Current Bladder Dysfunction Reports (2020) 15:332–339
https://doi.org/10.1007/s11884-020-00611-2

INFLAMMATORY/INFECTIOUS BLADDER DISORDERS (MS MOURAD, SECTION EDITOR)

Management of Chronic Bacteriuria in Neurogenic Bladders

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Accepted: 10 September 2020 / Published online: 3 November 2020

Abstract

Purpose of the Review Lower urinary tract dysfunction is a major cause of morbidity in patients with neurogenic conditions. One of the significant issues in this group is urinary tract infections. In this review, the causes of bacteriuria along with the symptoms, diagnosis, prevention and treatment options will be discussed.

Recent Findings As in other areas of neuro-urology there is a lack of randomized controlled trials in this field. Most of the evidence is from retrospective cohort studies. Nonetheless, there are a number of guidelines and consensus statements from international organizations to standardize the treatment of recurrent urinary infections in this complex group of patients.

Summary The management of recurrent urinary infections symptoms in neurogenic patients is challenging as these patients do not always exhibit classical signs and symptoms. The evidence base is not so strong for treatment pathways. We need structured randomized control studies to better understand and manage this complex condition in this cohort of patients.

Keywords Neurogenic bladder · Urinary tract infections · Chronic bacteriuria · Multifactorial · Prophylaxis · Regular follow-up

Introduction

Lower urinary tract dysfunction (LUTD) is almost invariably associated with spinal cord injury (SCI) and other neurological conditions like multiple sclerosis (MS), Parkinson's disease (PD) and spina bifida. LUTD in these patients is referred as neurogenic bladder dysfunction (NBD). NBD is known to cause incontinence, autonomic dysreflexia (AD), urinary tract infection (UTI), renal failure and can occasionally result in death [1]. Over past few decades, the incidence of most of these complications has reduced with better understanding of disease process, technological advances and provision of better health care.

This article is part of the Topical Collection on *Inflammatory/Infectious Bladder Disorders*

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UTI continue to be most common morbidity in patients with NBD with approximately one in five individuals suffering from recurrent urinary tract infections (rUTI). This results in substantial morbidity and mortality and has significant impact of quality of life [2]. UTIs are the most common cause of septicaemia in SCI patients with increased risk of mortality [3]. UTIs are often recurrent in patients with NBD with the bacterial strains that are difficult to treat [4]. There are various factors related to risk of UTI in NB patients. These include storage and voiding dysfunction or method applied for bladder management [1, 5]. A significant proportion of these patients have either indwelling catheter (IDC) or are dependent on clean intermittent self-catheterization (CISC) which makes bacterial colonization and/or biofilm formation a common phenomenon. The other less understood mechanisms include cellular, immunological and inflammatory factors that can predispose these patients to UTI [6].

Diagnostic Evaluation

Urine Culture and Urinalysis

Urine culture and urinalysis are the optimum test for diagnosis of UTI in NBD patients. Based on most updated guidance, a urine dipstick is useful to exclude than to diagnose UTI [7–8, 9••].

The overall consensus is to treat only symptomatic UTI, and bacteriuria should not be considered as an indication for antibiotic prescription as it causes resistant strains [10]. According to the most recent guidelines, the definition of UTI is not much different for NBD and defined as the combination of bacteriuria, leukocyturia and clinical symptoms [11••]. Diagnosis of UTI following this definition can be challenging in patients with NBD as they are not always able to demonstrate symptoms, likely due to LUTD.

The International Spinal Cord Injury (SCI) Society has developed a data set to define and document UTI [12]. Based on this, all these patients must have urine culture and leukocyte esterase activity or urine microscopy should be used for the evaluation of leukocyturia. There is no evidence-based cut off value for quantification. The overall consensus is to consider $> 10^2$/ml colony forming units (cfu) as significant bacteriuria if the urine specimen is obtained by catheter and $> 10^4$ cfu/ml if collected by normal void. It is very important to consider any detectable concentration from suprapubic aspirate as significant [10]. According to International Clinical Practice Guidelines from the Infectious Diseases Society of America (IDSA), urine screening for asymptomatic bacteriuria (AB) is not indicated for patients; however, exceptions include research purpose or pregnant women (Grade of recommendation A, level of evidence III) [13]. IDSA has defined catheter-associated UTI (CA-UTI) as the presence of signs and symptoms compatible with UTI with no other identified source and presence of 10^3 cfu/ml of one or more bacterial species in a single catheter specimen or in a midstream specimen of voided urine from a patient who had catheter (urethral, suprapubic or condom) removal in last 48 h [13]. IDSA opposes the idea of using pyuria to differentiate between the diagnosis of CA-UTI and catheter-associated asymptomatic bacteriuria (CA-AB). In fact, IDSA follows a strict criterion of the microbial growth of $> 10^5$ cfu/ml in the absence of symptoms compatible with UTI. This not only improves specificity in diagnosis but also helps to avoid unnecessary antibiotic prescription.

In 1993, National Institute on Disability and Rehabilitation Research (NIDDR) published a consensus statement on prevention and management of UTI among patients with SCI. According to their definition, bacterial colony count of $\geq 10^2$ in CISC specimen, $\geq 10^4$ in condom catheter specimen and any detectable concentration in indwelling catheter should be considered as UTI [14].

Urodynamics and Other Diagnostics

Urodynamics (UDS) plays a very important role in the management of patients with NBD presenting with rUTIs with or without the presence of reflux [15]. However, videourodynamics (VUDS) must be performed to exclude reflux that can result in pyelonephritis, reflux nephropathy, scarring and renal failure. NBD patients often need periodic VUDS to guide their management plan; however, the optimal interval has not been assessed [16]. At a minimum, baseline UDS/VUDS must be performed following the diagnosis of neurological condition to monitor treatment response and progression [1].

Ultrasound of the urinary tract has been recommended as a safe, non-invasive and cost-effective screening method as it has good sensitivity to detect urinary tract stones (LE 1–3, GR A-B) [16, 17].

Recent publications do not recommend routine cystoscopy for post SCI NBD patients (LE 1–4, GR D) [17–18, 19••], and the subgroup with IDC does not need biopsy of bladder or catheter tract [18].

Follow-up plan must be modified in patients who manifest risk factors, report change in bladder symptoms or present with pre-existing complication of NBD [17].

Signs and Symptoms

Patients with NBD exhibit variable sign and symptoms of UTI in comparison to general population. It depends on underlying neurological condition, level and completeness of injury. International SCI society data set has included fever, urinary incontinence/peri-catheter leak, spasticity, malaise, lethargy, sense of unease, cloudy urine, malodorous urine, back and bladder pain, dysuria and AD [12]. Fever and AD have highest specificity (99% and 99% respectively) but very low sensitivity (0 and 7% respectively). However, cloudy and malodorous urine has highest accuracy score (83% and 79% respectively) with much better sensitivity (66% and 48%). This study population were comprised of SCI patients using IDC and CISC. The study reported that all sign and symptoms, except spasticity, were reliable predictor of UTI when compared with subjective response. Interestingly, the patients were highly likely to predict when they do not have infection (negative predictive value 82%) in contrast to when they have (positive predictive value 32%) [20]. IDSA has recommended that unique neurogenic symptoms like increased spasticity, sense of unease or AD may be suggestive of a CA-UTI [13]. The knowledge and understanding of these signs and symptoms is fundamental in early recognition of UTI to prevent complications.

Risk Factors for UTI in NBD

There are various risk factors that can contribute in development of UTI and has been previously mentioned in the introduction. However, the most important risk factor for UTI in NBD is use of catheters [1]. IDSA has described the contributing factors as skin inoculation with faecal bacteria, uropathogen migration from the urethral meatus to the bladder

through mucosal-catheter interface, intraluminal spread of pathogens due to violation of closed drainage system that leads to contamination and urinary stasis below the catheter bulb that serves as mode of iatrogenic transmission [13].

Following catheter insertion, the device provides enhanced microbial adhesions that lead to biofilm formation. This biofilm formation has a fundamental role in CA-UTI [21]. These are composed of exopolysaccharides with microcolonies of replicating bacteria [22]. Soon after attachment to surfaces the pathogens colonize and form a sessile communal biofilm that can develop on both biotic and abiotic surface [23]. The biofilm can start to develop in the bladder 1–3 days of catheter insertion [24]. It acts as a adhesive surface and defence barrier that prevents the detachment of embedded cells by shear flow [25]. Once matured, this biofilm is refractory to clearance by both the host immune response and antimicrobial treatment [26]. Interestingly, the bacterial pathogens embedded in biofilms exhibit 100- to 1000-fold higher antibiotic tolerance in comparison to their free-swimming counterparts [27]. Biofilms produced by certain species including Proteus, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae* and Providencia lead to hydroxyapatite, struvite and encrustations that causes catheter blockage [13].

Prevention of UTI in NBD

(1) Catheter management

(a) Closed catheter drainage system

Closed catheter drainage system is strongly recommended to prevent CA-UTI and CA-AB in all patients with IDC and SPC [1]. Frequent despoliation of closed drainage system has been shown to significantly increase the risk of CA-AB [28, 29]. These studies also confirmed that catheters with preconnected junctions are less likely at risk of developing CA-AB [28–30]. The urine drainage bag and tubing should always be placed below the level of the bladder as the CA-bacteriuria follows contamination of the urinary bag [31].

(b) Catheter changes

There is no clear guidance on the interval at which the IDC and SPC should be changed in NBD. It varies anywhere between every 2 and 6 weeks [1]. In authors' practice, the catheter exchange is offered at 6 weeks' interval, but there is a subgroup of NBD patient, who need catheter exchange as early as 2 weeks. This is mainly due to encrustation leading to frequent catheter blockages and CA-UTI. This could possibly be explained by the fact that frequent catheter exchange keeps the microbial load controlled by completely removing the intra and extraluminal biofilm [1]. This has been supported by the studies that compared the urine cultures of patients with long-term catheters and those immediately after catheter exchange exhibit reduction in bacterial species both quantitatively and qualitatively [13, 32, 33].

(c) Bladder management

The selection of the most appropriate method of bladder management for NBD patients depends on various factors including: lower urinary tract status, duration of catheterization, mobility, sensation and dexterity, access to health care professional and patient preference [1]. A study comparing different methods of bladder management showed the incidence of CA-UTI per 100 person-days of 0.06 in the normal voiding group, 0.34 in the SPC group, 0.36 in the condom catheter group, 0.41 in CISC group and highest in IDC group (2.72). These figures should be carefully interpreted as the sample size was particularly small for SPC and Condom catheter group. Moreover, the SPC group was comprised of only females [2]. In comparison to other methods, CISC is associated with fewer complications and UTIs [13, 34]. One study compared the incidence of UTI in quadriplegic patients managed with SPC and CISC. The incidence of UTI was comparable; however, the risk of vesical stone in the SPC group was significantly higher [35].

Condom catheter can be a useful alternative in carefully selected patients with acceptable bladder storage pressures and bladder emptying. This is determined by urodynamics study in NBD patients. It is non-invasive but still associated with bacteriuria although less than IDC and SPC. The studies have shown Pseudomonas and Klebsiella to be most common species in condom catheter associated UTI in NBD patients [36, 37]. Patients should also be warned about skin breakage and scarring if they choose to use condom catheter.

IDSA supports CISC as optimal bladder management option in NBD patients to minimize CA-UTI and CA-AB [13].

(d) Device washout

The body of evidence does not support catheter irrigations and drainage bag washouts with saline, antimicrobial or antiseptic agents for prevention of CA-UTI and CA-AB [38–41].

(e) Impregnated catheters

These catheters have shown to have some short-term effect on bacteriuria and infection [42, 43]. Concerns were raised about silver toxicity when using silver nitrate catheter for UTI prevention when used in long term. Similarly, antimicrobial coated catheters came under question as it may cause antimicrobial resistance [30, 43].

(2) Medical management

(a) Antibiotic prophylaxis

Recurrent UTI and chronic bacteriuria are common in patients with NBD [4]. In most instances, chronic bacteriuria can be inevitable, and hence, it is important to inform the patients and physicians that treatment of AB is not required in these patients [11••].

The IDSA does not recommend use of antibiotic for prevention of CA-UTI and CA-AB in patients with NB. A meta-analysis published in 2002 reported reduction in incidence of AB in acute (< 90 days) patients when compared with non-acute patients, and one patient would need 3.7 weeks of antibiotic prophylaxis to prevent one episode of UTI. The antibiotic prophylaxis resulted in two fold increase in antibiotic resistance [44]. A Cochrane database review on long-term catheter drainage was unable to propose practical guidance on UTI prophylaxis, primarily due to poor quality literature on the topic and multiple biases in the included studies [45].

Recent systematic review and practice policy statement on UTI prophylaxis in spina bifida patient also recommend against antibiotic prophylaxis [4].

The concept of weekly oral cyclic antibiotic (WOCA) was introduced in 2006 by Salomon and colleagues. The WOCA regimen consisted of the alternate administration of two antibiotics once per week, over a period of at least 2 years. There was significant reduction in the incidence of UTI and antimicrobial resistance. They reported decrease in the UTI incidence from 9.4 UTIs per patient-year before intervention to 1.8 UTIs per patient-year. They did not report any adverse effect or emergence of multidrug resistance (MDR) organism [46]. A more recent study on WOCA regimen reported reduction in episodes of febrile and non-febrile UTIs as well as the MDR colonization [47].

A single dose of preprocedural antibiotic prophylaxis is safe and effective for UTI prophylaxis [48], but most recent studies do not recommend regular preprocedural prophylaxis for UDS [49]. However, high-risk group should be given special consideration, as shown in a recent study [50•]. This includes patients with vesico-renal reflux, previous symptomatic UTI after UDS; immunosuppression should be given special consideration [11••].

(b) Non antibiotic prophylaxis

(i). Probiotics

Lactobacillus has been found to be beneficial in UTI prophylaxis in post-menopausal women; however, in a recent randomized control trial, probiotics were not found to be effective in prevention of UTI in NB [51•].

(ii). Cranberry prophylaxis

The literature including the most recent guidelines from European Association of Urology do not support use of cranberry for UTI prophylaxis [52, 53••, 54]. Cranberry proanthocyanidins have bacterial anti-adhesion activity on uropathogenic P-fimbriated *Escherichia coli*, and its efficacy may vary with different bacteria; however, this has not been evaluated as yet [55].

It is worth mentioning that a single study showed benefit of using cranberry tablets in prevention of UTI and the episodes of UTI were reduced from 1.0 to 0.3 per year. This study was criticized due to small sample size, short study duration and inclusion bias of 74% patients using condom catheter [56].

(iii). D-mannose

It is a sugar, monomer of the aldohexose series of carbohydrates. It blocks bacterial adhesion on uroepithelial cells and antagonize invasion and biofilm formation [57]. In a recent study the use of D-mannose was found to safe and effective in NB patients [58•].

(iv). Methenamine

The antimicrobial activity of methenamine salt depends on the concentration of formaldehyde in urine that is produced due to hydrolysis of methenamine salt. This largely correlates with concentration of urinary methenamine, pH and dwell time [1]. This is found to be beneficial in UTI prevention in a subgroup of post renal transplant patients [59•] but did not demonstrate the benefit in patients with NBD or renal tract abnormalities [60]. Currently, the evidence does not support use of methenamine in NBD patients [9••].

(v). Urine acidification

The evidence is not sufficient to recommend use of L-methionine for urine acidification [9••]. This drug may cause rise in serum homocysteine level that has been identified as risk factor for cardiovascular disease.

(vi). Immuno-stimulation

The use of vaccine for UTI prevention has been documented to be successful but the data on NBD is rather sparse. A recent RCT evaluated the safety of a new tetravalent *E. coli* bioconjugate vaccine, administered by intramuscular.

Injection has shown to be safe and elicited antibody response against all vaccine serotypes. Phase 2 study is in progress [61•]. One study on NBD patients showed significant reduction in bacteriuria but no significant effect on UTI [62].

(vii). Inoculation of non-pathogenic bacteria

Bacterial interference by inoculation of non-pathogenic bacteria, mostly E-coli, was initially found

to be effective [63]. but high-quality data is lacking to suggest use of this strategy to manage UTI in NBD [11••, 64].

(viii). Intravesical instillation

Hyaluronic acid serves as a protective barrier of the urothelium. The instillation of hyaluronic acid and chondroitin sulphate aimed to repair the damaged layer of glycosaminoglycans that can possibly cause bacterial adherence and infection [65]. A recent study on use of intravesical heparin has concluded heparin to be a safe and effective treatment option for rUTI [66•]. There is no available literature on the use of these agents in patients with NBD.

(ix). Complementary medicine

It is interesting to note that the use of complementary and alternate medicine is high in NBD patients [67••]. One study reported this to be as high as 74%. The most common indications were pain and UTIs, while the two common techniques were acupuncture and homoeopathy (31% each). These techniques were used as supplementary treatment, and patients reported very high overall satisfaction rate of 85%, but in particular for management of UTI, it was 90.5% [68].

(x). Bowel management

Bowel management is an integral component in overall care and assessment of patients with neurological conditions. Optimal bowel management including trans-anal irrigation has shown to reduce the episodes of UTI [69]. The exact mechanism is however unknown.

Treatment of UTI in NBD

(1) Acute bacterial UTI

In line with IDSA recommendation, the catheter should be exchanged if placed more than 2 weeks ago and urine specimen should be collected from the new catheter before commencing antimicrobial treatment [13]. Once the bacterial pathogen is identified and antimicrobial sensitivities are determined, it is crucial to assess the extent and severity of infection specifically in relation to patient specific risk factors [34]. The term 'UTI' encompasses many infective conditions, ranging from simple cystitis to prostatitis and pyelonephritis, that need specific management, although the role of antimicrobial therapy remains central [1].

The overall consensus is to treat UTI with narrow spectrum antibiotic, if possible, for the shortest duration that is clinically safe. By definition, UTI in NBD is considered complicated, and hence, single shot or short-term treatment (1–3 days) is not recommended. A meta-analysis suggested 5 days of antibiotic treatment in UTI during chronic SCI without fever, 7 days in acute SCI without fever and a minimum of 14 days in patients with UTI and fever (level III) [70]. The IDSA recommends a 7-day antibiotic treatment for patients with prompt clinical response, although patients with delayed response or significant infection, the duration of treatment should be extended to 10–14 days (Grade 3, LOE III) [13]. A non-inferiority RCT evaluated patients with CA-UTI and randomized them to receive either a 5-day regimen of antibiotics after catheter exchange (experimental group) or a 10-day regimen of antibiotics with catheter retention (control group). All patients were clinically cured at the end of treatment. The rates of resolution of pyuria were 89.3% in the experimental group and 88.9% in the control group; however, the patients in the experimental group had higher rates of CA-UTI recurrence than the control group [71].

Nitrofurantoin is considered as a safe option to treat mild UTI without systemic involvement (e.g. UTI) as it causes minimal alteration to bowel or vaginal flora [1, 70]. Trimethoprim should be considered for patients with more severe symptoms or having fever although it does not cover more resistant strains like Pseudomonas [1]. Fluoroquinolones is good option to cover these infections, in particular for Pseudomonas species. It has good bioavailability, decrease bacterial adherence to biofilm in addition to its coverage to more resistant strains [13, 34]. The cure rate with monotherapy versus dual therapy is similar [72]. If there is suspicion of methicillin resistant *Staphylococcus aureus* (MRSA), then treatment should be decided based on severity of infection and clinical setting. Trimethoprim is a reasonable treatment option in outpatient setting, while vancomycin is drug of choice for more serious infection in hospitalized patients [1, 73].

In summary, the duration and choice of antibiotic treatment depend on severity of infection, but all UTIs in NB patients must be considered as complicated. The local resistance pattern and antibiogram should always be reviewed. In case of non-resolution of symptoms of UTI despite adequate antimicrobial treatment, it is important to identify and treat the factors that help these UTI to sustain. These factors include urinary tract stones, elevated PVR or underlying abscess formation [34].

(2) AB in NB patients

The available literature is very clear with guidance on not to treat AB in NBD patients. There is strong evidence against the screening and treatment of CA-AB in patients with IC and CIC, respectively (Grade A, LOE I-II) [9••, 13]. IDSA however recommend screening and treatment of CA-AB in pregnant patients and those who are undergoing urological procedure where mucosal breach may be encountered [13].

Conclusion

The management of UTI in NBD is challenging as these patients do not always exhibit classical signs and symptoms of UTI. Urine culture must be obtained to confirm the diagnosis and prior to commencement of antimicrobial therapy but routine screening of CA-AB is not recommended. The symptomatic UTI must be treated according to evidence-based practice. Based on current available literature, there is no prophylaxis for rUTI available for these patients that can be recommended without limitation. It is still important to pursue prophylaxis, but it will be mainly based on trial and error method. We need well-structured randomized controlled trials to optimize the treatment strategies for long-term control of symptoms in this complex group of patients.

Compliance with Ethical Standards

Conflict of Interest Mehwash Nadeem reports no conflict of interest.

Rizwan Hamid is trial investigators for Allergan. He is a consultant for Allergan, Coloplast and Contura outside the submitted work.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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