Stratégie préventive originale des infections urinaires symptomatiques chez les patients porteurs d'une vessie neurologique : l'interférence bactérienne, état de l'art

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Prise en charge des infections urinaires sur vessie neurologique

Urinary tract infections in patients with neurogenic bladder

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Résumé

Les infections urinaires sur vessie neurologique (IUVN) sont un problème majeur de santé publique en raison de leur incidence élevée et de leur gravité éventuelle, ainsi que de la prévalence élevée de bactéries multi-résistantes.

Les facteurs de risque de survenue d'IUVN sont l'utilisation de sonde à demeure, le résidu post-mictionnel (stase urinaire), les pressions de remplissage vésicales élevées et la présence de lithiase urinaire.

Les critères diagnostiques ne sont pas établis et les signes cliniques sont souvent non spécifiques. Un prélèvement microbiologique des urines doit être réalisé dans des conditions appropriées et avant toute antibiothérapie.

La plupart des recommandations définissent un seuil de bactériurie $\geq 10^3$ UFC/ml qui, associé à des symptômes, constitue une association acceptable pour définir l'IUVN en pratique clinique quotidienne.

La prise en charge optimale des IUVN repose sur peu de preuves scientifiques. Un traitement par monothérapie d'une durée courte de moins de 10 jours semble suffisant.

Les antibiotiques doivent être choisis selon la résistance du pathogène incriminé. Une bactériurie asymptomatique ne doit pas être traitée, ce qui permet d'éviter l'émergence de résistance.

Concernant les mesures préventives, le recours au cathétérisme intermittent, les injections intra-vésicales de toxine botulique, et l'antibiocycle sont des outils efficaces. L'interférence bactérienne est une piste prometteuse mais sa réalisation reste complexe.

Abstract

Urinary tract infections (UTIs) in patients with neurogenic bladder are a major public health issue due to their high incidence and major consequences. Despite their frequency and potential severity, their physiopathology and management are poorly known. We provide a narrative literature review on epidemiology, physiopathology, diagnostic criteria, microbiology, antimicrobial management, and prevention.

UTIs among patients with neurogenic bladder are associated with high morbidity and healthcare utilization. Risk factors for UTI among this population are indwelling catheter, urinary stasis, high bladder pressure, and bladder stones.

Their diagnosis is a major challenge as clinical signs are often nonspecific and rare.

A urinary sample should be analyzed in appropriate conditions before any antibiotic prescription. According to most guidelines, a bacterial threshold $\geq 10^3$ CFU/mL associated with symptoms is acceptable to define UTI in patients with neurogenic bladder.

The management of acute symptomatic UTI is not evidence-based. A management with a single agent and a short antibiotic treatment of 10 days or less seems effective. Antibiotic selection should be based on the patient's resistance patterns.

Asymptomatic bacteriuria should not be treated to avoid the emergence of bacterial resistance.

Regarding preventive measures, use of clean intermittent catheterization, intravesical botulinum toxin injection, and prevention using antibiotic cycling are effective. Bacterial interference is promising but randomized controlled trials are needed.

Large ongoing cohorts and randomized controlled trials should soon provide more evidence-based data.

1. Introduction

Neurogenic bladder can be caused by a large panel of neurological diseases, such as spinal cord injury (SCI), the most studied model, multiple sclerosis, Parkinson's disease, cerebral palsy, and stroke [1].

The clinical spectrum of urinary tract infections (UTIs) can vary widely among patients with neurogenic bladder, from afebrile lower UTIs to urosepsis and septic shock, possibly leading to the diagnosis of abscess, lithiasis, or urinary obstruction.

They can also induce chronic renal failure and hemodialysis. They remain a major cause of morbi-mortality and healthcare consumption, despite important progress in their management [2,3]. UTIs also considerably affect the patient's quality of life [4]. Therefore, prevention is a major goal, but few strategies are available despite UTIs being the most frequent complications of neurogenic bladder.

Considerable effort should be made to better understand their physiopathology, especially their occurrence or recurrence, to optimize diagnosis, prevention, and treatment. Urinary microbiota could play an important role in this approach.

2. Epidemiology

In the United States, approximately 250,000 individuals are spinal cord injured, and around 150,000 have cerebral palsy, multiple sclerosis, or Parkinson’s disease, potentially leading to neurogenic bladder [5].

By comparison, European data indicates an incidence of spinal injury of all etiologies from 10.4 to 29.7 per million inhabitants per year [6]. In the United States, the incidence is estimated at 40 per million inhabitants (11,000 new cases per year) [6].

From a neuro-urological point of view, the management of patients presenting with SCI has greatly improved in recent years, with an increase in life expectancy. However, UTIs remain the first cause of morbidity and the second cause of mortality in this population [7].

These patients have a high rate of asymptomatic bacteriuria [8]. The prevalence of asymptomatic bacteriuria in patients using intermittent catheterization is estimated at >50% (23-89% depending on studies) [8].

The overall rate of UTIs among SCI patients is estimated at 2.5 per patient and per year [9]. In a large study on medical claims from 2002 to 2007 among neurogenic bladder patients presenting with SCI and multiple sclerosis in the United States, more than 31% of patients were diagnosed with UTI within one year of diagnosis, and 21% required hospitalization [3].

According to a retrospective cohort of Canadian veterans, UTIs accounted for 51.2% of visits at the emergency room among SCI patients [10]. In Turkey, Unsal-Delialioglu *et al.* reported that 70% of febrile SCI patients hospitalized in the rehabilitation unit presented with UTIs [11]. This event significantly prolonged their hospital stay [11].

3. Microbiology

Enterobacteriaceae are the most frequently involved bacteria in UTIs. In the general population, *Escherichia coli*, *Klebsiella*, and *Proteus* species are the most common causative agents. In patients with neurogenic bladder, they are still the predominant microorganisms involved but their frequency is lower. Also, other microorganisms, usually nosocomial bacteria such as *Pseudomonas aeruginosa* (8%-15%), *Acinetobacter* spp. (15%), *Enterococcus* spp. (6-12%), and *Staphylococcus* spp., have a higher incidence [12,13].

Polymicrobial UTIs are frequent (up to 26%) comparatively to non- neurogenic bladder UTIs [1].

Antimicrobial exposure and multidrug-resistant organisms

The emergence of resistance of Gram-negative bacteria in the general population, which are responsible for UTIs, constitutes a major public health issue [14].

Due to frequent hospitalizations and antimicrobial treatments, SCI patients have a high incidence of multidrug-resistant organisms (MDRO) carriage and infections, which seems stable over the years [15].

In a retrospective study describing the epidemiology of MDRO during bloodstream infections, MDRO were responsible for 41.8% of bloodstream infections, and this prevalence was stable over 16 years [15]. No significant associated factor for MDRO bloodstream infection could be identified in univariate and multivariate analyses.

The authors suggested that this might be due to the already high proportion of MDRO in this specific population because of high antimicrobial exposure. It is also difficult to measure an increasing prevalence as it is already substantial [15]. Two studies among SCI patients reported that 50% of strains isolated in urinalysis were MDRO [12,16]. In another recent study, 41.7% of strains were classified as extended-spectrum beta-lactamase (ESBL)-positive and 50% were resistant to fluoroquinolones [13].

4. Pathogenesis

Due to neurological impairment, modifications of structure, physiology, and local immunology in the bladder and vesicoureteral tract occur.

Some uropathogens acquire the potential to be internalized in the urothelium cells. They also adhere to the cell walls and provoke inflammation that can lead to infections [17].

4.1 Physiopathology

Bladder ischemia due to neurogenic bladder can be responsible for a mild inflammatory reaction and a lower antibiotic delivery, by decreasing the capillary blood flow to the infection site [18].

It can result from two factors: bladder overdistention and increased intravesical pressure.

Indeed, depending on the SCI degree, the degree of bladder-sphincter coordination varies, possibly leading to several bladder dysfunctions [9].

For instance, bladder overdistention and the resulting absence of physiological voiding, can induce a chronic urinary retention and prevent the mechanical action of urine flow. This usually provides a clearing effect to diminish bacterial colony counts and to avoid bacterial binding [18,19]. Voiding dysfunction can be caused by a detrusor muscle problem (areflexia) and/or sphincter dysfunction (detrusor sphincter dyssynergia) [18]. Rates of UTI reported in a study of SCI patients seemed to depend on the residual urine volumes after voiding [20].

Also, as SCI patients' bladder has little to no contractile ability, it may be subject to high intravesical pressure during filling [9]. It can lead to reduced blood flow and vesicoureteral reflux which is a risk factor for pyelonephritis and UTI in neurogenic bladder patients [9,18]. A prospective study of 128 SCI patients demonstrated that patients with vesicoureteral reflux were at higher risk of UTI recurrence [21]. Effects of high intravesical pressure were also observed in a study of 74 SCI patients, reporting high rates of complications and upper tract deterioration in those patients [22].

4.2 Immune system alterations

Due to the use of urinary catheters to void the bladder in neurogenic bladder patients, several natural mechanisms to fight UTIs are altered.

- The protective perineal microbiota is modified, especially vaginal microbiota. Commensal *Lactobacilli* are replaced by Enterobacteriaceae and other potentially virulent pathogens [18]. Those pathogens are also observed in the urine during UTI [23].
- The glycosaminoglycan (GAG) layer of the urothelium, which plays a protective role against bacterial invasion, is also disrupted due to multiple factors such as disruption of the urinary bladder uroepithelium, vesical overdistention, or chronic inflammation [18,19,24].
- The rate of immunoglobulins A, which are part of the local innate immunity preventing bacterial adherence to the urothelium [18], is lower in patients with neurogenic bladder than in non-neurogenic bladder patients [25].
- The mechanism in which urothelial umbrella cells usually present, when infected, a rapid apoptosis to prevent UTI, is also altered or even absent [18,26].
- The pro-inflammatory signaling and leukocyte components are modified in neurogenic bladder, and antimicrobial peptides are down-regulated, leading to a local over-inflammation in the bladder and an attenuated innate immune response to infections [27,28].

4.3 Bladder management

In case of neurogenic bladder from various origins, catheterization can be used to void. However, it contributes to introducing enteric bacteria mostly via catheter-mucosal interface and to the development of biofilms [29].

Microbial adherence is also enhanced and bacteria enter directly in the bladder whose surface cells are altered [29]. This enables asymptomatic bacteriuria and infection by uropathogens [30].

Once in the bladder, bacteria can produce biofilms composed with microcolonies with slow metabolism [31].

Usual natural host defense, such as Tamm-Horsfall proteins and urinary salts, are then ineffective and become part of the biofilm's exopolysaccharide matrix [32]. Moreover, biofilm can lead to urinary lithiasis [33].

Thanks to biofilms, bacteria are resistant to antimicrobial agents as they become physically difficult to reach [29]. Bacteria can also exchange resistance mechanisms between them, via quorum sensing [31].

4.4 New data on pathogenesis

4.4.1 Microbiome and UTI

Exploration of urine microbiome is now possible thanks to 16S rRNA gene (16S rDNA) sequencing and metaproteomics [34].

Fouts *et al.* performed a cross sectional study comparing the microbiome of healthy volunteers and subjects with SCI-related neurogenic bladder using those techniques [34]. They observed that urine microbiomes vary depending on bladder function (normal vs. neurogenic bladder), gender, type of bladder management, and duration of neurogenic bladder.

In healthy urine, they identified *Lactobacillus* spp. and *Corynebacterium* spp. as the most preponderant bacterial species in women and men, respectively. However, a reduced prevalence of these species was observed in patients with neurogenic bladder. We can hypothesize that the flora of healthy patients is protective against UTI. Therefore, the implantation of normal urinary flora could be a novel way to prevent UTI in neurogenic bladder patients [34].

4.4.2 Experimental models

Several experimental mice models studying UTI in neurogenic bladder patients exist, as their neurogenic bladder phenotype and their urodynamic profiles are similar to humans presenting with SCI [35,36].

Risk factors for UTI among humans are well established, but susceptibility to UTI during neurogenic bladder remains unexplained.

In an SCI rat model, a decreased immunological response and a persistent inflammation after clearance of bacteria have been reported after injection of *E. coli* compared with control rats [28]. This study also showed that SCI rats were more susceptible to UTI (a lower inoculum of *E. coli* is necessary to cause infection) and less able to control the inflammation [28].

In another study, Balsara *et al.* observed a delayed clearance of infection and excessive inflammatory responses in bladder and kidneys in SCI rats [27].

More research is required to fully understand these mechanisms of local modified response.

5. Diagnosis

Diagnosis of UTI in patients with neurogenic bladder is challenging as asymptomatic bacteriuria is common in these patients.

No gold standard is currently available, often leading to antimicrobial treatment overuse or delay for effective treatment. The definitions of UTI vary between studies and guidelines.

5.1 Microbiological criteria

Urine dipstick test in patients with neurogenic bladder and suspected UTI is not recommended as negative nitrites are associated in 55% of cases with a positive urine culture [37].

Therefore, in patients with neurogenic bladder, priority should be given to urine culture and a urinalysis with complete susceptibility testing is of paramount importance.

However, the method to collect the sample should be precise and standardized for a correct interpretation of results.

According to the 2010 Infectious Diseases Society of America (IDSA) guidelines for catheter-associated UTIs, patients with indwelling catheter should have their catheter removed prior to antibiotic therapy and then benefit from specimen collection following insertion of the new catheter [29]. Urine sample should never be collected from the drainage bag [29].

Standard definition for bacteriuria does not exist to the best of our knowledge. The IDSA stated that catheter-associated UTI could be defined in patients with indwelling catheter, suprapubic catheter, or intermittent catheterization, by the presence of symptoms and bacteriuria $\geq 10^3$ colony forming units (CFU)/mL of at least one bacterial species [29]. However, for clinical research, they recommended a 10^5 CFU/mL threshold to optimize specificity [29].

The National Institute on Disability and Rehabilitation Research (NIDRR) recommended in 1994 to use a threshold of 10^2 CFU/mL for patients with intermittent catheterization and 10^4 CFU/mL for patients with condom catheter [38].

A recent systematic review reported that bacteriuria $\geq 10^2$ CFU/mL was a reasonable threshold for patients with intermittent catheterization [39].

Thus, there is no consensus on the exact threshold of bacteriuria in UTI among patients with neurogenic bladder.

Nevertheless, irrespective of the chosen significant threshold, clinical signs should always prevail [29]. According to international consensus, bacteriuria without clinical signs should

never be treated, irrespective of the threshold [40]. However, clinical signs with bacteriuria $\geq 10^2$ CFU/mL should be considered as UTI.

5.2 Clinical criteria

Clinical symptoms of UTI among patients with neurological disease are scarce and often nonspecific. They also depend on the underlying neurological disease.

Neurogenic bladder was not specifically discussed in the IDSA guidelines for catheter-associated UTIs [29].

Accordingly, pyuria is not a positive criteria for UTI *per se* [29], but the absence of pyuria has a high negative predictive value as illustrated by a recent review [39].

Other symptoms could be related to vesicoureteral disorders: pollakiuria, urinal leak, urgency for catheterization, cloudy and malodorous urine, incontinence, back pain, and bladder pain.

Some signs could be extra-urinary, such as headache, sweat, high blood pressure, spasticity, malaise, lethargy, and autonomic dysreflexia. However, these signs are nonspecific [41].

Fever is a sign of severity that indicates urinal parenchyma impairment, which could lead to general sepsis [42].

In a prospective study by Massa *et al.*, fever and autonomic dysreflexia were the most specific signs of UTI but had low sensitivity [43].

Linsemeyer *et al.* reported that 32% of SCI patients falsely believed they had UTI while having a negative urine culture [44]. This study reinforced the need for a complete clinical evaluation before prescribing antibiotics to rule out other causes such as fecal impaction or pressure ulcer.

It also seems that neurogenic bladder patients are better at predicting when they are free from UTI than when they actually have UTI [43].

The most prevalent signs according to a prospective study comparing symptomatic versus non-symptomatic UTIs in male SCI patients are cloudy and malodorous urine, and urinary incontinence [45]. Fever and high spasticity are less sensitive signs. Moreover, one third of patients experienced only one sign, one third experienced two signs, and the last third three signs.

Also, in the same study, quantitative bacteriuria and leukocyturia could not help establishing UTI diagnosis as, when performing ROC curves, no threshold could be determined with good sensitivity and specificity [45].

An International SCI UTI Basic Data Set presenting a standardized format for collecting and reporting information on UTIs in daily practice or research is freely available at https://www.iscos.org.uk [41,46]. It has been reviewed and approved by the Executive Committee of the International SCI Standards and Data Sets, and by the International Spinal Cord Society (ISCoS) Scientific Committee and the American Spinal Injury Association (ASIA) Board. It presents all possible clinical signs, biological and morphological examination linked to UTI. This registry could help to determine clinical symptoms of UTI among patients with neurogenic bladder.

5.3 Morphological criteria

Cystoscopy is not of interest for systematic evaluation of acute UTI in patients with neurogenic bladder [47]. However, in case of recurrent infections or obstructive infection, cystoscopy should be performed to identify urinary lithiasis or local abnormalities such as diverticula.

Annual examinations with urodynamic tests are highly recommended as it has been shown that elevated bladder pressures are associated with UTI and deterioration of the upper urinary

tract [9,18,48]. Ultrasound should also be performed at least annually for detection of lithiasis and hydronephrosis [39].

Presence of positive urine culture is therefore of most importance, and its presence associated with clinical symptoms of UTI and no argument for other source of infection is sufficient to establish UTI diagnosis.

6. Treatment

Symptomatic UTI in patients with neurogenic bladder should always be treated with the most specific and narrow spectrum antibiotics available for the shortest possible duration (Figure 1) [9].

Yet, we should differentiate febrile UTI from non-febrile UTI.

6.1 Non-febrile UTIs

Non-febrile UTIs are not urgent to treat, and waiting for urinalysis and susceptibility results is preferable so that a targeted antimicrobial treatment can be used. If empirical antimicrobial treatment should be started, nitrofurantoin is the preferred molecule as there is little associated resistance and high urine elimination. It also does not seem to alter bowel or vaginal flora [49].

Treatment duration should be comprised between 5 and 7 days [29].

6.2 Febrile UTIs

During febrile UTI, prescription of antimicrobials should be prompt to prevent acute sepsis, and is mostly empirical.

Due to the high prevalence of bacterial resistance in the neurogenic bladder population, the choice of empirical antimicrobial treatment is challenging. Complete urine culture should be obtained prior to any antibiotic treatment [29]. Previous urine culture results and antimicrobial prescriptions should be considered, as well as the patient's intolerance or allergies. Moreover, ecology of the medical ward in case of hospital-acquired infection should be taken into account.

At first, parenteral beta-lactam is the preferred choice, though an oral switch should be performed as early as possible (as complete antibiotic susceptibility testing is available in 48-72 hours). A broad-spectrum molecule is required in case of previous MDRO infection; otherwise we recommend parenteral third-generation cephalosporin.

Treatment should be reevaluated depending on the urinalysis results and the patient's clinical course. Antimicrobials with good bioavailability and urinary diffusion should be preferred as the definitive antimicrobial drug.

Fluoroquinolones are a dilemma as they have effective urine diffusion and 100% bioavailability, but they also have a high potential selection of bacterial resistance. Thus, sulfamethoxazole/trimethoprim is an adequate alternative, with good bioavailability and excellent urinary diffusion.

Treatment duration should be as short as possible.

In a retrospective cohort of 96 patients with neurogenic bladder presenting with febrile UTI, the cure rates were not significantly different with various treatment durations: <10 days, between 10 and 15 days, and >15 days with a cure rate of 71.4%, 54.2%, and 57.1%, respectively (p=0.34). No significant difference in cure rate between monotherapy and dual therapy was observed (44% for monotherapy *versus* 40% for dual therapy; p=0.71) [50].

Moreover, Darouiche *et al.* performed a non-inferiority clinical trial with a small sample size of 55 patients [51]. They compared 5 days of antibiotic treatment associated with catheter exchange *versus* 10 days of antibiotic treatment without catheter exchange. They observed no significant difference in terms of clinical cure.

In another trial, Dow *et al.* compared 3 days *versus* 14 days of ciprofloxacin (250 mg bid) in 60 SCI patients [7]. Microbiological cure was significantly higher in the longer treatment duration group. Nevertheless, some patients were infected with enterococci resistant to ciprofloxacin, and the population was heterogeneous mixing febrile and non-febrile UTIs. As a short treatment duration of 3 days seems to be insufficient, we could hypothesize that a 7-day treatment is enough for febrile UTI.

Thus, a short course of 7 days for patients with prompt clinical response, and 10 to 14 days for patient with delayed response, is sufficient considering catheter-associated UTI according to the IDSA [9].

In our center, patients with febrile UTI are treated for 7 days when they present a prompt clinical response.

Some authors recommend using intravesical antibiotics [52].

In our opinion, UTIs in neurogenic bladder patients need to be managed as non-neurogenic bladder UTIs when the bladder is stabilized and when the antibiotic treatment is microbiologically effective.

6.3 Asymptomatic bacteriuria

Asymptomatic bacteriuria should not be treated, especially in neurogenic bladder patients. Thus, it should not be tested, and no urine culture should be performed.

Treatment of asymptomatic bacteriuria does not prevent from febrile UTI or recurrence of infection, and contributes to an increase in bacterial resistance and toxicity due to antibiotics [5,9,29].

Treating asymptomatic bacteriuria also seems to lead to symptomatic UTI [53].

However, there are two exceptions: pregnancy and urological procedure with potential urethral bleeding [29].

7. Prevention

7.1 Catheter-related measures

7.1.1 Closed catheter drainage

One of the most important method of UTI prevention for patients with indwelling catheters is the use of closed catheter drainage system, with the drainage bag below the bladder [29].

Indwelling urinary catheter should not be changed systematically but only in case of obstruction, hematuria, or UTI [8].

7.1.2 Method of bladder management

Intermittent catheterization is associated with fewer UTIs compared with other voiding methods [9,29].

Regarding the choice of catheter, a recent meta-analysis did not observe any benefit to hydrophilic-coated catheters compared with uncoated catheter use [54].

Impregnated catheters with antibiotics or silver-coated catheters have only shown impact on bacteriuria and infection in the very short term [48,54]. However, antibiotic resistance and silver toxicity have been reported after long-term use [48].

7.1.3 Other measures

Use of antimicrobials or antiseptics in the urinary drainage bag is not recommended due to their absence of effect [55].

Moreover, catheter irrigation with antimicrobials or normal saline is not effective and could be deleterious [56].

7.2 Medical measures

7.2.1 Antibiotic prophylaxis

The effectiveness of antibiotic prophylaxis for UTI is under debate in patients with neurogenic bladder.

Two meta-analyses did not support the use of daily antibiotic prophylaxis for the prevention of symptomatic UTI in neurogenic bladder patients and reported a rising incidence of antimicrobial resistance [57,58].

However, these studies included several methods of bladder drainage and mixed male and female patients [58–60].

Nonetheless, daily antibiotic prophylaxis is not recommended for the prevention of UTI in neurogenic bladder patients [60].

A before-after study evaluated the impact of weekly oral antibiotic cycling in SCI patients with intermittent catheterization, stabilized bladder, and more than six UTIs per year [61]. Antimicrobials were chosen according to their urinary flora. A significant reduction in UTIs and MDRO carriage was observed.

The same team studied this strategy in a more heterogeneous population: patients with multiple sclerosis, brain damage, stroke, with different types of bladder management (indwelling catheter, condom drainage as intermittent catheterization) [62]. They confirmed the effectiveness of the strategy. They also confirmed the absence of bacterial resistance emergence during a long follow-up period (mean duration: 5.25 years).

7.2.2 Cranberry prophylaxis

Current literature data does not show evidence of positive effects of cranberries in the prevention of UTIs in neurogenic bladder patients [29,63]. A prospective, double-blind, placebo-controlled, crossover study failed to observe a statistically significant favorable effect for cranberry use among 21 patients with neurogenic bladder [64].

Only a small randomized study observed a significant reduction in the incidence of UTIs with cranberry prophylaxis *versus* placebo in the neurogenic bladder population [65].

Lavigne *et al.* performed a randomized crossover human trial including five volunteers who followed six different regimens, with or without variable doses of cranberry and propolis [66]. They concluded that propolis had an additional effect with cranberry and prevented bacterial adherence.

7.2.3 Methenamine salt prophylaxis

Methenamine did not show any significant effect on UTI during neurogenic bladder in a meta-analysis [29]. Thus, it is not recommended.

7.2.4 D-mannose

D-mannose is a monosaccharide closely related to glucose. As the surface of urothelial cells is naturally covered by glycoprotein receptors, which interact directly with bacterial fimbriae [67], an exogenous intake of D-mannose could inhibit this interaction by competition [68].

A recent clinical trial evaluated daily D-mannose treatment in preventing UTI recurrence among 22 patients with multiple sclerosis [69]. The authors observed a significant reduction in UTI recurrence (by 75% in patients with urinary catheters and by 63% in those without urinary catheters), but could not draw any conclusion as it was a feasibility study.

Therefore, randomized controlled trials are required to further investigate its efficacy.

7.3 Interventions

7.3.1 Intravesical botulinum toxin A injections

Injections of intravesical botulinum toxin have demonstrated positive effects on neurogenic detrusor activity.

They improve urodynamic parameters, specificity bladder capacity, and detrusor maximum pressure [70].

They also probably have a positive effect on the prevention of UTIs [71].

7.3.2 Bacterial interference

Bacterial interference is a promising non-antibiotic way to fight UTI in patients with neurogenic bladder. It consists in instillation of a non-pathogenic strain of *E. coli* in the bladder of patients presenting with recurrent UTIs. This strain competes with natural pathogenic strains and struggles for nutriment and adherence.

Two strains of *E. coli* are currently available: each with deletion of genes coding for adherence [72,73]. Several studies have been performed with patients with neurogenic bladder [48,72–75].

In a multicenter, non-randomized, controlled trial, Darouiche *et al.* compared the effectiveness of bacterial interference *versus* placebo [74]. Adult patients with neurogenic bladder after SCI and a history of recurrent UTIs were included. Overall, 65 patients were randomized to receive either *E. coli* HU2117 or sterile saline. Patients were evaluated if they remained colonized with *E. coli* HU2117 for >4 weeks. Eventually, 27 patients were evaluable (17 in the experimental group and 10 in the placebo group). The average number of episodes of UTI/patient-year in the experimental group was lower than in the control group (0.50 *versus* 1.68 respectively, p=0.02, Wilcoxon rank-sum test) [74].

In another prospective clinical trial, adult inpatients, diagnosed with SCI for more than one year, with neurogenic bladder that required indwelling (transurethral or suprapubic) catheter drainage and who had had at least one UTI in the past, were enrolled [76]. At the end of antibiotic therapy, a urinary catheter that had been incubated in broth with *E. coli* HU2117 for 48 hours was inserted and then removed after 28 days. Ten of 12 patients were successfully colonized for 14 days or more. The rate of symptomatic UTI during asymptomatic bacteriuria was 0.15 per 100 patient-days (one case).

Other studies also showed the effectiveness of this strategy [75,77].

However, the main limit is the difficulty in obtaining asymptomatic bacteriuria with the non-pathogenic strains, which sometimes requires several inoculation sessions.

7.3.3 Vaccination

Vaccination with *E. coli* by oral route has shown effectiveness to prevent UTI in non-neurogenic bladder patients [78]. Nevertheless, its effect is temporary, and the procedure is burdensome.

No data is available for patients with neurogenic bladder despite it being another means to prevent UTI.

7.3.4 Sacral neuromodulation

Sacral neuromodulation is used for detrusor overactivity. In one study, it has shown efficacy against UTI [79].

7.4 Prevention of infection during urological procedure

Prevention of UTI and preservation of the upper urinary tract are essential in this population. Bladder-sphincter balance should be monitored regularly by urodynamic assessments. It is

recommended to perform urodynamic assessment at least twice a year during the first two years, then annually depending on the patient's urodynamic risk factors (high endovesical pressure, method of voiding) and the neurological lesion localization [6].

The role of antibiotics for preventing UTI in this situation is unclear.

Prophylactic urinary antibiotics are usually recommended for invasive urological procedures with a risk of hematuria such as transurethral resection of the prostate and prostate biopsies [80].

However, to the best of our knowledge, no randomized controlled trial on urodynamic assessments is available to this day. In an era of ever-increasing microbial resistance, data is urgently needed to avoid unnecessary antimicrobial exposure.

8. Conclusions

UTIs are a major issue for patients with neurogenic bladder, as they are frequent and difficult to treat, with a high prevalence of MDRO involved. The physiopathology involves bladder ischemia and local immunity impairment but is not fully understood. The diagnosis is challenging with no specific clinical signs and clear cut off value for bacteriuria. They are also associated with a high rate of recurrence.

Antibiotic treatment should be limited to symptomatic cases and shortened as much as possible to limit the emergence of MDRO.

Several prophylactic strategies are available. Optimal bladder management is essential. Prophylactic antibiotic therapy, cranberries and D-mannose treatments, bacterial interference, or urinary vaccines are still under evaluation but seem promising.

Further data on this topic is required, especially concerning their diagnosis, physiopathology, optimal antibiotic treatments, and non-antibiotic prevention methods.

Disclosure of interests

The authors declare no conflict of interests.

Contribution of authors

All authors contributed to the discussion, to drafting the initial text, and proofread the final version of the article.

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Figure 1. Management algorithm for urinary tract infection in patients with neurogenic bladder

Figure 1. Algorithme de prise en charge des infections urinaires sur vessie neurologique