

Evaluation of Treatment Practices for Urinalyses and Urine Cultures at an Outpatient Multiple Sclerosis Clinic

Nicole C. Griffith, PharmD; Brandon K. Hill, PharmD; Myla D. Goldman, MD; S. Ross Tingen, PharmD

CE Information

Activity Available Online: To access the article, post-test, and evaluation online, go to <https://www.highmarksce.com/mscare>.

Target Audience: The target audience for this activity is physicians, physician assistants, nursing professionals, pharmacists, and other health care providers involved in the management of patients with multiple sclerosis (MS).

Learning Objectives:

- 1) Describe the characteristic factors of MS disease that can confound the identification of symptomatic urinary tract infection (UTI).
- 2) Distinguish appropriate, potentially appropriate, and inappropriate testing and treatment practices for the diagnosis and treatment of UTIs in patients with MS.

Accreditation Statement:



In support of improving patient care, this activity has been planned and implemented by the Consortium of Multiple Sclerosis Centers (CMSC) and Delaware Media Group. The CMSC is jointly accredited by the Accreditation Council for Continuing Medical Education (ACCME), the Accreditation Council for Pharmacy Education (ACPE), and the American Nurses Credentialing Center (ANCC), to provide continuing education for the healthcare team.

Physician Credit: The CMSC designates this journal-based activity for a maximum of 0.5 *AMA PRA Category 1 Credit(s)*[™]. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Nurse Credit: The CMSC designates this enduring material for 0.5 contact hour of nursing continuing professional development (NCPD) (none in the area of pharmacology).

Pharmacist Credit: This knowledge-based activity (UAN # JA4008165-9999-21-021-H01-P) qualifies for 0.5 contact hour (0.05 CEUs) of continuing pharmacy education credit.

Disclosures: **Francois Bethoux, MD**, Editor in Chief of the *International Journal of MS Care* (IJMSC), has served as Physician Planner for this activity. He has disclosed relationships with Springer Publishing (royalty); Qr8 (receipt of intellectual

property rights/patent holder); Biogen (receipt of intellectual property rights/patent holder, speakers' bureau); MedRhythms (consulting fee, contracted research); GW Pharmaceuticals, Genentech, Heliuss Medical Technologies, Osmotica, Ipsen (consulting fee); and Adamas Pharmaceuticals (contracted research). **Alissa Mary Willis, MD**, Associate Editor of IJMSC, has disclosed relationships with Greenwich Biosciences (consulting fee); Alexion (consulting fee, speakers' bureau, contracted research); Genentech (consulting fee, speakers' bureau); and Biogen, Bristol Myers Squibb (speakers' bureau). **Nicole C. Griffith, PharmD**, has disclosed no relevant financial relationships. **Brandon K. Hill, PharmD**, has disclosed no relevant financial relationships. **Myla D. Goldman, MD**, has disclosed relationships with Adamas Pharmaceuticals, Biogen, Brainstorm Cell Therapeutics Ltd, EMD Serono, Genentech, Greenwich Biosciences, Immunic, MedDay, and Sanofi Genzyme (consulting fees). **S. Ross Tingen, PharmD**, has disclosed a relationship with Novartis (advisory board). The staff at IJMSC, CMSC, and Delaware Media Group who are in a position to influence content have disclosed no relevant financial relationships. **Laurie Scudder, DNP, NP**, Continuing Education Director CMSC, has served as Reviewer for this activity. She has disclosed no relevant financial relationships. One peer reviewer for IJMSC has disclosed relationships with EMD Serono, Novartis, Bristol Myers Squibb, and Genentech (consulting fees). The other peer reviewer has disclosed no relevant financial relationships. *Note:* Financial relationships may have changed in the interval between listing these disclosures and publication of the article.

Method of Participation:

Release Date: October 1, 2021

Valid for Credit Through: October 1, 2022

In order to receive CME/NCPD/CPE credit, participants must:

- 1) Review the continuing education information, including learning objectives and author disclosures.
- 2) Study the educational content.
- 3) Complete the post-test and evaluation, which are available at <https://www.highmarksce.com/mscare>.

Statements of Credit are awarded upon successful completion of the evaluation and the post-test with a passing score of >70%. The post-test may be retaken if necessary. There is no fee to participate in this activity.

Disclosure of Unlabeled Use: This educational activity may contain discussion of published and/or investigational uses of agents that are not approved by the FDA. The CMSC and Delaware Media Group do not recommend the use of any agent

Note: Supplementary material for this article is available at ijmsc.org.

DOI: 10.7224/1537-2073.2021-034

© 2021 Consortium of Multiple Sclerosis Centers.

outside of the labeled indications. The opinions expressed in the educational activity are those of the faculty and do not necessarily represent the views of the CMSC or Delaware Media Group.

Disclaimer: Participants have an implied responsibility to use the newly acquired information to enhance patient outcomes and their own professional development. The information presented in this activity is not meant to serve as a guideline for

patient management. Any medications, diagnostic procedures, or treatments discussed in this publication should not be used by clinicians or other health care professionals without first evaluating their patients' conditions, considering possible contraindications or risks, reviewing any applicable manufacturer's product information, and comparing any therapeutic approach with the recommendations of other authorities.

Background: Patients with multiple sclerosis (MS) experience disease flares that can be precipitated by the presence of infection. Discerning asymptomatic bacteriuria from urinary tract infection (UTI) in patients with MS is complicated by lower urinary tract dysfunction, leading to potentially inappropriate antimicrobial use. In this study the antimicrobial treatment practices for positive urine cultures in patients with MS were evaluated.

Methods: In this single-center, retrospective study, positive cultures in patients with MS were included. The primary outcome was the proportion of patients appropriately treated with or without antimicrobial therapy. Secondary end points included antimicrobial selection and urinalysis positivity.

Results: Two hundred thirty-six cultures from 139 patients were evaluated. Treatment was inappropriate in 81 of 201 treated cultures (40%). Frequency, nocturia, dysuria, and foul-smelling urine were reported by patients in 54 (23%), 10 (4%), 25 (11%), and 14 (6%) cultures, respectively. The antimicrobial selected was too broad in spectrum for 35 of 201 (17%). Of those, fluoroquinolones were the agents used in 33 of 35 cases (94%). A urinalysis was sent in 203 cases (86%), with 197 (84%) positive for at least one predefined positivity criteria.

Conclusions: Urinalyses and urine cultures are performed frequently in patients with MS, often independent of symptoms. Patients with MS could be treated for asymptomatic bacteriuria at higher rates than the general population, and traditional urinary symptoms may not be appropriate indicators of infection. Empirical therapy for UTI is frequently used in this population, often resulting in inappropriate and/or too broad of antimicrobial therapy. *Int J MS Care.* 2021;23:234-238.

Multiple sclerosis (MS) is a progressive, neuro-inflammatory, demyelinating disease of the central nervous system.¹ The disease is incurable and affects approximately 2 million people worldwide.¹ The characteristic plaque development in the central nervous system in MS often leads to lower urinary tract dysfunction (LUTD), referred to as neurogenic bladder, in many patients with MS. Approximately 65% of patients with MS reported moderate-to-severe urinary tract symptoms in survey data published in 2007.¹⁻³

Patients with LUTD often have difficulty voiding and develop problems with incontinence, sometimes leading to the requirement for self-catheterization. Urinary stasis and catheter use for disease management puts patients with MS at an increased risk of urinary tract infections (UTIs), which can exacerbate disease activity and mimic an acute flare or disease progression.⁴ Also, LUTD creates difficulty in discerning asymptomatic bacteriuria (ASB) from UTI in patients with MS, and patients are frequently evaluated for UTI as a routine part of their MS disease management.^{4,5} Routine screening for UTI with urinalyses and urine cultures is often accompanied by empirical antimicrobial treatment.^{4,5} This patient population presents both diagnostic and treatment dilemmas for the practicing clinician, with essentially no definitive guidelines or recommended practices. Guidance that does exist encourages against the treatment of ASB in patients with MS but does not define how to distinguish ASB from UTI.^{4,6,7} In patients

From the Department of Pharmacy Practice, University of Illinois at Chicago College of Pharmacy, Chicago, IL, USA (NCG); Department of Pharmacy Clinical Services, University of Virginia Health, Charlottesville, VA, USA (BKH [now at GenMark Diagnostics]); Department of Neurology (MDG) and Department of Pharmacy (SRT), Virginia Commonwealth University Health System, Richmond, VA, USA. *Correspondence:* Brandon K. Hill, PharmD, 5964 La Place Court, Carlsbad, CA 92008, USA; e-mail: brandonkhill@gmail.com.

without an MS diagnosis, antimicrobial treatment of ASB has not been found to improve rates of symptomatic UTIs during the following 2 to 12 months, and neither has it been found to affect the rate of developing complications compared with no antimicrobial treatment.⁸ The purposes of this study were to evaluate the antimicrobial treatment practices of clinicians working in an outpatient MS clinic for patients with positive urine cultures and to assist in the discernment between symptomatic and asymptomatic presentation.

Methods

Study Setting

This was a retrospective cohort study conducted at an academic medical center's outpatient MS specialty clinic staffed by MS/neuroimmunology fellowship-trained neurologists or an MS-certified nurse practitioner. Adult patients (≥ 18 years old) with an MS diagnosis (*International Statistical Classification of Diseases, Tenth Revision* code G35) and a positive urine culture between January 1, 2017, and April 1, 2019, were included in the study. Urine cultures were required to grow 100,000 CFU/mL or more of an identifiable organism to be included in the study. Multiple cultures from the same patient were eligible for inclusion in the study, except for repeated cultures within 72 hours that remained consistent with the previous culture's identified organism(s). This study was approved by the Institutional Review Board for Health Sciences Research at the University of Virginia.

Definitions

Urinalysis positivity was evaluated based on the following four criteria: bacteria greater than or equal to moderate, white blood cell count greater than or equal to 10 per high-powered field, and positive leukocyte esterase and nitrite tests. Urinary symptoms included urgency, nocturia, or dysuria differing from baseline symptoms. The MS phenotype was defined by the provider and extracted from the clinical medical record. Flare or progression of MS was defined as worsening neurologic symptoms or disability, or specific documentation of "flare" or "progression" per the provider note at the time of evaluation. Definitions related to the appropriateness of antimicrobial therapy are detailed in Table S1, which is published in the online version of this article at ijmsc.org. Antimicrobial agent spectrum of activity was considered adequate if the organism on culture was susceptible to the agent selected, based on either susceptibility report or accepted standards per the Clinical and Laboratory Standards Institute.⁹ Antimicrobial agent spectrum of activity was considered too broad if the organism on culture was susceptible to a more preferred antimicrobial agent with a more narrow spectrum of activity.

End Points

The primary end point was the proportion of patients who were appropriately treated with or without antimicrobial therapy. Secondary end points included antimicrobial selection and spectrum of activity and urinalysis positivity.

Results

There were 277 positive urine cultures with 100,000 CFU/mL or more of an identified organism screened for inclusion in the study; 41 cultures were excluded for absence of an MS diagnosis. There were 236 positive cultures from 139 unique patients included in the study. Baseline characteristics of the population and baseline disease characteristics at the time of culture are outlined in Table 1. The mean age of the patients included at the time of first culture was 54 years, and 120 (86%) were female. Relapsing MS was the most common phenotype of MS reported, and the incidence of neurogenic bladder increased with repeated urine cultures in the same patients during the study.

Of the 236 cultures included in the study evaluation, 201 (85%) were treated. Based on the predefined criteria for appropriateness, 67 of the 201 cultures (33%) were treated appropriately, 49 (24%) were potentially appropriately treated, and 81 (40%) were treated inappropriately; four cultures were not able to be evaluated for appropriateness due to the retrospective nature of this study and unavailable data. Thirty-five of the 236 positive cultures (15%) were not treated with antimicrobials: 22 (63%) were appropriately untreated, six (17%) were potentially appropriately untreated, and one (3%) was considered inappropriately untreated; six cultures were not able to be evaluated for appropriateness due to the retrospective nature of this study and unavailable data.

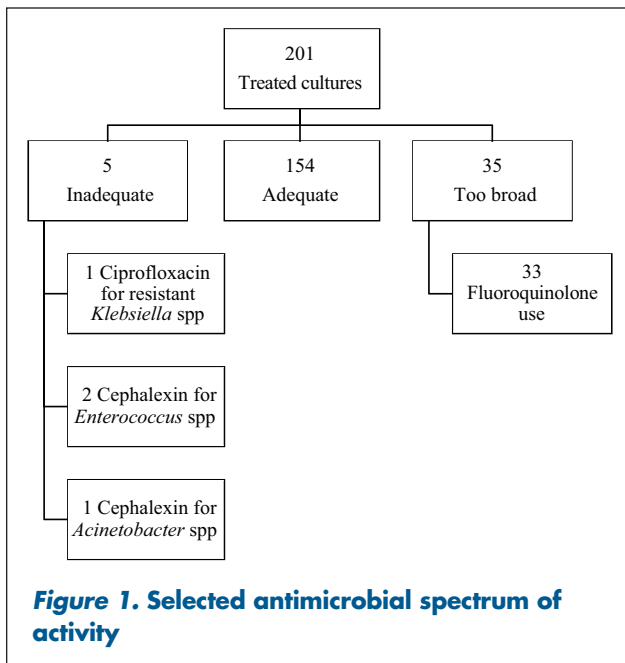
An evaluation of antimicrobial spectrum of activity is detailed in Figure 1. Dipstick urinalysis was performed before culture in 36 of the 236 positive urine cultures evaluated (15%), and dipstick plus microscopic urinalysis was obtained in 167 of these cases (71%). Urinalysis was not performed in 33 of the 236 positive cultures

Table 1. Baseline characteristics

Characteristic	Patient population (N = 139)	Per positive culture (N = 236)
Age, mean, y	54	NA
Female sex	120 (86)	NA
Type of MS (may overlap)		
RMS	74 (53)	119 (50)
PPMS	21 (15)	39 (17)
SPMS	27 (19)	41 (17)
EDSS score >6	40 (29)	73 (31)
Neurogenic bladder	18 (13)	45 (19)

Note: Data are given as number (percentage) unless otherwise indicated.

Abbreviations: EDSS, Expanded Disability Status Scale; MS, multiple sclerosis; NA, not applicable; RMS, relapsing MS; PPMS, primary progressive MS; SPMS, secondary progressive MS.



identified (14%). Of the 203 urinalyses performed, 197 (84%) met at least one of the four criteria evaluated for positivity per the predefined definitions. One hundred ten urinalyses (56%) were nitrite positive, 169 (86%) were leukocyte esterase positive, 137 (70%) demonstrated pyuria, and 143 (73%) demonstrated bacteriuria. Frequency, nocturia, dysuria, and foul-smelling urine were reported by patients in 54 (23%), 10 (4%), 25 (11%), and 14 (6%) cultures, respectively. A breakdown of positivity criteria met on urinalysis is detailed in Table 2.

Discussion

Given the symptoms of MS, patients with the disease are at increased risk of developing true UTIs and of being treated for ASB. Historically, the focus was on having a low threshold for the empirical treatment of UTIs in patients with MS due to concern for the negative repercussions of an untreated infection, such as

Table 2. Rates of positivity criteria met on urinalysis

Type of urinalysis	No. of positivity criteria ^a met on urinalysis				
	0	1	2	3	4
Dipstick (n = 36) ^b	1 (3)	20 (56)	15 (42)	NA	NA
Dipstick + microscopic (n = 167)	3 (2)	15 (9)	24 (14)	54 (32)	71 (43)

Note: Data are given as number (percentage).

Abbreviation: NA, not applicable.

^aPositivity criteria: bacteria greater than or equal to moderate, white blood cell count greater than or equal to 10 per high-powered field, positive leukocyte esterase test, positive nitrite test.

^bOnly two positivity criteria are possible on dipstick urinalysis.

worsening disease, and concern that the use of immunosuppression in the treatment of MS may put patients at increased risk of infection.^{6,10,11} However, growing concern for antimicrobial resistance and findings that the treatment of ASB, including in patients with spinal dysfunction, is not associated with beneficial outcomes has transitioned the focus to distinguishing symptomatic UTI from ASB in patients with MS before antimicrobial treatment.^{6,12,13} Unfortunately, previously published literature has not sufficiently defined UTI-associated symptoms in this unique patient population or reviewed prescribing practices.

The present study highlights an uncertainty regarding when bacteriuria warrants treatment versus when treatment will only lead to more health care exposure, more antimicrobial exposure, and potentially infection with more resistant bacteria. Further compounding potentially inappropriate treatment, empirical therapy for UTIs is frequently used in patients with MS and is often too broad for the organism identified. In this study population, 94% of agents considered to have a spectrum of activity too broad were due to empirical fluoroquinolone use. Fluoroquinolones have been associated with many adverse reactions, including central nervous system toxicity, that may be of particular concern in patients with MS.¹⁴

Urinalyses and urine cultures are performed as part of routine screening at many MS clinic visits, regardless of patient symptoms. Due to the LUTD associated with MS disease progression, the symptoms of UTIs may not be the same as in the general population. One study identified previous UTI, walking impairment, and foul-smelling urine as risk factors for UTI in the MS population, which is consistent with the common reporting of foul-smelling urine in the present study.⁵ Further research into MS-specific UTI risk factors and symptoms will help direct future therapy rather than evaluating patients based on traditional symptoms and self-reported UTIs. The Infectious Diseases Society of America guidelines for ASB largely avoid making recommendations for this patient population, and proposed treatment algorithms are based on the differentiation between asymptomatic versus symptomatic, categories that are not defined for the MS population.^{15,16} The patients in the present study were commonly treated at the time of their clinic appointment, often without signs or symptoms indicative of a UTI, which supports the hypothesis that patients with MS could be treated for ASB at higher rates than the general population.

There are some limitations to this study. This was a retrospective study conducted via manual medical record review. Most information was collected from nonstandardized clinic progress notes. Available information depended on the level of detail provided by the clinician, and when data were absent they were classified as “unknown.” In addition, there was often an inability to verify details provided with objective information. We were interested in the impact of corticosteroid and catheter use on the performance and treatment of UTIs in patients with MS, but given the retrospective nature of the study and the inconsistency among provider documentation, the specific rates of use were not discernable.

Future areas of study should focus on determining MS-specific symptoms of UTIs, the rate of urine culture performance in all patients with MS seen for routine appointments in a specified period, and whether refraining from treating positive urine cultures in patients with MS leads to subsequent seeding of infections, potentially with multidrug-resistant organisms, or other negative clinical repercussions. The empirical treatment of UTIs in patients with MS can be a key focus for antimicrobial stewardship programs, specifically in encouraging treatment until organism speciation to prevent the frequent use of broad-spectrum antibiotics.

In conclusion, patients with MS are often empirically treated for UTIs with broad-spectrum antimicrobials as a result of routine screening with urinalyses and urine cultures, regardless of the presence of specific infectious signs or symptoms. The current literature is unanimous in the recommendation that ASB should not be treated in patients with MS; however, no data are available to guide the diagnosis of symptomatic UTI. Further

research is needed to support development of guidance for the evaluation of MS-specific signs and symptoms of UTI. This information will aid in preventing unnecessary antimicrobial treatment and optimizing the care of patients with MS. □

Acknowledgments: The authors thank J. Cameron Crowe, PharmD, for his contribution to data collection.

Financial Disclosures: Dr Goldman reports personal compensation for consulting from Adamas Pharmaceuticals, Biogen, Brainstorm Cell Therapeutics Ltd, EMD Serono, Genentech, Greenwich Biosciences, Immunic, MedDay, and Sanofi Genzyme. Dr Tingen reports Novartis advisory board participation. The other authors declare no conflicts of interest.

Funding/Support: None.

Prior Presentation: These data were shared via platform presentation at the UNC Research in Education and Practice Symposium Virtual Meeting in June 2020 and at the IDWeek 2020 Virtual Annual Meeting in October 2020.

References

1. Reich DS, Lucchinetti CE, Calabresi PA. Multiple sclerosis. *N Engl J Med*. 2018;378:169-180.
2. Aharony SM, Lam O, Corcos J. Evaluation of lower urinary tract symptoms in multiple sclerosis patients: review of the literature and current guidelines. *Can Urol Assoc*. 2017;11:61-64.
3. Marrie RA, Cutter G, Tyry T, Vollmer T, Campagnolo D. Disparities in the management of multiple sclerosis-related bladder symptoms. *Neurology*. 2007;68:1971-1978.
4. Mahadeva A, Tanasescu R, Gran B. Urinary tract infections in multiple sclerosis: under-diagnosed and under-treated? a clinical audit at a large University Hospital. *Am J Clin Exp Immunol*. 2014;3:57-67.
5. Fitzgerald KC, Cassard LA, Fox SR, et al. The prevalence and utility of screening for urinary tract infection at the time of presumed multiple sclerosis relapse. *Mult Scler Relat Disord*. 2019;35:61-66.
6. Donze C, Papeix C, Lebrun-Frenay C, et al. Urinary tract infections and multiple sclerosis: recommendations from the French Multiple Sclerosis Society. *Rev Neurol*. 2020;176:804-822.
7. Medeiros Junior WLG, Demore CC, Mazaro LP, et al. Urinary tract infection in patients with multiple sclerosis: an overview. *Mult Scler Relat Disord*. 2020;46:102462.
8. Zalmanovici Trestioreanu A, Lador A, Sauerbrun-Cutler MT, Leibovici L. Antibiotics for asymptomatic bacteriuria. *Cochrane Database Syst Rev*. 2015;4:CD009534.
9. Clinical and Laboratory Standards Institute. *Performance Standards for Antimicrobial Susceptibility Testing*. 30th ed. CLSI supplement M100. Clinical and Laboratory Standards Institute; 2020.
10. Edlich RF, Westwater JJ, Lombardi SA, Watson LR, Howards SS. Multiple sclerosis and asymptomatic urinary tract infection. *J Emerg Med*. 1990;8:25-28.
11. O’Herlihy F, John NA, Li V, et al. Screening for urinary tract colonisation prior to corticosteroid administration in acute multiple sclerosis relapses: validation of an updated algorithm. *J Neurol Sci*. 2019;407:116456.
12. Phe V, Pakzad M, Curtis C, et al. Urinary tract infections in multiple sclerosis. *Mult Scler*. 2016;22:855-861.
13. Maghzi AH, Minagar A. Urinary tract infection in multiple sclerosis: a practical algorithm for a common problem. *Eur J Neurol*. 2013;20:408-409.
14. Golomb BA, Koslik HJ, Redd AJ. Fluoroquinolone-induced serious, persistent, multisymptom adverse effects. *BMJ Case Rep*. 2015;2015:bcr2015209821.
15. Nicolle LE, Gupta K, Bradley SF, et al. Clinical practice guideline for the management of asymptomatic bacteriuria: 2019 update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2019;68:1611-1615.
16. Nikseresh A, Salehi H, Foroughi AA, Nazeri M. Association between urinary symptoms and urinary tract infection in patients with multiple sclerosis. *Glob J Health Sci*. 2015;8:120-126.

PRACTICE POINTS

- Screening for urinary tract infections (UTIs) in patients with MS occurs frequently despite consensus in the literature that asymptomatic bacteriuria (ASB) should not be treated in this patient population.
- Traditional symptoms of UTIs are difficult to discern in patients with MS, and determination of MS-specific symptoms will aid in distinguishing symptomatic UTI from ASB in this population.
- Appropriate identification of ASB in patients with MS will curb inappropriate empirical antimicrobial therapy and the use of broad-spectrum antimicrobials for the treatment of suspected UTIs.