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Practice guidelines

Urinary tract infections and multiple sclerosis: Recommendations from the French Multiple Sclerosis Society

suppl. Informations

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ABSTRACT

Objectives. – Establish recommendations for the management of UTIs in MS patients.
Background. – Urinary tract infections (UTIs) are common during multiple sclerosis (MS) and are one of the most common comorbidities potentially responsible for deaths from urinary sepsis.
Methods. – The recommendations attempt to answer three main questions about UTIs and MS. The French Group for Recommendations in MS (France4MS) did a systematic review of articles from PubMed and universities databases (01/1980–12/2019). The RAND/UCLA appropriateness method, which has been developed to synthesize the scientific literature and expert opinions on health care topics, was used for reaching a formal agreement. 26 MS experts worked on the full-text review and a group of 70 multidisciplinary health care specialists validated the final evaluation of summarized evidences.
Results. – UTIs are not associated with an increased risk of relapse and permanent worsening of disability. Only febrile UTIs worsen transient disability through the Uhthoff phenomenon. Some immunosuppressive treatments increase the risk of UTIs in MS patients and require special attention especially in case of hypogammaglobulinemia. Experts recommend to treat UTIs in patients with MS, according to recommendations of the general population. Prevention of recurrent UTIs requires stabilization of the neurogenic bladder. In some cases, weekly oral cycling antibiotics can be proposed after specialist advice. Asymptomatic bacteriuria should not be screened for or treated systematically except in special cases (pregnancy and invasive urological procedures).
Conclusion. – Physicians and patients should be aware of the updated recommendations for UTis and MS.

1. Abbreviations

EAU	European Association of Urology
AFU	Association Française d'Urologie
RPC IUAS	Révision des recommandations de bonne Pratique pour la prise en charge des Infections Urinaires Associées aux Soins de l'adulte
SPILF	Société de Pathologie Infectieuses de Langue Française
IDSA	Infectious Disease Society of America
ISCOS	International Spinal Cord Society

2. Introduction

Urinary tract infections (UTI) are among the most frequent infections encountered in community medicine and hospitals. Fifty to 60% of women and 10% of men develop a UTI at least once during their lifetime and 25% of women experience a second episode within 6 to 12 months [1]. UTI can be specifically defined as: basic UTI, UTI without a risk of complication, recurrent UTI and serious UTI (Table 1) [2]. Colonization or asymptomatic bacteriuria (ABU) is defined as the presence of microorganisms in the bladder without associated clinical signs. No threshold exists for ABU except for pregnant women, which is defined as 10.5CFU/ml. The definition of ABU does not include taking into account leukocytes [2].

Diagnosis of UTI implies the presence of symptoms suggestive of an associated UTI with leukocyturia $> 10^4$ CFU/ml and significant bacteriuria depending on the microorganism and on the sex (Table 2) [2].

Recommendations for screening and the care of UTI have already been published by scientific societies such as the society of infectious pathologies of the French language (SPILF) and the European association of urology (EAU). They concern not only UTI in the general public but also associated with care in the context of neurologic bladder [2,5–7].

Bladder dysfunction often occurs in 50 to 90% of multiple sclerosis (MS) patients [8]. After 10 years with the disease 90% of MS patients develop UTI [8,9]. They are inaugural in 10% of cases and the average delay of emergence is 6 years. Among the urological complications of UTI the most frequent are lower UTI (13 to 74%) and 8% upper UTI (0 to 25%). UTI contributes to the most frequent comorbidities and are potentially responsible for deaths from urinary sepsis [10,11].

The risk factors of developing a UTI are the same as those of the general population: female sex, menopause, intercourse and age [12]. Specific risk factors have been described for neurologic bladder that encompass MS: urinary voiding difficulties (post void residual volume > 120 cc), inter-micturition pressure > 40 cm H_2O, disease duration > 15 years, a high EDSS score, bladder and kidney stones, a history of indwelling catheterization [8,9,13,14]. Anorectal problems and more specifically constipation have been suggested to be risk factors but are not well described and are mostly associated with incomplete bladder emptying induced by stercoral stasis [15].

Finally, the long-term use of immunosuppressors in MS promote potential immunosuppression leading to UTI [4].

Table 1 – Definitions of the different types of UTI.

Basic UTI: UTI occurring in patients without a risk of complications	Recurrent UTI: at least 4 episodes in 12 months
UTI with a risk of complications	Serious UTI
UTI occurring in patients with at least 1risk factor of serious UTI requiring complex treatment	Acute pyelonephritis and male UTI
	Serious sepsis
Organic or urinary tract functional abnormality	Septic shock
Male sex	Surgical drainage indicated or interventional
Age < 65 yrs with Fried[a] criteria of fragility or > 75 yrs	
Serious immunosuppression[b]	
Severe renal failure (Cl < 30 ml/min)	
	Colonization (asymptomatic bacteriuria)
	Presence of micro-organism in the urine without associated clinical signs of UTI
	Absence of a threshold for asymptomatic bacteriuria except for pregnant women (10^5 CFU/ml)
	Leukocyturia does not come into the definition

[a] Fried criteria: involuntary loss of weight during the preceding year–Slow walking speed–Poor endurance–Weakness/fatigue–Reduced physical activity [3].
[b] Serious Immunosuppression: neutropenia < 500/mm^3 and/or hypogammaglobulinemia IgG < 400 mg/dl [4].

Table 2 – Significant bacteriuria according to the micro-organism and the sex.

Bacterial species	Significant threshold (CFU/ml)	Significant threshold (CFU/ml)
	Men	Women
E. coli, *S. saprophyticus*	$\geq 10^3$	$\geq 10^3$
Enterobacteria other than E. coli, *entérocoque*, *C. urealyticum*, *P. aeruginosa*, *S. aureus*	$\geq 10^3$	$\geq 10^4$

Why did the SFSEP decide to initiate re-examination of the recommendations into urinary tract infections and multiple sclerosis?

Due to the intrinsic risk factors of this pathology and in particular to the development of neurologic bladder the risk of UTI is substantial. Increased risk of morbidity-mortality must therefore be taken into account.

In addition, the immune response induced by UTI could provoke relapse or aggravation of the neurological status, so the screening and treatment of UTI becomes part of the care of patients with this disease. More and more immunosuppressors are now labeled in MS. Their use may increase UTI risk.

Last and not least, one of the reasons for these recommendations is environmental and economic. In fact, antibiotics resistance is presently a major preoccupation and requires precise indications to provide a cure or prophylaxis of UTIs by limiting the inappropriate consumption of antibiotics.

These recommendations aim to provide the different players of the health care system (professionals, patients and users, decision-makers) with a robust synthesis of the state of the art and scientific data to help taking decisions on the choice of care, harmonizing practice, and reducing symptomatic treatments.

3. Methods

The abundance of scientific literature containing methodological limitations that do not allow a conclusion to be reached justifies the methodological choice to formulate recommendations by formalized consensus (RAND) according to the recommendations of the French High Authority of Health [16].

The ''Formal consensus'' method is both a method for development of good practice guidelines and a consensus method, derived from the RAND/UCLA Appropriateness Method [17]. Its main objective is to formalize the degree of agreement among experts by identifying and selecting, through iterative ratings with feedback, the points on which experts agree and on which the recommendations are secondarily based, and the points on which experts disagree or are undecided, to provide professionals and patients with assistance in deciding on the most appropriate care in given clinical circumstances.

The Steering Committee defined 3 clinical questions within the scope of the recommendations (Appendix 1):

- Are UTIs associated with an increased risk of relapse or symptoms? Of a transient worsening disability? Of a prolonged worsening disability?
- Is the risk of UTI increased by treatments for MS?
- Should multiple sclerosis patients be treated for bacteriuria?
  - Symptomatic (urinary tract infection)?
  - Asymptomatic (colonization)?
  - Asymptomatic (colonization) before treatment with immunosupressors?
  - Asymptomatic (colonization) before urodynamic evaluation?
  - Asymptomatic (colonization) in a patient with urinary catheter?

Table 3 – Level of scientific evidence and grading of the recommendations (https://has-sante.fr/portail/upload/docs/application/pdf/2018-03/good.practice_guidelines_fc_method.pdf).

Grading of recommendations	Level of scientific evidence provided by the literature
A Established scientific evidence	Level 1 High-power randomized comparative studies Meta-analysis of randomized comparative studies Decision analysis based on well-conducted studies
B Scientific presumption	Level 2 Low-power randomized comparative studies Well-conducted non-randomized comparative studies Cohort studies
C Low level of evidence	Level 3 Case control studies Level 4 Comparative studies with major bias Retrospective studies Case series

The literature search for publications in English and French was performed with the help of professional librarians, using the Medline database (http://www.ncbi.nlm.nih.gov/pubmed), the main websites referencing publications on recommendations and consensus conferences, and grey literature. An initial search was made with the following keywords: multiple sclerosis, central nervous system demyelination, clinically isolated syndrome, relapse, disability, progression, urinary tract infection, recurrent urinary tract infection, urodynamic, self-intermittent catheterization, long term indwelling catheter, asymptomatic bacteriuria, immunomodulators, immunosuppressors, interferon beta, glatiramer acetate, teriflunomide, dimethyl fumarate, fingolimod, natalizumab, cyclophosphamide, methotrexate, cladribine, ocrelizumab, rituximab, alemtuzumab, azathioprine, mycophenolate, fampridine. A subsequent search was done by analyzing the references of each selected paper.

Readers from the steering committee then conducted a systematic analysis of the literature using reading grids and wrote a critical and hierarchical synthesis of the literature, including a referenced text and summary tables with mention of the levels of evidence of the studies. Members of the steering committee met to discuss the evidence reported and to prepare the list of proposals to be submitted to the rating group. Proposals were classified into grade A, B or C according to the HAS guidelines (Table 3). In the absence of sufficient data, proposed recommendations corresponded to an expert agreement only. In the absence of expert agreement, the alternatives were exposed without any recommendations in favor of one or the other.

Thereafter, proposals were submitted to a rating group that did not participate in the initial drafting. Each rater had to decide on his/her level of agreement with each proposal, giving a score between 1 (total disagreement) and 9 (totally agree). All members of the steering committee and rating group collaborated in the drafting of the final recommendations during a face-to-face meeting.

A reading group made of neurologists and other health care professionals was asked to review the final version of the recommendations, giving a score between 1 (total disagreement) and 9 (total agreement) and making comments. Proposals were then classified as appropriate (median value ≥ 7), inappropriate (median value ≤ 3.5) or uncertain (median value 4–6.5), with a different degree of agreement (Table 4). After analysis and discussion of ratings and comments from the reading group, initial recommendations were modified according to the following rules:

- recommendations based on a high level of evidence (grade A or B): consideration of relevant comments to improve the form, changes to the content, if any, based on data provided, changing the grade of the recommendation if necessary;
- recommendations based on a low level of evidence (grade C) or on agreement within the rating group: when the reading group confirmed the appropriate nature of the recommendation ($\geq$ 90% of responses from the reading group within the range [5–9]), the recommendation was retained and relevant comments were considered to improve the form, when the reading group was more widely undecided or disagrees with the initial recommendation ($<$ 90% of responses from the reading group within the range [5–9]), the steering group, after debate with the rating group, proposed possible modifications based on comments or the rejection of the recommendation.

Table 4 – Conditions for expert agreement and judgement, according to the median value and the distribution of the ratings. (Development of Good Practice Guidelines. "Formal consensus" Method. December 2010, updated March 2015. https://www.has-sante.fr/portail/upload/docs/application/pdf/2018-03/good_practice_guidelines_fc_method.pdf).

Proposal judged	Degree of agreement of the group	Conditions for obtaining	
		Median value	Distribution of rating in the interval
Appropriate	Strong agreement	≥ 7	[7–9]
	Relative agreement	≥ 7	[5–9]
Inappropriate	Strong agreement	≤ 3	[1–3]
	Relative agreement	≤ 3.5	[1–5]
Uncertain	Undecided	$4 \leq$ median ≤ 6.5	[1–9]
	Lack of consensus	All other situations	

4. Results

An extensive French version of the summary of evidence, including tables with mention of the levels of evidence of the studies, is available on the website of the SFSEP (http://www.sfsep.org) or upon request to the authors. Detailed results of the final rating are provided in Table 5.

Question 1: are urinary tract infections associated with an increased risk of relapse? Of transient worsening disability? Of prolonged worsening disability in patients with MS

Recommendation 1.
1a. Urinary tract infections are not associated with an increased risk of relapse in patients with multiple sclerosis (Level C).
Rating: Appropriate [5–9]; Relative agreement (median 9, min–max 6–9)

1b. Non-febrile urinary tract infections are not associated with an increased risk of transient worsening disability in patients with multiple sclerosis (expert recommendation).
Rating: Appropriate [5–9]; Relative agreement (median 8, min–max 6–9)

1c. Febrile-urinary tract infections are associated with an increased risk of transient worsening disability of patients with multiple sclerosis (expert recommendation).
Rating: Appropriate [7–9]; strong agreement (median 9, min–max 8–9)

1d. Urinary tract infections are not associated with an increased risk of prolonged disability aggravation in patients with multiple sclerosis (Level C).
Rating: Appropriate [7–9]; strong agreement (median 9, min–max 7–9)

No studies dedicated to investigating the specific risk of relapse following a UTI exist but through extrapolation of the data of studies into other types of infection, mostly of the upper airways, some authors have raised the possibility of an increased risk of relapse following a UTI. Thus, infectious antigenic stimulation may be an element that triggers relapse

In a study [18] dedicated to the risk of relapse following all types of infection, in which UTI constituted a minor part, the risk of severe relapse and of aggravation of permanent disability was increased during a defined at-risk period of two weeks before and until five weeks after the detection of clinical infection. In this study UTI were rare, and while no relapse occurred during the at-risk period, which encompassed that of a UTI, it is difficult to draw conclusions concerning the question of interaction between UTI and the risk of relapse as well as that of long-term progression.

In another study of a similar design, the authors reported an increased risk of relapse in the two weeks following infection (respiratory, gastro-intestinal or UTI) [19]. Even if this subgroup of UTI was not specifically studied the number of infections was higher (42.3%) and the risk of relapse was identical be it a bacterial or viral infection. The authors also found increased lesion load in magnetic resonance Imagery in this period (20 patients) and an increase in the number of pro-inflammatory cells in the blood (35 patients). Thus, it is also difficult to draw conclusions from this work, admittedly different from the first study but still lacking a specific subgroup ''UTI'' and concerning a small number of patients. In this study, an increased risk of prolonged aggravation of disability was not specifically demonstrated for UTI.

An association between UTI and a risk of aggravation of transitory disability has not been studies in a robust framework in terms of methodology. Only three publications [20–22], evaluating clinical cases with febrile UTI (renal abscess and urinary sepsis) reported transient worsening of disability in terms of the neurological state that improved after treatment. The authors concluded that the Uhthoff phenomenon secondary to the hyperthermia provoked by the UTI was the cause of symptoms aggravation.

No publication reports the specific study of the risk of transient worsening of disability in case of non-febrile UTI. The experts concluded that UTI were associated with a higher risk of aggravation of temporary disability only for cases of febrile UTI as a consequence of the Uhthoff phenomenon.

Question 2: Is the risk of a urinary tract infection increased by treatments for MS?

Interferon betas, glatiramer acetate, teriflunomide, dimethylfumarate, fingolimod, natalizumab, mitoxantrone, alemtuzumab, cladribine, ocrelizumab, cyclophosphamide, mycophenolate mofetil, azathioprine, rituximab, plasma exchange, high dose methylprednisolone and fampridine.

The risk of contracting a UTI during treatment of MS has not been specifically studied. Studies mostly report the efficacy of treatments and note adverse events including complications of infection. Neither UTI have been precisely defined (clinical criteria, microbiology, association of the two) nor the delay to onset with respect to the administration of treatment. The type of infection is rarely indicated: cystitis, pyelonephritis, masculine UTI pauci-symptomatic or not. Finally, the voiding mode and the detrusor-sphincter balance of patients has not been described. Yet this has a major impact on the definition of a UTI as well as the risk of recurrence.

Interferon beta

Recommendations 2a. Treatment with interferon beta is not associated with an increased risk of developing a urinary tract infection (Level B).
Rating: Appropriate [7–9]; strong agreement (median 9, min–max 7–9)

The 3 large multi centric randomized trials that compared interferon beta with placebo including 1300 patients did not find UTI during follow-up [23–25]. In addition, Calabresi et al., in a multicentric study including 1512 patients compared

Table 5 – Summary of the recommendations of the French multiple Sclerosis society (SFSEP) on urinary tracts infection and multiple sclerosis.

Questions	Responses	Recommendations
Question 1a: Are urinary tract infections associated with an increased risk of relapses??	1a. Urinary tract Infections are not associated with an increased risk of relapse in patients with multiple sclerosis	Level C
1b. Are urinary tract infections associated with an increased risk of a transitory aggravation of disability?	1b. Non-febrile urinary tract infections are not associated with an increased risk of transient worsening disability in patients with multiple sclerosis	Expert recommendation
1c. Are urinary tract infections associated with an increased risk of a transitory aggravation of disability?	1c. Febrile-urinary tract infections are associated with an increased risk of transient worsening disability of patients with multiple sclerosis	Expert recommendation
1d. Are urinary tract infections associated with an increased risk of prolonged aggravation of disability?	1d. Urinary tract infections are not associated with an increased risk of prolonged disability aggravation in patients with multiple sclerosis	Level C
Question 2: Is the risk of a urinary tract infection increased by treatments for MS?	2a. Interferon beta Treatment with interferon beta is not associated with an increased risk of developing a urinary tract infection	Level B
	2b. Glatiramer acetate Treatment with glatiramer acetate is not associated with an increased risk of developing a urinary tract infection	Level B
	2c. Teriflunomide Treatment with teriflunomide is not associated with an increased risk of developing a urinary tract infection	Level B
	2d. Dimethylfumarate Treatment with diméthylfumarate is not associated with an increased risk of developing a urinary tract infection	Level B
	2e. Fingolimod Treatment with fingolimod is not associated with an increased risk of developing a urinary tract infection	Level B
	2f. Cladribine Treatment with cladribine is not associated with an increased risk of developing a urinary tract infection	Level B
	2g. Mitoxantrone Treatment with mitoxantrone is associated with an increased risk of developing a urinary tract infection	Level B
	2h. Natalizumab Treatment with natalizumab is not associated with an increased risk of developing a urinary tract infection	Level B
	2i. Alemtuzumab Treatment with alemtuzumab is associated with an increased risk of developing a urinary tract infection	Level B
	2j. Ocrelizumab Treatment with ocrelizumab is not associated with an increased risk of developing a urinary tract infection Due to the effect of anti-CD20 the risk of infection was increased in cases of hypogammaglobulinemia	Level B Expert recommendation
	2k. Cyclophosphamide (off label use) Treatment with cyclophosphamide is associated with an increased risk of developing a urinary tract infection	Level B
	2l. Mycophenolate mofetil (off label use) Treatment with mycophenolate mofetil is not associated with an increased risk of developing a urinary tract infection	Level B
	2m. Azathioprine (off label use) Treatment with azathioprine is not associated with an increased risk of developing a urinary tract infection	Level B
	2n. Rituximab (off label use) Treatment with rituximab is associated with an increased risk of developing a urinary tract infection	Level B
	2o. Plasma exchange (off label use) Treatment with plasma exchange is not associated with an increased risk of developing a urinary tract infection	Level C
	2p. Methylprednisolone Treatment with high doses of methylprednisolone is not associated with an increased risk of developing a urinary tract infection	Level C
	2q. Fampridine Treatment with fampridine is not associated with an increased risk of developing a urinary tract infection	Level B

Table 5 (*Continued*)

Questions	Responses	Recommendations
Question 3: Should multiple sclerosis patients be treated for bacteriuria? 3a. Symptomatic bacteriuria (urinary tract infection)?	It is recommended to treat symptomatic bacteriuria (urinary tract infection) in MS patients in the case of a neurologic bladder or not and whatever the voiding mode (voluntary/catheterization). Treatment of symptomatic bacteriuria follows the recommendations for the general population	Level A
3a. Symptomatic bacteriuria (urinary tract infection)?	Prevention of recurrent urinary tract infections with alternative complementary medicine has not been established	Level B
3a. Symptomatic bacteriuria (urinary tract infection)?	The interest of treating urinary tract infection in spinal cord injury with weekly oral cycling antibiotics has been established (Level C). By analogy, this approach can be considered for patients with multiple sclerosis in the case of recurrent urinary tract infections after obtaining specialist advice	Level C, Expert recommendation
3b. Asymptomatic bacteriuria (colonization)?	Screening and systematic treatment of asymptomatic bacteriuria (colonization) in patients with multiple sclerosis is not recommended, with the exception of situations recommended for the general population (pregnancy, invasive urological procedure)	Level C
3c. Asymptomatic bacteriuria (colonization) before treatment with immunosuppressors?	Screening or systematic treatment of asymptomatic bacteriuria (colonization) before treatment with immunosuppressors of patients with multiple sclerosis are not recommended except in the case of hypogammaglobinemia	Expert recommendation
3d. Asymptomatic bacteriuria (colonization) before urodynamic evaluation?	Screening and treatment of asymptomatic bacteriuria (colonization) before urodynamic evaluation in absence of known urinary tract infection risk factors are not recommended in patients with multiple sclerosis	Level C
3d. Asymptomatic bacteriuria (colonization) before urodynamic evaluation?	Screening and treatment of asymptomatic bacteriuria (colonization) before urodynamic evaluation in the presence of known urinary tract infection risk factors (recurrent urinary tract infection, vesico-ureteral reflux, high detrusor pressure > 40 cmH_2O) are recommended in patients with multiple sclerosis	Level C
3e. Asymptomatic bacteriuria (colonization) in patients with urinary catheter?	Screening and systematic treatment of asymptomatic bacteriuria (colonization) of patients with multiple sclerosis with intermittent or indwelling catheters are not recommended with the exception of situations recommended in the general population (pregnancy, invasive urological surgery)	Level C, Expert recommendation

different schedules of administration of pegylated interferon versus placebo and did not note an increased incidence of UTI in patients treated with pegylated interferon (2 UTI for 1000 patients on pegylated interferon versus 1 UTI for 500 patients on placebo) [26]. Finally, the authors of 2 reviews concerning the treatment of MS did not find a reported increase in the risk of UTI in a population on interferon beta [27,28].

Glatiramer acetate

Recommendation2b. Treatment with glatiramer acetate is not associated with an increased risk of developing a urinary tract infection (Level B).
Rating: Appropriate [7–9]; strong agreement (median 9, min–max 7–9)

A randomized trial (glatiramer acetate vs placebo) including 251 patients did not report a UTI when describing the side-effects [29]. In another cohort (208 patients) no UTI was reported [30]. A randomized study by Mikol et al., that compared glatiramer with interferon beta found 5% of UTI in the 2 arms i.e. 1% of the total undesirable side-effects [31]. Ford et al. reported that their series of patients on glatiramer showed frequent UTI but neither the incidence nor the characteristics and/or definition of the UTI were given [32]. Finally, there was also no mention of the voiding mode and the detrusor-sphincter balance of patients. A review mentioned that acute pyelonephritis could occur but the incidence was not mentioned [28]. Another study did not find an increase in the risk of general infection [27]. In all the studies, the EDSS score was below or equal to 7. No study defined either UTI, the voiding mode or the detrusor-sphincter balance.

Teriflunomide

Recommendations 2c. Treatment with teriflunomide is not associated with an increased risk of developing a urinary tract infection (Level B).
Rating: Appropriate [7–9]; strong agreement (median 9, min–max 7–9)

The data concerning tolerance are issued mainly from pivotal studies (TOPIC, TEMSO and TOWER) [33–35]. Two doses of teriflunomide (14 and 7 mg/day) were tested over a period of

2 years. No increase in the risk of UTI was reported in all these studies for teriflunomide versus placebo. Of note, the average EDSS of patients was relatively low, from 1.5 for TOPIC to 2.7 for TEMSO and TOWER [33–35]. The phase 3 TENERE [36] study included 348 RR MS patients followed for 48 weeks. Unfortunately, no data was provided concerning the incidence or severity of UTI. Likewise, an observational study comparing 1057 RR MS patients on teriflunomide to 713 on dimethylfumarate did not provide information concerning UTI [37]. An extended study of 147 patients, some of which were followed for a maximum of 8.5 years, showed a tendency toward an increase in UTI compared to the pivotal studies. These patients had an initial average EDSS of 2.7. Three cases of pyelonephritis were reported but only for the group treated with 14 mg/day of teriflunomide [33].

None of these studies reported the existence of factors favoring UTI such as bladder dysfunction or a high EDSS score. However, the criteria of exclusion of the pivotal studies excluded patients with an EDSS score > 5.5. A maximal EDSS score of 6.0 was observed in the extended study mentioned above.

Dimethylfumarate

Recommendations 2d. Treatment with diméthylfumarate is not associated with an increased risk of developing a urinary tract infection (Level B).
Rating: Appropriate [7–9]; strong agreement (median 9, min–max 7–9)

The pivotal studies CONFIRM and DECIDE [38–40] did not identify an increased risk of developing a UTI among patients treated with dimethylfumarate. This tolerance was confirmed by an extended study that followed patients for a minimum of 5 years [39,41]. In the ENDORSE study, the level of UTI was relatively the same as that reported in the CONFIRM study, from 8% (placebo for 2 years then dimethylfumarate 3 times a day for 3 years) to 19% (dimethylfumarate 2 times a day for 5 years) [Gold et al., 2017]. Five serious UTIs were identified in the latter study but the type was not specified. However, no conclusions into a strong effect of dimethylfumarate on the development of infection can be inferred from the data on 3/day dimethylfumarate for 5 years group. A study evaluating dimethylfumarate 3/day with add-on of interferon ($n = 57$) or glatiramer acetate ($n = 47$) for 1 year reported 12 and 17% infection, respectively, without specifying the type [42].

None of these studies reported the existence of factors favoring UTIs such as detrusor-sphincter dysfunction or a high EDSS. The average EDSS score at baseline in CONFIRM, DECIDE and ENDORSE ranged from 2.3 to 2.6.

Fingolimod

Recommendations 2e. Treatment with fingolimod is not associated with an increased risk of developing a urinary tract infection (Level B).
Rating: Appropriate [7–9]; strong agreement (median 9, min–max 7–9)

The pivotal studies (FREEDOMS I, II, TRANSFORMS) as well as pooled data from these studies did not find an increase in the risk of UTIs in patients treated with 1.25 mg/day or 0.5 mg/day of fingolimod. The extended FREEDOMS I and TRANSFORMS studies as well as other studies of cohorts comparing a smaller number of patients also obtained similar results [43–51].

Cladribine

Recommendations 2f. Treatment with cladribine is not associated with an increased risk of developing a urinary tract infection (Level B).
Rating: Appropriate [7–9]; strong agreement (median 8, min–max 7–9)

The pivotal studies ORACLE and CLARITY did not specifically record the number of urinary tract infections [52,53]. In contrast, the data from the extended study CLARITY reported an incidence of urinary tract infections that varied from 4.3% in the group treated with cladribine and placebo (cladribine 5.25 mg/kg for 2 years then placebo for 2 years) to 9.1% for the group receiving cladribine 3.5 mg/kg for 4 years. When considering the patients receiving the highest dose (cladribine 5.25 mg/kg for 2 years then 3.5 mg/kg for 2 years) the percentage reached 8.6% [52–54]. When the data of the three above mentioned studies were pooled no significant difference between the groups on cladribine 3.5 mg/kg and placebo were found. Two cases of pyelonephritis were recorded in the cladribine group with withdrawal of treatment in one case. A case of an opportunistic fungal urinary tract infection was found in the cladribine group [55,56].

Mitoxantrone

Recommendations 2g. Treatment with mitoxantrone is associated with an increased risk of developing a urinary tract infection (Level B).
Rating: Appropriate [7–9]; strong agreement (median 9, min–max 7–9)

Treatment of cancers (lymphoma, leukemia, breast cancer) with mitoxantrone is often associated with UTIs (frequency > 1/10). Mitoxantrone use for MS is also associated with an increased risk of UTIs with the different tested doses (12, 8 and 5 mg/m^2) when compared to the placebo group. The EDSS of patient's studies in not so recent studies was between 3.5 [57] and 4.5 [58,59], which constitutes a sub group [60].

Natalizumab

Recommendations 2h. Treatment with natalizumab is not associated with an increased risk of developing a urinary tract infection (Level B).
Rating: Appropriate [7–9]; strong agreement (median 9, min–max 7–9)

The pivotal phase 3 studies regrouping more than 1500 patients treated with natalizumab did not report an increased risk of UTI compared to the placebo or interferon groups. It is possible to generalize based on these results since they concern patients with different profiles with an average EDSS of 2.3 for RR MS patients of the AFFIRM and SENTINEL studies [61,62] and 6.0 for SP MS patients of the ASCEND study [63]. Finally, a review reassessed all the cases of UTIs on natalizumab and found they represented 1–18.6% of the undesirable side-effects provoked by this product and found that the majority of the infections were not severe [64].

Alemtuzumab

Recommendations 2i. Treatment with alemtuzumab is associated with an increased risk of developing a urinary tract infection (Level B).
Rating: Appropriate [7–9]; strong agreement (median 9, min–max 7–9)

A substantial increase in the risk of developing a UTI during the 2 years of treatment was demonstrated when 12 and 24 mg/day of alemtuzumab was compared with interferon. This result was drawn from 3 major studies grouping together 1400 patients [65–67]. At the beginning of this study the patients had an average EDSS that varied from 1.9 to 2.7 for whom the conclusion was the same irrespective of the level of handicap. Cases of severe pyelonephritis and cystitis were recorded for the alemtuzumab group but none for the interferon group [68].

Ocrelizumab

Recommendations 2j. Treatment with ocrelizumab is not associated with an increased risk of developing a urinary tract infection (Level B). Due to the effect of anti-CD20 the risk of infection was increased in cases of hypogammaglobulinemia (expert recommendation).
Rating: Appropriate [7–9]; strong agreement (median 8, min–max 7–9)

In the pivotal studies (OPERA and ORATORIO) composed of 1300 patients treated with 600 mg of ocrelizumab each semester for a minimum of 2 years no increase in the risk of UTI compared to placebo or interferon was noted. No opportunistic infection was reported on ocrelizumab [69,70].

None of these studies indicated that there were existed factors favoring UTI, such as bladder dysfunction or a high EDSS score. The EDSS at baseline for RR MS patients in these studies ranged from 2.8 to 3.5 [69,71] while the average EDSS was 4.7 in studies concerning SP MS patients [70]. Despite the risk of UTI in this population of this study (progressive form and EDSS > 4), ocrelizumab was well tolerated with respect to the urinary tract.

Potential hypogammaglobulinemia induced by anti-CD20 may increase the risk of infection so the experts considered that in the case of hypogammaglobulinemia with ocrelizumab the risk of UTI could not be excluded. We have to keep in mind that actually we lack long term-follow-up with ocrelizumab on the risk of UTIs.

Cyclophosphamide (off label use)

Recommendations 2k. Treatment with cyclophosphamide is associated with an increased risk of developing a urinary tract infection (Level B).
Rating: Appropriate [7–9]; strong agreement (median 9, min–max 8–9)

Only one comparative randomized study of a phase 3 trial of MS patients given cyclophosphamide at the usual dose each month exists. No increase in the risk of contracting a UTI specifically associated to the 59 patients followed over 2 years was reported [72]. This absence of an increase in UTI was also noted in the Cochrane meta-analysis despite the fact that the studies included in this analysis used mostly cyclophosphamide in addition to corticoids (methylprednisone or adrenocorticotropic hormone (ACTH)) at high doses up to 18 g for 22 weeks [73]. Other studies using cyclophosphamide at a high dose (50 mg/kg intra-venous (IV) perfusion, each day, for 4 days) including 41 patients found 3 UTIs with Koch Bacillus in the urine of 2 patients with dysuria and a third patient with a non-specified bacterial UTI [73]. Finally, one cohort study demonstrated a risk of UTI in 56% of patients but the average reference EDSS score was 5.8 and treatment with cyclophosphamide given over 2 years instead of 1 as usual for MS [74]. In a series of cases Reggio et al. found 17% of UTIs in 30 MS patients but no detail concerning the type of infection was given [75].

In total, a possible increase in the frequency of UTI on cyclophosphamide but based on very heterogeneous data from the literature that lacks controlled randomized strong powered level 1 studies, for very variable doses of cyclophosphamide in the protocol, and for a lack of systematic reporting the infections in the study, for the lack of a control group in most of the studies and for the absence of data on the status of the development of bladder dysfunction while a large number of patients were SP.

Mycophenolate mofetil (off label use)

Recommendations 2l. Treatment with mycophenolate mofetil is not associated with an increased risk of developing a urinary tract infection (Level B).
Rating: Appropriate [7–9]; strong agreement (median 9, min–max 7–9)

Few randomized studies with a large number of MS patients receiving mycophenolate mofetil exist. The largest study included 35 patients of which 16 were treated with mycophenolate mofetil and no increase in the risk of UTI compared to a group on interferon was reported [76]. Prospective and retrospective cohort studies increase the overall number of patients in the data collection but the precise result is questionable [77–79]. The risk of UTI was not increased in these studies. One case of hemorrhagic cystitis was reported in a cohort of 64 patients with a progressive form of MS but some of the patients had first received cyclophosphamide [80]. Finally, consultation of the French national EDMUS database gave 344 patients treated with mycophenolate mofetil mono therapy all of whom were without infection [81].

Azathioprine (off label use)

Recommendations 2m. Treatment with azathioprine is not associated with an increased risk of developing a urinary tract infection (Level B).
Rating: Appropriate [7–9]; strong agreement (median 9, min–max 7–9)

Only one randomized study of 150 MS patients compared azathioprine to interferon and no UTI were reported [82]. Other studies present the results of trials in which azathioprine was given in association with interferon beta and/or corticoids. The incidence of UTI was comparable between the groups of these studies [83,84]. A cohort study, an extension of the Havrdova et al., study, was not able to draw conclusions on the subject due to adverse events that were not detailed [84]. A retrospective study analyzed the data of 85 MS patients on interferon associated with azathioprine and reported 6% of infection non-specified with two pyelonephritis [85]. A literature review by La Mantia et al. analyzed the results of randomized studies and the follow-up of cohorts between 1971 and 2007, and did not find an increase in the risk of UTI on azathioprine [86]. The Cochrane review of 2007 did not show any difference between the incidence of infection between the treated and placebo groups [87].

Rituximab (off label use)

Recommendations 2n. Treatment with rituximab is associated with an increased risk of developing a urinary tract infection (Level B).
Rating: Appropriate [7–9]; strong agreement (median 8, min–max 7–9)

In two studies examining either the PP form: OLYMPUS [88] or the RR form of MS HERMES [89], the frequency of UTI of patients on rituximab at 2 g per week was higher than that of the placebo group. A number of other observational studies of either the PP or RR forms reported UTIs and a few cases of pyelonephritis [90,91], including 2 urinary sepsis (seminal event unknown) in patients on rituximab but in the absence of comparative data. In 2008, Bar-Or et al. reported 7.7% of UTIs in 26 RR MS patients receiving two courses of 2 g of rituximab 6 months apart and followed for 72 weeks [92]. None of the studies reported factors favoring UTI such as detrusor-sphincter dysfunction or high EDSS score. The average EDSS score at baseline in HERMES was 2.5 while that of OLYMPUS was 4.8

Plasma exchange (off label use)

Recommendations 2o. Treatment with plasma exchange is not associated with an increased risk of developing a urinary tract infection (Level C).
Rating: Appropriate [7–9]; strong agreement (median 9, min–max 8–9)

Five studies examined plasma exchange including 4 with less than 100 MS patients. Tombak et al. and Weinshenker et al. did not report any UTI [93,94]. Ehler et al., in a retrospective series noted 4 systemic infections the origin of which was not given [95]. The largest series included 2502 patients and none developed a UTI [96].

Methylprednisolone

Recommendations 2p. Treatment with high doses of methylprednisolone is not associated with an increased risk of developing a urinary tract infection (Level C).
Rating: Appropriate [7–9]; strong agreement (median 8, min–max 7–9)

No UTIs were identified in 4 randomized trials and a meta-analysis of patients treated with methylprednisolone per os or IV [97–100]. However, no mention of whether the patients were on antibiotics or presented with asymptomatic bacteriuria (ABU) when the bolus was given. Analysis of 2 cohorts of patients treated with a bolus of methylprednisolone found 2 cases of cystitis among 350 patients and 7 cases of ABU among 249 patients but no sepsis or bacteremia [101,102]. Donze et al. did not find a difference in the incidence of UTI for patient receiving a bolus of methylprednisolone whether or not they were on antibiotics in case of positive ABU before bolus [103].

Thus, it appears that high dose corticoids do not increase the risk of developing a UTI but it is usual to treat UTI before treatment.

Fampridine

Recommendations 2q. Treatment with fampridine is not associated with an increased risk of developing a urinary tract infection (Level B).
Rating: Appropriate [7–9]; strong agreement (median 9, min–max 8–9)

A summary of the characteristics of fampridine indicated a variable incidence of UTI (2% to 14%). No information was given in this publication concerning the status of the detrusor-sphincter of patients and no result of urine culture (UC) was provided. However, a randomized versus placebo trial did not find any difference in the frequency of UTIs in the 2 arms [104]. Another trial in which different doses of fampridine were compared did not find any significant difference in the occurrence of UTI compared to placebo but with a possible tendency to a dose dependent increased risk [105]. Consequently, no proof of an increased risk of UTIs exists for patients with fampridine [106].

Question 3: Should multiple sclerosis patients be treated for bacteriuria?

Symptomatic (urinary tract infection)?

Recommendations 3a. It is recommended to treat symptomatic bacteriuria (urinary tract infection) in MS patients in the case of a neurologic bladder or not and whatever the voiding mode (voluntary/catheterization) (Level A). Treatment of symptomatic bacteriuria follows the recommendations for the general population (Level A)
Rating: Appropriate [7–9]; strong agreement (median 9, min–max 7–9)

Recommendation 3b. Prevention of recurrent urinary tract infections with alternative complementary medicine has not been established (Level B)
Rating: Appropriate [7–9]; strong agreement (median 9, min–max 7–9)

Recommendation 3c. The interest of treating urinary tract infection in spinal cord injury with weekly oral cycling antibiotics has been established (Level C). By analogy, this approach can be considered for patients with multiple sclerosis in the case of recurrent urinary tract infections after obtaining specialist advice (expert recommendation).
Rating: Appropriate [7–9]; strong agreement (median 8, min–max 7–9)

The arguments are essentially based on the recommendations published by scientific societies [2,6,7]. These recommendations do not concern directly MS but raise the question of UTI in a relatively large context that includes neurologic bladder, nosocomial or common UTIs. In these cases, there is no ambiguity to the treat UTIs. The difficulty is that clinical signs of UTI case of neurologic bladder or in patients with urinary catheter have not been established. A number of propositions exist for neurologic bladder, in particular for spinal cord injury but none specifically for MS [107]. A single study by Fitzgerald et al., 2019 evaluated the signs of UTIs associated with a positive UC at the time of admission of 63 patients with RR MS and only found ''foul smelling urine'' as a predictive sign of UTI (odds ratio (OR) 7.6) [108]. In a recent review, Kennely et al., 2019, summarized the risk of UTIs in patients with intermittent catheterization in the context of neurologic bladder, which included MS patients in addition to other patients [107]; the authors mentioned that it was difficult to determine the specific clinical symptoms of UTIs in those patients since they have variable pathologies and were studies mostly concerned spinal cord injury (definitions of the European and American scientific societies: EAU; IDSA and ISCOS [107]. Isolated aggravation of neurological symptoms (spasticity, motor deficit) does not seem to be linked to UTIs in MS. This is mostly the consequence of associated fever and corresponded more to an Uhthoff phenomenon. Nikseresht et al. found more frequent urinary symptoms in patients with a positive UC [109]. In case of suspected UTI, the authors suggest looking for a change in urinary status associated or not with signs of neurological deterioration.

The prevention of recurrent UTIs with alternative and complimentary medicines (acidification of urine, cranberries, methenamine, D-mannose) has been studied in cases of neurologic bladder and no effective preventive effect on recurrent UTIs was demonstrated [7,13]. A single study specifically dedicated to MS patients by Gallien et al. evaluated in 171 MS patients the efficacy of cranberries in a randomized controlled study versus placebo but did not find a difference between the two groups [110]. However, in case of recurrent UTIs it is strongly advised to offer a neuro-urological assessment ton control detrusor-sphincter balance [7–13].

The efficacy of long term prophylactic antibiotics with daily intake of an antibiotic to prevent recurrent UTIs is debatable in the case of neurologic bladder. Two meta-analyses do not recommend this approach for this indication and report an increase in antibiotic resistance [111,112]. Even if the populations of these studies were relatively heterogeneous concerning the voiding mode (indwelling catheter, suprapubic catheter, and self-intermittent-catheterization) and the populations of spinal cord injury studied, long term prophylactic antibiotic treatment was not recommended.

The use of weekly oral cycling antibiotics was evaluated in an open study of 38 patients with spinal cord dysfunction who practice self-intermittent-catheterization who have presented

6 UTIs. The authors reported a significant decrease in UTIs in this population [113]. In a study of a more heterogeneous population composed of para- and tetraplegic patients with different modes of urinary voiding the same team confirmed the efficacy of this approach and reported no bacterial resistance to the antibiotics [114]. So, the experts concluded that this treatment can be proposed to MS patients with neurologic bladder but after obtaining advice from a specialist.

Asymptomatic (colonization)?

Recommendations 3. Screening and systematic treatment of asymptomatic bacteriuria (colonization) in patients with multiple sclerosis are not recommended, with the exception of situations recommended for the general population (pregnancy, invasive urological procedure) (Level C).
Rating: Appropriate [7–9]; strong agreement (median 9, min–max 7–9)

ABU is defined as the presence of microorganisms in urine without associated clinical signs associated with a threshold of 10^3 UFC/ml [SPILF, 2015]. Very little literature is available concerning the management of ABU (colonization) exclusively in MS. So, evaluation of the literature was extended to studies concerning the general population (elderly patients) as well as populations of patients with neurologic bladder in the case of spinal cord injury.

The treatment of ABU of elderly institutionalized patients did not modify the morbidity-mortality but increased the emergence of multidrug-resistant bacteria [115,116].

ABU in cases of neurologic bladder was studied mainly with respect to self-intermittent catheterization of patients with spinal cord injury and the prevalence was high, reaching sometimes 89% [103]. In this population treatment of ABU did not reduce the risk of either subsequent colonization or UTIs. In contrast, the risk of antibiotic resistance was increased [117–119].

Fakas et al. reported a prevalence of 71.48% ABU in MS patients with intermittent catheterization [120]. There are few publications concerning patients with a spontaneous mode of voiding. Only three authors investigated the prevalence of ABU in MS patients. In 2013, Rakusa et al. reported 11% of patients with ABU in a cohort of 267 patients [102]. Fakas et al. reported 10.7% of patients with ABU for 75 MS patients with spontaneous voiding [120]. Donzé et al., based on UC performed systematically before bolus of methylprednisolone found 32, 98% ABU in MS patients [103].

The 167 MS patients studied by Fakas et al. were divided into three groups: those with self-intermittent catheterization (A), those for whom self-intermittent catheterization was considered but not chosen for the patient (B) and those for whom self-intermittent catheterization was not indicated (C). The incidence of ABU was 72.0% in group A (39 patients) versus 10.7% in group C (75 patients). Monthly UC were performed in this longitudinal controlled study and patients received antibiotic therapy for 5 to 7 days. The recurrence of ABU was 65% and 15% respectively, in groups A and B. Frequent emergence of resistant bacteria was noted (60 to 65% of cases). The authors reported no recurrence of bacteriuria in group C but due to the design of the study it is not possible to say if this reduced the occurrence of UTIs (no control group) [120]. Finally, in the observational non-randomized study of Donze et al., of patients with ABU before bolus treatment with methylprednisolone (MP), 17 patients were treated versus 15 who were not treated. No difference in the frequency of UTIs in the months following treatment with MP was noted [103].

In 2009 Fowler et al. published expert recommendations concerning management of urological dysfunction in MS but without considering randomized studies [121]. The experts concluded that it was not recommended to treat ABU (colonization) in MS patients with intermittent catheterization.

Several scientific societies recommended not treating ABU in the general population [2,6,7,122]. These recommendations are based on a few randomized studies as well as on non-controlled observational cohorts. Treatment of ABU is recommended in two situations, pregnancy and before invasive urological procedures. Two systematic reviews of the literature published in 2006 and 2016 reported similar conclusions [123,124].

The prevalence of ABU in MS patients can be high and some patient present neurologic bladder. The relevance of systematic screening or treatment of ABU has not been demonstrated and is not recommended, except for situations indicated for the general population (pregnant women or prevention before invasive urological procedures).

Asymptomatic (colonization) before treatment with immunosuppressors?

Recommendation 3. Screening or systematic treatment of asymptomatic bacteriuria (colonization) before treatment with immunosuppressors of patients with multiple sclerosis is not recommended except in the case of hypogammaglobinemia (expert recommendation).
Rating: Appropriate [7–9]; strong agreement (median 9, min–max 7–9)

No precise answer exists to date in the literature concerning this question. MS patients with immunosuppressors and drugs inducing lymphopenia experience more UTI than the patients on placebo. So, it is possible to rely on already existing recommendations concerning the screening for ABU to propose recommendations for the above specific situation.

In 2002, the SPILF indicated that ''ABU is not an indication for systematic treatment with antibiotics, disregarding whether the patient is catheterized or not, diabetic, elderly or presenting with neurologic bladder. However, the treatment of ABU (colonization) may be justified in certain cases, in particular: subjects for whom ABU is a factor of risk of morbidity-mortality: neutropenia, immunosuppression or pregnancy'' [5].

''RPC IUAS final 7 May 2015'' this article provides the most precise and reliable expert recommendations concerning the

question. After reviewing the literature, the authors emitted the following recommendations: ''In other situations of immunosuppression (other organ transplantations, corticosteroids, other forms of immunosuppression including neutropenia and hematopoietic stem cell grafts) no evidence in the literature favors treatment of ABU (colonization)'' So the authors expressed the following recommendations: ''Screening or treatment of urinary colonization in immunosuppressed patients is not recommended'' [6]. The level of proof concerns an expert opinion, results of clinical experience, descriptive studies or results of professional consensus. The 2 consensual situations for screening and treatment of urinary colonization (ABU) include: invasive urological surgery and pregnancy from the 4th month.

The recommendation issued by EAU 2018 dealt with the question from the point of view of asymptomatic candidiasis and recommended taking precautions in the case of immunosuppressed patients and/or patients with severe disability and to screen and treat asymptomatic candidiasis case by case [7].

Hypogammaglobinaemia potentially induced by immunosuppressor treatment can increase the risk of UTIs. So, in the case of hypogammaglobinemia the experts considered that risk of UTIs could not be excluded and screening and treatment of ABU may be considered case by case.

Asymptomatic (colonization) before urodynamic evaluation?

Recommendation 3a. Screening and treatment of asymptomatic bacteriuria (colonization) before urodynamic evaluation in absence of known urinary tract infection risk factors are not recommended in patients with multiple sclerosis (Level C).
Rating: Appropriate [7–9]; strong agreement (median 9, min–max 7–9)

Recommendation 3b. Screening and treatment of asymptomatic bacteriuria (colonization) before urodynamic evaluation in the presence of known urinary tract infection risk factors (recurrent urinary tract infection, vesico-ureteral reflux, high detrusor pressure > 40 cmH_2O) are recommended in patients with multiple sclerosis (Level C).
Rating: Appropriate [7–9]; strong agreement (median 9, min–max 7–9)

No specific data concerning MS patients and the need to treat ABU before urodynamic evaluation (UDE) was found in the literature. So, recommendations are based on studies of patients presenting with neurologic bladder and in particular populations with spinal cord injury [7,125,126].

The incidence of UTIs after UDE varied from 1 to 16% for patients with neurologic bladder [127–130].

Based on studies of patients with spinal cord injury systematic antibiotic prophylaxis before UDE when a UC is sterile is not recommended [126–129].

However, patients with a risk of developing a UTI: old age, anatomical anomalies of the urinary tract, malnutrition, tobacco intoxication, long-term corticosteroids, immunosupression, neurologic bladder in patients with an indwelling catheter, patients with other infections or hospitalized for long periods. In this context, in cases of UTI risk factors experts recommended screening and treatment of ABU before UDE [7,125,126,131]. The experts proposed following this recommendation for MS patients presenting with a risk of developing a UTI.

Asymptomatic (colonization) in a patient with urinary catheter?

Recommendation 3. Screening and systematic treatment of asymptomatic bacteriuria (colonization) of patients with multiple sclerosis with intermittent or indwelling catheters are not recommended with the exception of situations recommended in the general population (pregnancy, invasive urological surgery) (Level C, expert recommendation).
Rating: Appropriate [7–9]; strong agreement (median 9, min–max 7–9)

Only one study performed by Fakas et al., on a cohort of 167 MS patients with neurologic bladder, has examined the impact of prophylactic antibiotic therapy. This non-controlled, non-randomized prospective study compared 3 groups of MS patients with different voiding modes [120]. Group A ($n = 39$) with self-intermittent catheterization (SIC), group B ($n = 53$), for whom SIC was proposed but refused or abandoned by the patient and group C ($n = 75$), patients with voluntary voiding. A UC was performed monthly and patients treated with antibiotics in case of a urinary tract infection and then with furadantin for 6 months. In the case of a second episode of infection adapted treatment was proposed and then norfloxacin for 6 months. An EDSS > or equal to 6, post-voiding residue (PVR) and presence of multi resistant bacteria composed the factors of risk for failure of antibiotic prophylaxis. However, the incidence of UTI was not evaluated and so it is difficult to conclude on the efficacy of the preventive treatment. In addition, antibiotic treatment of ABU patients is not recommended due to the real possibility of a risk of resistance.

In 2018, a controlled randomized multi centric trial by Fisher et al. evaluated the clinical efficacy of daily low dose antibiotic prophylaxis for 12 months on development of UTIs in patients with self-intermittent-catheterization (203 treated versus 201 controls non-treated patients) [132]. If patients performed self-intermittent-catheterization for at least 12 months and at least 2 episodes of UTI treated for 12 months with antibiotics or were hospitalized with a febrile urinary tract infection they were included. The patients were followed for 1, 2, 3, 6, 9 and 12 months. The incidence of UTI in the treated group was 1.3 infections/Patient/year versus 2.6 infections/Patient/year for the non-treated group. However, significant antibiotic resistance was noted in the treated group. While the authors concluded that antibiotic prophylaxis was effective in self-intermittent-catheterization

patients they did not recommend routine use of this treatment for this population due to the emergence of resistance of the antibiotics tested but also of other antibiotics after 12 months.

Finally, in 2002 in a meta-analysis by Morton et al., the authors did not recommend treating ABU of patients with spinal cord dysfunction. The risk of emergence of multi-resistant bacteria was increased by two in this population on long-term of antibiotic prophylaxis [111].

Arguments concerning the question are based on existing recommendations published by scientific societies: SPILF 2002; 2015; RPC IUAS 2015; EAU 2018. While these societies did not refer specifically to MS they studied the question of UTIs in catheterized patients and did not recommend screening and treatment of ABU patients with a catheter (indwelling or intermittent catheterization) [5–7].

Endorsement

The 2020 recommendations on urinary tract infection and multiple sclerosis have been organized by the French Multiple Sclerosis Society (Société francophone de la sclérose en plaques [SFSEP]).

They are also endorsed by the French Neurological Society (Société française de neurologie [SFN]), the French Federation of Neurology (Fédération française de neurologie [FFN] and Société de pathologies infectieuses de langue française [SPILFS]).

An extensive French version including tables describing all contributing studies is available on sfsep.org/UTI.

A tutorial iOS application SFSEP is available on AppStore

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Author contribution

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Disclosure of interest

The authors declare that they have no competing interest.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.neurol.2020.02.011.

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