Clinical Infectious Diseases

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Association of Adverse Events With Antibiotic Treatment for Urinary Tract Infection

Anne M. Butler,[1,2] Michael J. Durkin,[1] Matthew R. Keller,[1] Yinjiao Ma,[1] William G. Powderly,[1] and Margaret A. Olsen[1,2]

[1]Division of Infectious Diseases, Department of Medicine, Washington University School of Medicine, St Louis, Missouri, USA; and [2]Division of Public Health Sciences, Department of Surgery, Washington University School of Medicine, St Louis, Missouri, USA

Background. Little is known about the relative harms of different antibiotic regimens prescribed to treat uncomplicated urinary tract infection (UTI). We sought to compare the risk of adverse events associated with commonly used oral antibiotic regimens for the outpatient treatment of uncomplicated UTI.

Methods. Using data from the IBM® MarketScan® Commercial Database, we identified 1 169 033 otherwise healthy, nonpregnant women aged 18–44 years with uncomplicated UTI who initiated an oral antibiotic with activity against common uropathogens from 1 July 2006 to 30 September 2015. We used propensity score–weighted Kaplan-Meier methods and Cox proportional hazards regression models to estimate the association between antibiotic agent and adverse events.

Results. Of 2 first-line agents, trimethoprim-sulfamethoxazole (vs nitrofurantoin) was associated with higher risk of several adverse drug events including hypersensitivity reaction (hazard ratio, 2.62; 95% confidence interval, 2.30–2.98), acute renal failure (2.56; 1.55–4.25), skin rash (2.42; 2.13–2.75), urticaria (1.37; 1.19–1.57), abdominal pain (1.14; 1.09–1.19), and nausea/vomiting (1.18; 1.10–1.28), but a similar risk of potential microbiome-related adverse events. Compared with nitrofurantoin, non–first-line agents were associated with higher risk of several adverse drug events and potential microbiome-related adverse events including non–*Clostridium difficile* diarrhea, *C. difficile* infection, vaginitis/vulvovaginal candidiasis, and pneumonia. Treatment duration modified the risk of potential microbiome-related adverse events.

Conclusions. The risks of adverse drug events and potential microbiome-related events differ widely by antibiotic agent and duration. These findings underscore the utility of using real-world data to fill evidentiary gaps related to antibiotic safety.

Keywords. administrative data; antibiotics; comparative safety; adverse events; urinary tract infection.

The majority of antibiotics are prescribed in the outpatient setting [1, 2], and uncomplicated urinary tract infection (UTI) is among the most common indications for antibiotics [3, 4]. Clinical practice guidelines for the treatment of uncomplicated UTI in women recommend empirical antibiotic therapy [3]. Nitrofurantoin and trimethoprim-sulfamethoxazole (TMP/SMX) are recommended as first-line agents; fluoroquinolones and β-lactams are non–first-line agents [3]. These recommendations are based on efficacy in randomized clinical trials (RCTs), rates of in vitro resistance among urinary pathogens, ecological adverse effects (eg, the selection of drug-resistant organisms and colonization or infection with multidrug-resistant organisms), and adverse effects [3]. The first-line agents are advantageous because of high efficacy and low propensity for ecological adverse effects. Additionally, for nitrofurantoin, resistance among uropathogens is uncommon [5–7]. TMP/SMX has long been considered a "workhorse" antibiotic for UTI therapy; however, resistance rates to TMP/SMX may be rising, and tolerability remains problematic. Fluoroquinolones are highly efficacious but have a high propensity for uropathogen resistance; guidelines suggest reserving them for important uses other than uncomplicated UTI [3, 8]. β-Lactam agents, particularly amoxicillin and ampicillin (AMX/AMP), have lower efficacy and a higher prevalence of antibiotic resistance versus other UTI antibiotics [3]. However, the evidence base remains limited regarding the relative benefits and harms of various antibiotic regimens for UTI therapy; consequently, clinical equipoise exists regarding selection of agent, as demonstrated by wide variation in prescribing practices [9–12].

Estimates on the comparative safety of antibiotic agents to treat uncomplicated UTI remain limited, despite the importance for informing guideline development and antibiotic prescribing. Existing evidence is predominantly from RCTs, which are limited by small sample size, short follow-up, heterogeneous study populations, and wide variation in duration of antibiotic prescriptions. Additionally, RCTs only compare antibiotic agents in limited combinations (eg, ciprofloxacin vs amoxicillin-clavulanate) [3]. Meta-analyses of RCTs demonstrate increased risk of skin rash (TMP/SMX vs nitrofurantoin; β-lactams vs fluoroquinolones) and a similar risk of diarrhea

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Correspondence: A. M. Butler, Division of Infectious Diseases, John T. Milliken Department of Medicine, Washington University School of Medicine, 4523 Clayton Ave, CB 8051-043-0015, St Louis, MO 63110, USA (anne.butler@wustl.edu).

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VIEWPOINTS

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Envisioning Future Urinary Tract Infection Diagnostics

Robin Patel,[1,2] Christopher R. Polage,[3] Jennifer Dien Bard,[4,5] Larissa May,[6] Francesca M. Lee,[7] Valeria Fabre,[8] Mary K. Hayden,[9] Sarah D.B. Doernberg,[10] David A. Haake,[11] Barbara W. Trautner,[12] Larissa Grigoryan,[13] Ephraim L. Tsalik,[14] and Kimberly E. Hanson[15]; on behalf of the Antibacterial Resistance Leadership Group and the Infectious Diseases Society of America

[1]Division of Clinical Microbiology, Mayo Clinic, Rochester, Minnesota, USA; [2]Division of Infectious Diseases, Department of Medicine, Mayo Clinic, Rochester, Minnesota, USA; [3]Department of Pathology, Duke University Health System, Durham, North Carolina, USA; [4]Department of Pathology and Laboratory Medicine, Children's Hospital Los Angeles, Los Angeles, California, USA; [5]Keck School of Medicine, University of Southern California, Los Angeles, California, USA; [6]Department of Emergency Medicine, University of California-Davis Health, Sacramento, California, USA; [7]Division of Infectious Diseases, Department of Pathology and Internal Medicine, The University of Texas Southwestern Medical Center, Dallas, Texas, USA; [8]Division of Infectious Diseases, Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA; [9]Division of Infectious Diseases, Division of Internal Medicine, Rush Medical College, Chicago, IL, USA, [10]Division of Infectious Disease, Department of Medicine, University of California San Francisco, San Francisco, California, USA; [11]Infectious Diseases Section, VA Greater Los Angeles Healthcare System, and the Division of Infectious Diseases, Department of Medicine, the David Geffen School of Medicine at UCLA, Los Angeles, California, USA; [12]Center for Innovations in Quality, Effectiveness and Safety, Michael E. DeBakey Veterans Affairs Medical Center and Department of Medicine, Baylor College of Medicine, Houston, Texas, USA; [13]Center for Innovation in Quality Effectiveness and Safety, Michael E. DeBakay Veterans Affairs Medical Centetr; and and 15 Department of Family and Community Medicine, Baylor College of Medicine, Houston, Texas, USA; [14]Duke University Center for Applied Genomics and Precision Medicine, Durham, NC, USA; Durham Veterans Affairs Health Care System, Durham, North Carolina, USA; and [15]Department of Internal Medicine and Department of Pathology, University of Utah, Salt Lake City, Utah, USA

Urinary tract infections (UTIs) are among the most common bacterial infections in the United States and are a major driver of antibiotic use, both appropriate and inappropriate, across healthcare settings. Novel UTI diagnostics are a strategy that might enable better UTI treatment. Members of the Antibacterial Resistance Leadership Group Laboratory Center and the Infectious Diseases Society of America Diagnostics Committee convened to envision ideal future UTI diagnostics, with a view towards improving delivery of healthcare, patient outcomes and experiences, and antibiotic use, addressing which types of UTI diagnostics are needed and how companies might approach development of novel UTI diagnostics.

Keywords. urinary tract infection; UTI; laboratory diagnosis; diagnostics.

Urinary tract infections (UTIs) are among the most common bacterial infections in the United States and are a major driver of antibiotic use, both appropriate and inappropriate, across healthcare settings. UTI treatment has become complex because of antibacterial resistance; one-quarter of urinary tract isolates of *Escherichia coli* in the United States in 2017 were resistant to fluoroquinolones and one-third to trimethoprim-sulfamethoxazole [1], agents with historically predictable activity against *E coli*. As a result, more broad-spectrum antibiotics are being used to treat UTIs, contributing to selection of further antibiotic resistance (Figure 1). This also exposes patients to adverse consequences, such as allergies, side effects, *Clostridioides difficile* infection, and microbiome disturbances [2]. Compounding the situation, many patients receive unnecessary antibiotics for abnormal urinalyses (eg, pyuria, bacteriuria) [3] or positive urine cultures (asymptomatic bacteriuria/bladder colonization) [4] in the setting of nonspecific symptoms (eg, fatigue) [5], without true UTI. Treatment directed at UTIs when no treatment is needed, alongside treatment with unnecessarily broad-spectrum antibiotics, are fueling antibiotic resistance, which is "one of the biggest public health challenges of our time" [6].

Diagnostic tests for UTIs have remained largely unchanged over the past half-century. Urine culture is the most common microbiologic test performed in the outpatient setting and remains the gold standard test for diagnosis of UTI despite its relatively long time to results, limited specificity for UTI requiring treatment, and bias toward isolation of classical uropathogens. 16S ribosomal RNA gene sequencing studies have revealed a lower urinary tract microbiome that is not detectable by routine culture methods [7]. Whether microbiome dysbiosis is associated with UTI is an area of active research. In addition, viable but nonculturable uropathogenic *E coli* (missed by standard laboratory evaluation) has been proposed as a potential cause of recurrent UTI in some cases [8]. Urinalysis for evaluation of pyuria (various cutoffs used [eg, >10 white blood cells/mm^3 [9]]) is also an imperfect test with limited positive predictive value [10]. Alternatively, a normal urinalysis can be useful for excluding UTI as the cause of symptoms in otherwise healthy adults [11]. Other tests used to diagnose UTIs include dipstick leukocyte esterase testing, other urine biochemical tests (eg, testing for nitrites), and urine Gram stain (read by a machine or person), with none being ideal.

Innovations in diagnostic testing for other infectious diseases, such as pneumonia, bloodstream infection, gastroenteritis, and most recently, coronavirus disease 2019, are being delivered at rapid rates. Many diagnostic companies have indicated an interest in developing improved UTI tests. Although certainly needed, defining the parameters of what will be most

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Correspondence: R. Patel, Division of Clinical Microbiology, Mayo Clinic, 200 First Street SW, Rochester, MN 55905 (patel.robin@mayo.edu).

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The utility of syndromic respiratory pathogen panels: the premise of flexible and customizable approaches

Julie M. Norton,[1] Gaby Dashler,[2] Eili Klein,[2,3] Heba H. Mostafa[1]

AUTHOR AFFILIATIONS See affiliation list on p. 10.

ABSTRACT Extended respiratory panels have been limited to specific patient populations due to cost and inconclusive clinical utility. Customizing syndromic panels offers a way to balance clinical utility and available resources. In this study, we evaluated strategies and assessed the value of flexible, customized respiratory panels. A total of 200 specimens from symptomatic patients (December 2023 to September 2024), negative for SARS-CoV-2/Flu/RSV, were tested with the LIAISON PLEX Respiratory Flex Assay—an extended respiratory panel that offers flexibility in target selection. The study assessed additional diagnoses, correlations with institutional and state-wide pathogen prevalence, and whether customizable panels could optimize diagnostic yield. Sixty-two samples (31%) negative for SARS-CoV-2/Flu/RSV tested positive for other targets, primarily rhinovirus/enterovirus (60%), correlating with local and state prevalence. Weighted estimates for 18,373 symptomatic patients during the study period modeled a prevalence of 14.3% for rhinovirus/enterovirus, followed by HPIV-3, adenovirus, and coronavirus. During the study period, 6% of patients received the standard of care extended respiratory panel order after a negative SARS-CoV-2/Flu/RSV result, duplicating SARS-CoV-2/Flu/RSV testing. Leveraging a flexible feature could have resulted in an estimated staff time reduction of 5,545 minutes for a second swab collection and running a second test, in addition to the cost of running two different panels during a single encounter. Local respiratory pathogen prevalence data can guide target selection in customized panels. The inclusion of high-prevalence targets can increase the likelihood of diagnosis from 12% to nearly 30%. Flexibility in customizing targeted pathogen panels could enhance diagnostic value while conserving institutional resources.

IMPORTANCE Rapid and accurate identification of pathogens causing respiratory tract infections can aid in guiding treatment decisions, reducing healthcare costs, and supporting real-time surveillance of infectious diseases within a community. Limitations of clinical utility beyond SARS-CoV-2/Flu/RSV are primarily driven by cost and the lack of specific treatment options. There is a need to balance clinical gaps with testing cost and diagnostic stewardship. In this study, we evaluated the utility of flexible, customized respiratory viral panels and reportable targets within a broader set of available targets in an extended respiratory panel.

KEYWORDS syndromic panels, respiratory panels, respiratory viral testing

Syndromic respiratory panels are molecular-based diagnostics that detect and differentiate between respiratory pathogens responsible for respiratory tract infections. Panels of 3–5 targets (e.g., SARS-CoV-2/Flu/RSV) are more commonly used, particularly during the respiratory or influenza season (1). Large panels of 12 or more targets have become a standard of care for specific patient populations, including immunocompromised individuals (2). Current procedure terminology (CPT) codes that

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Address correspondence to Eili Klein, eklein@jhu.edu, or Heba H. Mostafa, hmostaf2@jhmi.edu.

Julie M. Norton and Gaby Dashler contributed equally to this article. The author order was randomly selected.

Eili Klein and Heba H. Mostafa contributed equally to this article.

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