the usually recommended 3 months. This means changing the indwelling catheter every 1 to 2 weeks may prevent these infections because the biofilm usually will take 1 to 2 weeks to develop.

A recent meta-analysis revealed that silver alloy catheters were effective in preventing UTI, measured by bacteriuria evaluated by urine culture. The silver alloy catheters were also significantly more effective than silver oxide catheters.[69]

5.5 Bacterial Interference

The possibility of bacterial interference for prevention of urinary tract infection has been investigated in the past few years.[9,13,70,71] The idea is to let the group of bacteria, which do not cause symptoms of UTI, colonise the urinary bladder. With this benign colonisation there may be some protection against symptomatic infection with more pathogenic bacteria provided. Hull et al.[13] found that intravesical inoculation with *E. coli* 83972, successfully prevented symptomatic UTI in 13 of 21 men and women with SCL. The mean duration of colonisation was 12.3 months (range 2 to 40). In addition, colonised participants reported subjective improvement in quality of life with respect to UTI while colonised. The authors concluded that *E. coli* 83972 could be used safely to establish long term asymptomatic bladder colonisation in individuals with SCL. Similarly, in women with out SCL, 3 *Lactobacillus* spp. have been shown to colonise the vagina and act as a barrier to the ascension of uropathogens into the bladder.[72] The preliminary results are encouraging and studies are underway for further evaluation of its safety and preventive efficacy in humans.[70]

5.6 Vaccination

A recent study by Langermann et al.[73] in monkeys showed that inoculation with 100mg of *E. coli* FimCH adhesion-chaperone complex protected 3 of the 4 vaccinated monkeys from bacteriuria and pyuria after they were challenged with 1 ml of 108 *E. coli* cystitis isolate NU14, while all 4 control monkeys became infected. The findings suggest that a vaccine based on the FimH adhesion of *E. coli* type 1 pili may have utility in preventing cystitis in humans.

6. Conclusion

Much progress has been achieved in the management of UTI in individuals with SCL. The use of intermittent catheterisation, and new antibacterials for the therapy and prevention of UTI has decreased the mortality and morbidity resulting from UTI in the SCL population. Important future improvements in care will include methods to prevent periurethral colonisation with UTI pathogens as well as antibiotics with none or little impact on the intestinal flora. Likewise, catheters that prevent bacteria biofilm formation are desirable. In addition, we can hope that the development of bacterial interference and vaccination will result in a decreased frequency of UTI and improved quality of life for individuals with SCL.

References

1. DeVivo MJ, Kartus PL, Stover SL, et al. Cause of death for patients with spinal cord injuries. Arch Intern Med 1989; 149: 1761-6
2. Ducker TB. Treatment of spinal cord injury. N Engl J Med 1990; 322: 1459-61
3. Hartkopp A, Brønnum-Hansen H, Seidenschnur A-M, et al. Survival and cause of death after traumatic spinal cord injury. A long-term epidemiological survey from Denmark [Corrigendum Spinal Cord 1997; 35: 862-4]. Spinal Cord 1997; 35: 76-85
4. Hackler RH. A 25-year prospective mortality study in the spinal cord injury patient: comparison with long-term living paraplegics. J Urol 1977; 117: 486-8
5. Selzman AA, Hampel N. Urologic complications of spinal cord injury. Urol Clin North Am 1993; 20: 453-64
6. Biering-Sørensen F, Nielans H-M, Dørflinger T, et al. Urological situation five years after spinal cord injury. Scand J Urol Nephrol 1999; 33: 157-61
7. Cardenas DD, Hooton TM. Urinary tract infection in persons with spinal cord injury. Arch Phys Med Rehabil 1995; 76: 272-80
8. Elden H, Hizmetli S, Nacitarhan V, et al. Relapsing significant bacteriuria: effect on urinary tract infection in patients with spinal cord injury. Arch Phys Med Rehabil 1997; 78: 468-70

9. Galloway A. Prevention of urinary tract infection in patients with spinal cord injury – a microbiological review. Spinal Cord 1997; 35: 198-204
10. Waites KB, Canupp KC, DeVivo MJ. Epidemiology and risk factors for urinary tract infection following spinal cord injury. Arch Phys Med Rehabil 1993; 74: 691-5
11. Maynard FM, Diokno AC. Urinary infection and complications during clean intermittent catheterisation following spinal cord injury. J Urol 1984; 132: 943-6
12. Whiteneck GG, Charlifue SW, Frankel HL, et al. Mortality, morbidity, and psychosocial outcomes of persons spinal cord injured more than 20 years ago. Paraplegia 1992; 30: 617-30
13. Hull R, Rudy D, Donovan W, et al. Urinary tract infection prophylaxis using escherichia coli 83972 in spinal cord injured patients. J Urol 2000; 163: 872-7
14. Faarvang KL, Müller P, Lomberg B, et al. Screening for bacteriuria in patients with spinal cord lesion: dipstick test, microscopic examination and urine culture. Spinal Cord 2000; 39: 106-8
15. Gribble MJ, McCallum NM, Schechter MT. Evaluation of diagnostic criteria for bacteriuria in acutely spinal cord injured patients undergoing intermittent catheterization. Diagn Microbiol Infect Dis 1988; 9: 197-206
16. Stover SL, Lloyd K, Waites KB, et al. Urinary tract infection in spinal cord injury. Arch Phys Med Rehabil 1989; 70: 47-54
17. Biering-Sørensen F, Høiby N, Nordenbo A, et al. Ciprofloxacin as prophylaxis for urinary tract infection: prospective, randomised, cross-over, placebo controlled study in patients with spinal cord lesion [Erratum appears in J Urol 1994; 151: 1032]. J Urol 1994; 151: 105-8
18. Sotolongo JR, Koleilat N. Significance of asymptomatic bacteriuria in spinal cord injury patients on condom catheter. J Urol 1990; 143: 979-80
19. Moser C, Kriegbaum NJ, Larsen SO, et al. Antibodies to urinary tract pathogens in patients with spinal cord lesions. Spinal Cord 1998; 36: 613-6
20. Waites KB, Chen Y, DeVivo MJ, et al. Antimicrobial resistance in gram-negative bacteria isolated from the urinary tract in community-residing persons with spinal cord injury. Arch Phys Med Rehabil 2000; 81: 764-9
21. Larsen LD, Chamberlin DA, Khonsari F, et al. Retrospective analysis of urologic complications in male patients with spinal cord injury managed with and without indwelling urinary catheters. Urology 1997; 50: 418-22
22. Cardenas DD, Mayo ME. Bacteriuria with fever after spinal cord injury. Arch Phys Med Rehabil 1987; 68: 291-3
23. Prieto-Fingerhut T, Banovac K, Lynne CM. A study comparing sterile and nonsterile urethral catheterization in patients with spinal cord injury. Rehabilitation Nursing 1997; 22: 299-302
24. Bennett CJ, Young MN, Razi SS, et al. The effect of urethral introducer tip catheters on the incidence of urinary tract infection outcomes in spinal cord injured patients. J Urol 1997; 158: 519-21
25. Vaidyanathan S, Soni BM, Dundas S, et al. Urethral cytology in spinal cord injury patients performing intermittent catheterization. Paraplegia 1994; 32: 493-500
26. Biering-Sørensen F, Nielsen K, Hansen HV. Urethral epithelial cells on the surface on hydrophilic catheters after intermittent catheterization: cross-over study with two catheters. Spinal Cord 1999; 37: 299-300
27. Waller L, Jonsson O, Norlén L, et al. Clean intermittent catheterization in spinal cord injury patients: long-term followup of a hydrophilic low friction technique. J Urol 1995; 153: 345-8
28. Gallien P, Nicolas B, Robineau S, et al. Influence of urinary management on urologic complications in a cohort of spinal cord injury patients. Arch Phys Med Rehabil 1998; 79: 1206-9
29. Semeniuk H, Church D. Evaluation of the leukocyte esterase and nitrite urine dipstick screening tests for detection of bacteriuria in women with suspected uncomplicated urinary tract infections. J Clin Microbiol 1999; 37: 3051-2
30. Schlager TA, Dilks S, Trudell J, et al. Bacteriuria in children with neurogenic bladder treated with intermittent catheterization: natural history. J Pediatr 1995; 126: 490-6
31. Waites KB, Canupp KC, DeVivo MJ. Eradication of urinary tract infection following spinal cord injury. Paraplegia 1993; 31: 645-52
32. Høiby N. Ecological antibiotic policy. J Antimicrob Chemother 2000; 46 Suppl. S1: 59-62
33. Warren JW, Abrutyn E, Hebel JR, et al. Guidelines for antimicrobial treatment of uncomplicated acute bacterial cystitis and acute pyelonephritis in women. Clin Infect Dis 1999; 29: 745-58
34. Beaucaire G. Does once-daily dosing prevent nephrotoxicity in all aminoglycosides equally? Clin Microbiol Infect 2000; 6: 357-62
35. Jepson RG, Mihaljevic L, Craig J. Cranberries for treating urinary tract infections. Cochrane Database of Systematic Reviews. Issue 2, 2000
36. Harkins KJ. What's the use of cranberry juice? Age Ageing 2000; 29: 9-12
37. Bernardo NO, Smith AD: Chemolysis of urinary calculi. Urol Clin N Am 2000; 27: 355-66
38. Paik ML, Resnick MI. Is there a role for open stone surgery? Urol Clin N Am 2000; 27: 323-32
39. Caine M. The prsent role of alpha-adrenergic blockers in the treatment of benign prostatic hyperplasia. J Urol 1986; 136: 1-4
40. Wein AJ. Neuromuscular dysfunction of lower urinary tract. In: Walsh PC, Retik AB, Darracott Vaughan Jr E, et al., editors. Campbell's urology. Philadelphia: Saunders, 1998: 953-1006
41. Al-Ali AM, Salman G, Rasheed A, et al. Phenoxybenzamin in the management of neuropathic bladder following spinal cord injury. Aust N Z J Surg 1999; 69: 660-3
42. Perkash I. Efficacy and safety of terazosin to improve voiding in spinal cord injury patients. J Spinal Cord Med 1995; 18: 236-9
43. Swierzewski SJ, Gormley EA, Belville WD, et al. The effect of terazosin on bladder function in the spinal cord injured patient. J Urol 1994; 151: 951-4
44. Thind P, Lose G, Colstrup H, et al. The effect of alpha adrenoceptor stimulation and blockade on the static urethral sphincter function in healthy women. Scand J Urol Nephrol 1992; 26: 219-25
45. Catz A, Luttwak ZP, Agranov E, et al. The role of external sphincterotomy for patients with a spinal cord lesion. Spinal Cord 1997; 35: 48-51
46. Kim YH, Kattan MW, Boone TB. Bladder leak point pressure: the measure for sphincterotomy success in spinal cord injured patients with external detrusor-sphincter dyssynergia. J Urol 1998; 159: 493-5

47. Juma S, Mostafavi M, Joseph A. Sphincterotomy: long term complications and warning signs. Neurourol Urodyn 1995; 14: 33-41
48. Yang CC, Mayo ME. External urethral sphincterotomy: long term follow-up. Neurourol Urodyn 1995; 14: 25-31
49. Wein AJ. The role of external sphincterotomy for patients with spinal cord lesion. J Urol 1998; 160: 961
50. Chancellor MB, Gajewski J, Ackman CF, et al. Long-term followup of the North American multicenter UroLume trial for the treatment of external detrusor-sphincter dyssynergia. J Urol 1999; 161: 1545-50
51. Chancellor MB, Bennett C, Simineau AR, et al. Sphincteric stent versus external sphincterotomy in spinal cord injured men: prospective randomized multicenter trial. J Urol 1999b; 161: 1893-8
52. Chartier-Kastler EJ, Thomas L, Bussel B, et al. A urethral stent for the treatment of detrusor-sphincter dyssynergia. Br J Urol 2000; 86: 52-7
53. Brindley GS. The first 500 patients with sacral anterior root stimulator implants: general description. Paraplegia 1994; 32: 795-805
54. McDougal WS. Use of intestinal segments and urinary diversion. In: Walsh PC, Retik AB, Darracott Vaughan Jr E, et al., editors. Campbell's urology. Philadelphia: Saunders, 1998: 3121-61
55. Kevorkian CG, Merritt JL, Ilstrup DM. Methenamine mandelate with acidification: an effective urinary antiseptic in patients with neurogennic bladder. Mayo Clinic Proc 1984; 59: 523-9
56. Krebs M, Halvorsen RB, Fishman IJ, et al. Prevention of urinary tract infection during intermittent catheterization. J Urol 1985; 131: 82-5
57. Castelló T, Girona L, Gómez MR, et al. The possible value of ascorbic acid as a prophylactic agent for urinary tract infection. Spinal Cord 1996; 34: 592-3
58. Jepson RG, Mihaljevic L, Craig J. Cranberries for preventing urinary tract infections. Cochrane Database of Systematic Reviews. Issue 2, 2000
59. Darouiche RO, Smith MS, Markowski J. Antibiotic prophylaxis for urodynamic testing in patients with spinal cord injury: a preliminary study. J Hosp Infect 1994; 28: 57-61
60. Kuhlemeier KV, Stover SL, Lloyd LK. Prophylactic antibacterial therapy for preventing urinary tract infections in spinal cord injury patients. J Urol 1985; 134: 514-6
61. Mohler JL, Cowen DL, Flanigan RC. Suppresion and treatment of urinary tract infection in patients with an intermittently catheterized neurogenic bladder. J Urol 1987; 138: 336-40
62. Sandock DS, Gothe BG, Bodner DR. Trimethoprim-sulfamethoxazole prophylaxis against urinary tract infection in the chronic spinal cord injury patient. Paraplegia 1995; 33: 156-60
63. Anderson RU. Prophylaxis of bacteriuria during intermittent catheterization of the acute neurogenic bladder. J Urol 1980; 123: 364-6
64. Duffy L, Smith AD. Nitrofurantoin macrocrystals prevent bacteriuria in intermittent self-catheterization. Urology 1982; 20: 47-9
65. Gribble MJ, Puterman M. Prophylaxis of urinary tract infection in persons with recent spinal cord injury: a prospective, randomized, double-blind, placebo-controlled study of trimethoprim-sulfamethoxazole. Am J Med 1993; 95: 141-52
66. Montgomerie JZ, Gilmore DS, Canawati HN, et al. Ceftazidine in treatment of urinary tract infection in patients with spinal cord injury: comparison with moxalactam. Urology 1990; 35: 93-5
67. Waites KB, Canupp KC, DeVivo MJ. Efficacy and tolerance of norfloxacin in treatment of complicated urinary tract infection in outpatients with neurogenic bladder secondary to spinal cord injury. Urology 1991; 38: 589-96
68. McLean JC, Nickel JC, Olson ME. Biofilm associated urinary tract infections. In: Lappin-Scott HM, Costerton JW. Microbial biofilms. Chapter 16. Cambridge University Press 1995: 261-73
69. Saint S, Elmore JG, Sullivan SD, et al. The efficacy of silver alloy-coated urinary catheters in preventing urinary infection: a meta-analysis. Am J Med 1998; 105: 236-41
70. Darouiche RO, Hull RA. Bacterial interference for prevention of urinary tract infection: an overview. J Spinal Cord Med 2000; 23: 136-40
71. Wullt B, Connell H, Röllano P, et al. Urodynamic factors influence the duration of Escherichia Coli bacteriuria in deliberately colonized cases. J Urol 1998; 159: 2057-62
72. Reid G. Probiotic therapy and functional foods for prevention of urinary tract infections: state of the art and science. Curr Infect Dis Rep 2000; 2: 518-22
73. Langermann S, Mollby R, Burlein JE, et al. Vaccination eith FimH adhesion protects cynomolus monkeys from colonization and infection by uropathogenic Escherichia coli. J Infect Dis 2000; 181: 774-8

Correspondence and offprints: Dr *Fin Biering-Sørensen*, Clinic for Para- and Tetraplegia, The Neuroscience Center, Rigshospitalet TH2091, Blegdamsvej 9, DK-2100 Copenhagen, Denmark.
E-mail: finbs@rh.dk