Diagnostic Microbiology and Infectious Disease 94 (2019) 371–377

Contents lists available at ScienceDirect

Diagnostic Microbiology and Infectious Disease

journal homepage: www.elsevier.com/locate/diagmicrobio

Clinical Studies

# Rapid diagnostic testing in the management of urinary tract infection: Potentials and limitations☆,☆☆

Melissa A. Markowitz [a,*], Gabriel K. Monti [a,b], Ja-Hong Kim [a], David A. Haake [a]

[a] Department of Urology, UCLA Medical Center, David Geffen School of Medicine at UCLA, Los Angeles, CA 90095, United States
[b] John A. Burns School of Medicine at the University of Hawai'i at Mānoa, Honolulu, HI 96813, United States

ARTICLE INFO

*Article history:*
Received 9 January 2019
Received in revised form 31 January 2019
Accepted 24 February 2019
Available online 5 March 2019

*Keywords:*
molecular diagnostics
urinary traction infection
body fluid analysis
antibiotic resistance

ABSTRACT

Urine culture and sensitivity (C&S) remains the gold standard diagnostic for urinary tract infections (UTI). To reduce the use of inaccurate or broad-spectrum empiric antimicrobials, rapid identification and quantification (IDQ) and antimicrobial susceptibility testing (AST) with results within 30 and 150 min, respectively, are under development. To assess the impact of rapid diagnostics, five UTI vignettes were constructed, and ninety-one United States physicians were surveyed regarding their diagnostic, management, and antimicrobial choices before and after IDQ and AST results. Rapid diagnostics increased the postponement of antimicrobial therapy pending AST results from 16% to 38% and 5% to 54% in Vignettes 1 and 2 and reduced the use of ineffective antibiotics from 41% to 0% and 69% to 0% in Vignettes 2 and 4. Rapid diagnostics increased the use of narrow spectrum agents in the five vignettes, indicating its potential to revitalize physician responsibility in antimicrobial stewardship.


## 1. Introduction

Patients with urinary tract infection (UTI) are cared for by physicians across healthcare settings and specialties, accounting for over 10.5 million ambulatory visits in 2007 and 2 million hospital admissions in 2005 (Schappert and Rechtsteiner 2011). Self-reports of UTI in women 18 years or older reveal an even higher annual incidence of UTI in 10.8% of women, with a 60.4% calculated lifetime risk (Foxman et al. 2000). The associated costs of UTI diagnosis and management are estimated to be between $1.6 and $2.14 billion annually in the United States (U.S.) (Foxman 2002; Brown et al. 2005).

Despite the impact of UTIs on healthcare finances and patient well-being, physician management remains inconsistent. The U.S. Food and Drug Administration (FDA) continues to issue black box warnings to avoid prescribing fluoroquinolones in uncomplicated UTI, due to their association with peripheral neuropathy, tendon rupture, and mental health side effects (Food and Drug Administration, U.S. 2018). Nevertheless, U.S. studies reveal that physicians continue to overprescribe second and third-tier antimicrobials, such as ciprofloxacin, for UTI treatment (Zatorski et al. 2016; Grover et al. 2007). In Europe, a 2010 focus group showed that physicians fail to adhere to UTI guidelines due in part to inadequate microbiological testing and follow up (Lugtenberg et al. 2010). In the U.S., the diversity of UTI management approaches may be secondary to a lack of uniformity among U.S. medical subspecialty guidelines on the management, as well as prevention, of acute and recurrent UTIs, leading physicians to draw individualized conclusions on antimicrobial choice and UTI prophylaxis, rather than follow validated recommendations (Markowitz et al. 2018; Smith et al. 2018).

Limitations in current diagnostic technologies are a barrier to accurate and effective UTI management. Standard culture and sensitivity (C&S) assays take 48–72 h to return clinically actionable results, resulting in a delay that promotes the use of empiric antimicrobial therapy. Even when prior urine culture results are available, there is only a 57% correspondence with previously identified uropathogens if 4–8 weeks have elapsed between infections (MacFadden et al. 2014). Culture results are even less predictive if there is a longer time course between infections. Due to the delay between patient presentation and culture results, overly aggressive, ineffective, and unnecessary treatment for UTI frequently occurs, as the CDC estimates that 50% of antimicrobial prescriptions used in the outpatient setting are inappropriate (Measuring Outpatient Antibiotic Prescribing 2017).

Rapid diagnostic tools are urgently needed to improve the management of UTI. One study found that the presence of one or more symptoms of UTI (i.e. dysuria, frequency) was associated with only a 50% pre-test probability of UTI (Bent et al. 2002). Furthermore, history taking, physical exam and dipstick analysis are unable to rule out a

☆ Author contributions: All authors equally contributed to this paper with conception and design of the study, literature review and analysis, drafting and critical revision and editing, and approval of the final version.
☆☆ Potential conflicts of interest: Dr. David A. Haake is an inventor on relevant intellectual property and owns shares in MicrobeDx, Inc. and Qvella, Inc. Dr. Ja-Hong Kim received honorarium from MicrobeDx, Inc. Gabriel Monti was a previous employee of MicrobeDx, Inc.

* Corresponding author. Tel.: +1-714-858-1722.
*E-mail address:* mmarkowitz@mednet.ucla.edu (M.A. Markowitz).

https://doi.org/10.1016/j.diagmicrobio.2019.02.019
0732-8893/

UTI when a woman presents with one or more symptom of a UTI (Bent et al. 2002). New technologies for the rapid testing of urine specimens are emerging, including flow cytometry and electrochemical rRNA biosensors, which provide bacterial identification in less than 45 min, with up to a 96% correlation with C&S results (Mach et al. 2011; Scott et al. 2018; Davenport et al. 2017). Providing physicians with rapid data about the nature of a patient's infection (i.e. species identification, quantification, and antimicrobial susceptibility panel) has the potential to pivot UTI management from empiric guesswork to precision medicine. Herein, we describe results of a survey of physicians from various specialties examining the impact of rapid diagnostic testing on the clinical care of patients with UTI. To our knowledge, this is the first study to detail the impact of rapid diagnostics on physician management choices in standardized, simulated UTI scenarios.

## 2. Methods

This survey is part of a UCLA IRB-approved study of clinician management of uncomplicated and complicated UTI using urine C&S, as compared to rapid identification and quantification (IDQ) and antimicrobial susceptibility testing (AST).

### 2.1. Survey design

Five UTI vignettes were developed that are characteristic of common patient presentations in our UCLA urology clinic subspecializing in UTI management. The clinical vignettes are outlined in Table 1. Each vignette consists of three segments: Patient history and physical exam, rapid IDQ results, and rapid AST results. Following each of

**Table 1**
UTI clinical vignettes

| Vignette | Patient history and physical exam (PE) | Rapid IDQ result | Rapid AST result |
|---|---|---|---|
| 1 | 24-year-old female presenting with dysuria, urinary frequency and urgency<br>• Physical Exam: normotensive, afebrile, no costovertebral angle (CVA) tenderness<br>• Dipstick Result: (+) leukocyte esterase (LE) | >100,000 CFU/mL *E. coli* | ○ Ampicillin: **Resistant**<br>○ Ceftriaxone: Susceptible<br>○ Ciprofloxacin: Susceptible<br>○ Nitrofurantoin: Susceptible<br>○ First-generation cephalosporins: Susceptible<br>○ Fosfomycin: Susceptible<br>○ Trimethoprim/sulfamethoxazole: Susceptible |
| 2 | 46-year-old female with recurrent UTI presenting with urinary frequency<br>• Physical Exam: normotensive, afebrile, no CVA tenderness<br>• Dipstick Result: (+) leukocyte esterase (LE), (+) nitrite, (+) protein<br>• Most recent culture (6 months ago):<br>>100,000 CFU/mL *E. coli*<br>○ Ampicillin: **Resistant**<br>○ Ceftriaxone: Susceptible<br>○ Ciprofloxacin: Susceptible<br>○ Gentamicin: Susceptible<br>○ Nitrofurantoin: Susceptible<br>○ First-generation cephalosporins: Susceptible<br>○ Piperacillin-Tazobactam: Susceptible<br>○ Trimethoprim/sulfamethoxazole: **Resistant** | >100,000 CFU/mL *E. coli* | ○ Ampicillin: **Resistant**<br>○ Ceftriaxone: Susceptible<br>○ Ciprofloxacin: **Resistant**<br>○ Nitrofurantoin: Susceptible<br>○ First-generation cephalosporins: Susceptible<br>○ Fosfomycin: Susceptible<br>○ Trimethoprim/sulfamethoxazole: **Resistant** |
| 3 | 71-year-old female with recurrent UTI and immunosuppression from daily methotrexate use presenting with urinary frequency, urgency and pelvic pain<br>• Physical Exam: normotensive, afebrile, non-specific back pain, CVA tenderness cannot be ruled out<br>• Dipstick: (+) leukocyte esterase (LE)<br>• Most recent culture (3 months ago): >100,000 CFU/mL *Klebsiella pneumoniae*<br>o Amikacin: Susceptible<br>o Ampicillin: **Resistant**<br>o Ceftriaxone: Susceptible<br>o Ciprofloxacin: Susceptible<br>o Gentamicin: Susceptible<br>o Nitrofurantoin: Susceptible<br>o First-generation cephalosporins: Susceptible<br>o Piperacillin-Tazobactam: Susceptible<br>o Trimethoprim/sulfamethoxazole: Susceptible | No bacteria detected | N/A |
| 4 | 53-year-old female with recurrent UTI presenting with dysuria, urinary urgency, frequency and malaise × 3 days<br>• Physical Exam: normotensive, febrile (101.3 F), (+) CVA tenderness<br>• Dipstick: (+) LE, (+) nitrite<br>• No past cultures available | >100,000 CFU/mL *E. coli* | ○ Ampicillin: **Resistant**<br>○ Ceftriaxone: **Resistant**<br>○ Ciprofloxacin: **Resistant**<br>○ Nitrofurantoin: Susceptible<br>○ First-generation cephalosporins: **Resistant**<br>○ Fosfomycin: Susceptible<br>○ Trimethoprim/sulfamethoxazole: Susceptible<br>○ Ertapenem: Susceptible<br>○ Piperacillin-Tazobactam: Susceptible |
| 5 | 33-year-old female with prior UTI presenting with urinary frequency, urgency and very bothersome dysuria × 2 days<br>• Physical Exam: normotensive, afebrile, no costovertebral angle (CVA) tenderness<br>• Dipstick: (+) leukocyte esterase (LE)<br>• Most recent culture (1 year ago): >100,000 CFU/mL *E. coli*<br>○ Ampicillin: **Resistant**<br>○ Ceftriaxone: Susceptible<br>○ Ciprofloxacin: Susceptible<br>○ Gentamicin: Susceptible<br>○ Nitrofurantoin: Susceptible<br>○ First-generation cephalosporins: Susceptible<br>○ Piperacillin-Tazobactam: Susceptible<br>○ Trimethoprim/sulfamethoxazole: **Resistant** | No bacteria detected | N/A |

the three segments, questions were presented involving: (1) patient management, (2) antimicrobial treatment options and (3) physician comfort level with rapid UTI diagnostics. Of note, participants were unable to skip questions or alter their previous responses, although they could stop participating in the survey at any time. A demographic questionnaire on physician background, including level of training, number of years in practice, and type of practice was included at the beginning of each survey.

### 2.2. Survey administration

Surveys were distributed and completed from August 2017 to March 2018 both in-person and online by U.S. physicians who treat UTI. Physicians in emergency medicine, family medicine, infectious disease, internal medicine, obstetrics and gynecology, and urology were recruited by multiple means. The research team contacted UCLA department chairs and requested that they post a link to the survey on their departmental listserv. The survey was also posted on social media platforms for physicians in the above specialties. Lastly, the survey was distributed to physicians at departmental conferences. In all modes of distribution, participation in the survey was voluntary and anonymous, with no direct benefit to the physician. No prior knowledge of rapid UTI diagnostics was required for participation the in study, as a brief introduction was provided in the survey on the sensitivity and time course of IDQ and AST. The survey detailed that rapid identification testing detected bacteria at a level of ≥10,000 CFU/mL with an accuracy of >96% compared to traditional clinical microbiology.

### 2.3. Statistical analysis

All responses were coded via the Survey Monkey platform and exported electronically. These data were entered into Stata/IC for statistical analyses with *P* values from categorical data computed using the Fisher's exact test and *P* values from numerical data computed using the 2-tailed *t* test. Differences in antibiotic selection between specialties were calculated by chi-square analysis; however, because of small sample sizes, pair-wise statistics within specialties were not performed.

Several analyses examined whether antibiotic usage was considered "within guidelines" or "outside of guidelines," necessitating definition of the antimicrobial agents that were recommended for the specific vignette. These definitions were derived from Infectious Disease Society of America (IDSA) guidelines on the use of therapeutic agents in uncomplicated cystitis and acute pyelonephritis (Gupta et al. 2011). For the purposes of these analyses, "within guideline" therapy for uncomplicated cystitis was considered to be trimethoprim/sulfamethoxazole, nitrofurantoin, Fosfomycin, or pivmecillinam, and therapy for acute pyelonephritis was outlined as ciprofloxacin, trimethoprim/sulfamethoxazole, ceftriaxone, or an aminoglycoside.

## 3. Results

### 3.1. Demographic information

The clinical vignette survey yielded responses from ninety-one U.S. physicians representing a variety of specialties, levels of training, and clinical settings. Of all respondents, 52% were trainees (residents and fellows), 42% were attending physicians, and 5% were physicians in private practice. Most respondents (69%) had been in practice 10 years or less, while only 10% were in practice for 11–15 years and 21% for greater than 15 years. Physicians specializing in infectious disease (21%), urology (21%), and internal medicine (23%) comprised the majority of respondents, with the remaining 35% comprised of emergency medicine, family medicine, obstetrics and gynecology, and other subspecialties; 67% of respondents were based in an academic setting, while 13% were affiliated with a county healthcare facility and 11% with a community clinic. Physicians practicing at a single academic center in California comprised the majority of respondents (84.6%), while physicians sampled from out of state (15.4%) resided in Indiana, Iowa, Massachusetts, Michigan, Minnesota, Montana, Nevada, North Carolina, Oregon, Rhode Island, Tennessee, and Washington.

### 3.2. UTI vignettes

In the case of acute, uncomplicated cystitis, the majority of physicians chose to treat empirically and send urine for culture and sensitivity (Table 2). When a uropathogen with broad susceptibility to antibiotics was revealed, as in Vignette 1, 74% of treatment choices were unchanged. However, when rapid IDQ and AST results revealed an extended-spectrum beta-lactamase (ESBL) producing *E. coli* strain resistant to ciprofloxacin, cephalexin, and ceftriaxone, change in management was seen in 78% of respondents with effective therapy increasing from 31% to 100% (Fig. 1). Additionally, when AST results were

**Table 2**
**UTI vignettes: management.** Choice of antibiotic therapy, diagnostic testing and other management options are detailed following history and physical (H&P) and identification and quantification (IDQ) results. [1]Following IDQ results, the language of this question changed from "C&S" to "Rapid AST," as respondents now chose if they would like to send for rapid AST, rather than C&S testing. [2]Vignettes 3 and 5 revealed no bacterial growth on IDQ, negating the need for AST testing. Respondents were prompted with a different set of answer choices for further diagnostic workup or symptomatic management in these cases.

| | Vignette 1 – Uncomplicated cystitis | | Vignette 2 – Recurrent UTI | | Vignette 3 – immuno-suppressed, no UTI | | Vignette 4 – Pyelonephritis | | Vignette 5 – urethritis, no UTI | |
|---|---|---|---|---|---|---|---|---|---|---|
| Action Chosen | H&P | IDQ | H&P | IDQ | H&P | IDQ | H&P | IDQ | H&P | IDQ |
| Treat with an antibiotic and not send urine for culture and sensitivity (C&S)[1] | 31% | 33% | 10% | 9% | 0% | | 1% | 4% | 13% | |
| Treat with an antibiotic and send urine for C&S[1] | 52% | 29% | 84% | 37% | 91% | | 95% | 79% | 66% | |
| Send urine for C&S[1] and postpone treatment pending results | 5% | 31% | 1% | 43% | 5% | | 2% | 13% | 9% | |
| Send urine for C&S[1], prescribe Pyridium and postpone antibiotic treatment pending results | 11% | 7% | 4% | 11% | 3% | | 0% | 3% | 10% | |
| Other (please specify) | 1% | 0% | 0% | 0% | 1% | | 1% | 0% | 1% | |
| Choose all that apply[2] | | | | | | | | | | |
| Treat with an antibiotic | | | | | | 19% | | | | 13% |
| Send urine for culture and sensitivity (C&S) to detect low-count bacteriuria | | | | | | 52% | | | | 47% |
| Further diagnostic testing for pelvic pain | | | | | | 55% | | | | 62% |
| Prescribe Pyridium to relieve symptoms | | | | | | 31% | | | | 43% |
| Postpone antibiotic treatment pending results | | | | | | 33% | | | | 40% |
| Other (please specify) | | | | | | 0% | | | | 0% |

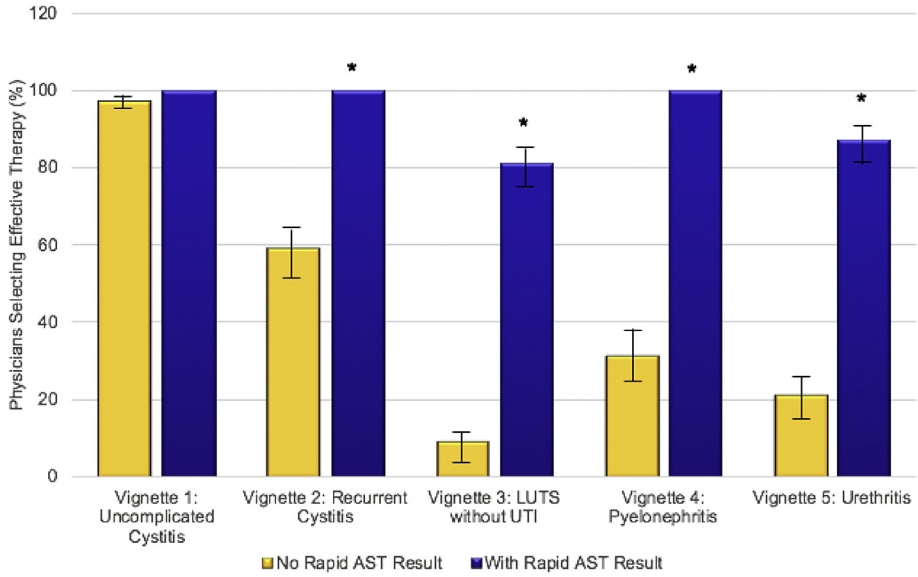


**Fig. 1. Selection of Effective Therapy Before and after AST results.** Effective therapy is based on IDSA guidelines for Vignettes 1, 2 and 4, and the selection of no antibiotic therapy in Vignettes 3 and 5, in which a uropathogen is not present. The standard error for each percentage within the binary sample is indicated with error bars. *The two-tailed Fisher exact test is significant at the 0.05 level.

revealed in the case of a recurrent UTI, effective therapy increased from under 59% to 100% (Fig. 1).

Antibiotic selection adherent to IDSA guideline was noted in 82% of the empiric selections in the uncomplicated cystitis case (Table 3). However, almost all of the antibiotics prescribed by trainees (residents and fellows) were guideline compliant, compared to only 66% of those prescribed by attending physicians. This divergence in treatment practices continued in the case of pyelonephritis, as significantly fewer attending physicians selected trimethoprim-sulfamethoxazole therapy compared to trainees ($P < 0.05$). Choice of an empiric antibiotic also varied significantly between physicians in primary care, infectious disease, urology and emergency medicine in the case of recurrent UTI and pyelonephritis, with $P$ values of 0.017 and 0.001, respectively (Table 4).

Vignettes 3 and 5 outlined cases in which no bacteria was present in urine specimens. After viewing a negative rapid IDQ test in these cases, a 72% and 66% reduction in antibiotic use was noted, respectively, significantly reducing the rate of unnecessary antimicrobial prescriptions (Fig. 1, Table 2).

Physicians felt very comfortable with rapid IDQ and AST testing in acute, uncomplicated cystitis cases, with confidence scores of 9.1 +/- 1.9 (scale of 0-10) for waiting 30 min after specimen collection for IDQ results and 8.6 +/- 2.3 for waiting 150 min for AST results prior to prescribing an antibiotic. However, only half of respondents (52.3%) were confident (comfort rating of 6-10) in deferring antibiotic therapy in an immunocompromised patient after receiving a negative rapid IDQ test, while many were neutral (22.1%) (comfort level of 5) or less confident (25.6%) (comfort rating of 0–4).

## 4. Discussion

While our study is limited by its small sample size, and heavily weighted toward California physicians in a single academic institution, the results of this study indicate that rapid diagnostic testing is valuable in many presentations of UTI. Rapid IDQ and AST increased the use of accurate, narrow-spectrum antimicrobials in cases of recurrent UTI and UTIs caused by ESBL producing *E. coli* strains. Rapid IDQ and AST allowed the patient to begin a successful treatment regimen for their uropathogen within 150 min of presentation, as opposed to 2 to 3 days later, as in the case of urine C&S. Respondents indicated a high level of comfort with rapid diagnostics, reporting a 9.1 +/- 1.9 comfort level with waiting 30 min after specimen collection for IDQ results in order to prescribe an antibiotic for acute, uncomplicated cystitis. Respondents also indicated an 8.6 +/- 2.3 comfort level with telling patients that their antibiotic prescription would be ready for pickup 150 min after AST results became available.

These data point to a shifting paradigm in UTI management, in which individualized, diagnostics-driven antimicrobial use is perceived as valuable not only to decrease patient symptomatology, but to reduce the "collateral damage" of multi-drug resistant organisms that otherwise proliferate in the management of acute UTIs (Paterson 2004). It is worth noting that physicians' comfort level with deferring antibiotic treatment when presented with an immunosuppressed patient with a negative IDQ result was closer to neutral at 6.1 +/- 2.6. This decrease in comfort reveals the more conservative approach that physicians have in managing complex UTI cases, in which the risk of delaying treatment could have serious consequences. As a result, many chose to treat broadly and rely on the gold standard C&S. Even in this context, a negative IDQ result could enable physicians to investigate other etiologies while awaiting C&S results, thus saving valuable time and resources. This principle extends to other complex cases, including pregnant women, patients with neurogenic bladder, and elderly patients with cognitive dysfunction.

Physician management of UTI veered from IDSA guidelines within our survey. In the acute cystitis vignette, 68% of respondents chose to send for C&S and 16% postponed treatment pending C&S results. A majority of physicians requesting C&S in a case of uncomplicated cystitis directly contradicts IDSA guidelines that recommend against sending for C&S in such cases (Gupta et al. 2011). This divergence from guidelines is significant because it implies that physicians either perceive a benefit to knowing the identity and antimicrobial susceptibility of their patient's uropathogen that exceeds the cost of ordering C&S, or are following healthcare delivery settings and reimbursement patterns that encourage ordering C&S. This choice may be motivated by physician experiences with treatment failure, UTI recurrences, or the misdiagnosis of a sexually transmitted disease or other urinary pathology (Stamm and Norrby 2001).

As UTI is one of the highest volume diagnoses seen in clinical and hospital settings, improved diagnosis and management has the potential to have major impacts on patient quality of life. A 2017 European study on recurrent UTI (rUTI) found that patients with two or more UTIs in the last six months, or three or more UTIs in the last year, took an average of 3.09 sick days due to UTIs, and 7.5% reported

**Table 3**
**Choice of Antimicrobial Agents: Residents and Fellows vs. Attendings.** Note the following abbreviations. R&F: residents and fellows. ATT: attendings. *P*: *P* value of statistical difference between treatment choices of residents/fellows and attendings. H&P: history and physical. IDQ: identification and quantification. AST: antimicrobial susceptibility testing. TMP/SMX: trimethoprim/sulfamethoxazole. Pip/Tazo: piperacillin/tazobactam

| | | ALL | R&F | ATT | *P* | ALL | R&F | ATT | *P* | ALL | R&F | ATT | *P* |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Vignette | **Antibiotic chosen** | | | **H&P** | | | | **IDQ** | | | | **AST** | |
| Vignette 1 – | TMP/SMX | 32% | 33% | 34% | | 34% | 40% | 32% | | 36% | 38% | 39% | |
| Uncomplicated | Nitrofurantoin | 48% | 63% | 29% | <.01 | 28% | 35% | 14% | <.05 | 47% | 56% | 31% | <.05 |
| Cystitis | Ciprofloxacin | 5% | 0% | 13% | <.05 | 4% | 2% | 8% | | 6% | 2% | 11% | |
| | Cephalexin | 7% | 0% | 13% | <.05 | 7% | 2% | 11% | | 11% | 4% | 19% | <.05 |
| | Fosfomycin | 2% | 2% | 3% | | 2% | 2% | 3% | | 0% | 0% | 0% | |
| | Ceftriaxone | 0% | 0% | 0% | | 0% | 0% | 0% | | 0% | 0% | 0% | |
| | Ertapenem | 0% | 0% | 0% | | 0% | 0% | 0% | | 0% | 0% | 0% | |
| | Pip/Tazo | 0% | 0% | 0% | | 0% | 0% | 0% | | 0% | 0% | 0% | |
| | No Antibiotic | 3% | 2% | 3% | | 23% | 19% | 30% | | 0% | 0% | 0% | |
| | Other | 2% | 0% | 5% | | 1% | 0% | 3% | | 0% | 0% | 0% | |
| Vignette 2 – | TMP/SMX | 4% | 4% | 6% | | 2% | 4% | 0% | | 0% | 0% | 0% | |
| Recurrent | Nitrofurantoin | 42% | 52% | 25% | <.05 | 29% | 42% | 11% | <.01 | 52% | 60% | 40% | |
| UTI | Ciprofloxacin | 27% | 27% | 28% | | 18% | 17% | 19% | | 0% | 0% | 0% | |
| | Cephalexin | 24% | 13% | 39% | <.01 | 15% | 8% | 22% | | 41% | 29% | 57% | <.05 |
| | Fosfomycin | 3% | 4% | 3% | | 3% | 6% | 0% | | 5% | 8% | 0% | |
| | Ceftriaxone | 0% | 0% | 0% | | 1% | 2% | 0% | | 2% | 2% | 3% | |
| | Ertapenem | 0% | 0% | 0% | | 1% | 0% | 3% | | 0% | 0% | 0% | |
| | Pip/Tazo | 0% | 0% | 0% | | 0% | 0% | 0% | | 0% | 0% | 0% | |
| | No Antibiotic | 0% | 0% | 0% | | 30% | 21% | 44% | <.05 | 0% | 0% | 0% | |
| | Other | 0% | 0% | 0% | | 0% | 0% | 0% | | 0% | 0% | 0% | |
| Vignette 3 – | TMP/SMX | 34% | 37% | 29% | | 14% | 20% | 6% | | | | | |
| Immuno- | Nitrofurantoin | 5% | 7% | 3% | | 1% | 2% | 0% | | | | | |
| suppressed, | Ciprofloxacin | 33% | 30% | 37% | | 14% | 13% | 17% | | | | | |
| No UTI | Cephalexin | 13% | 7% | 20% | | 7% | 7% | 6% | | | | | |
| | Fosfomycin | 0% | 0% | 0% | | 0% | 0% | 0% | | | | | |
| | Ceftriaxone | 7% | 11% | 3% | | 3% | 2% | 6% | | | | | |
| | Ertapenem | 0% | 0% | 0% | | 0% | 0% | 0% | | | | | |
| | Pip/Tazo | 2% | 4% | 0% | | 1% | 2% | 0% | | | | | |
| | No Antibiotic | 7% | 4% | 9% | | 58% | 54% | 66% | | | | | |
| | Other | 0% | 0% | 0% | | 1% | 0% | 0% | | | | | |
| Vignette 4 – | TMP/SMX | 19% | 27% | 6% | <.05 | 16% | 26% | 3% | <.05 | 62% | 62% | 60% | |
| Pyelonephritis | Nitrofurantoin | 1% | 2% | 0% | | 1% | 3% | 0% | | 4% | 3% | 7% | |
| | Ciprofloxacin | 30% | 20% | 42% | <.05 | 26% | 12% | 40% | <.05 | 0% | 0% | 0% | |
| | Cephalexin | 5% | 2% | 9% | | 6% | 6% | 7% | | 0% | 0% | 0% | |
| | Fosfomycin | 2% | 0% | 6% | | 1% | 3% | 0% | | 4% | 3% | 7% | |
| | Ceftriaxone | 34% | 38% | 36% | | 30% | 26% | 40% | | 0% | 0% | 0% | |
| | Ertapenem | 0% | 0% | 0% | | 0% | 0% | 0% | | 12% | 15% | 10% | |
| | Pip/Tazo | 5% | 9% | 0% | | 4% | 9% | 0% | | 17% | 18% | 17% | |
| | No Antibiotic | 0% | 0% | 0% | | 12% | 12% | 10% | | 0% | 0% | 0% | |
| | Other | 4% | 2% | 0% | | 3% | 3% | 0% | | 0% | 0% | 0% | |
| Vignette 5 – | TMP/SMX | 3% | 0% | 7% | | 0% | 0% | 0% | | | | | |
| Urethritis | Nitrofurantoin | 47% | 64% | 27% | <.01 | 18% | 24% | 10% | | | | | |
| | Ciprofloxacin | 10% | 6% | 17% | | 3% | 3% | 3% | | | | | |
| | Cephalexin | 21% | 12% | 30% | | 7% | 6% | 7% | | | | | |
| | Fosfomycin | 0% | 0% | 0% | | 0% | 0% | 0% | | | | | |
| | Ceftriaxone | 1% | 3% | 0% | | 1% | 0% | 3% | | | | | |
| | Ertapenem | 1% | 0% | 3% | | 0% | 0% | 0% | | | | | |
| | Pip/Tazo | 0% | 0% | 0% | | 0% | 0% | 0% | | | | | |
| | No Antibiotic | 15% | 15% | 13% | | 69% | 67% | 73% | | | | | |
| | Other | 1% | 0% | 3% | | 1% | 0% | 3% | | | | | |

greater than ten medical visits per year (Wagenlehner et al. 2018). A 2015 international study uncovered that 62% of patients with rUTI report some degree of depression, with these symptoms often unevaluated by a physician (Renard et al. 2015). Upfront determination of the microbiological nature of the UTI would avoid the problems that result from the diagnostic delay of C&S, as rapid diagnostics would decrease sustained UTI symptoms from the unsuccessful treatment of resistant uropathogens, sequelae that affect 39.6% of UTI patients in Poland and 53.2% in Russia, and which are likely also common within the U.S. (Wagenlehner et al. 2018).

While we did not power our study to detect a difference in attending and trainee choice in antimicrobials, data from our clinical vignette survey illustrate that physicians at various stages of training treat UTIs significantly differently. In Vignettes 1, 2 and 5, nitrofurantoin, a first-line, narrow spectrum therapy for acute, uncomplicated cystitis, was used at significantly higher rates by residents and fellows as compared to attending physicians. In contrast, attending physicians tended to prescribe the broader spectrum agents, ciprofloxacin and cephalexin, for the empiric therapy of uncomplicated cystitis. Notably, trainees did not utilize nitrofurantoin at higher rates in Vignette 3 or 4, cases with more complex presentations and potential for serious sequelae. This result implies that trainees chose antibiotics selectively, prescribing broad spectrum, tissue-penetrating antimicrobials when needed in more complex cases.

Overuse of broad spectrum antibiotics complicates antimicrobial stewardship efforts. Antimicrobial stewardship is a cornerstone of the fight against antimicrobial resistance (AMR), which remains on the rise worldwide (Prestinaci et al. 2015). In the case of UTI, a growing number of urinary isolates are becoming resistant to broad-spectrum antimicrobials. Urinary *E. coli* isolates from U.S. outpatients have demonstrated resistances rates of 18% to cephalothin, 24% to trimethoprim-sulfamethoxazole, 17% to ciprofloxacin, and 2.3% to ceftriaxone (Sanchez et al. 2012). Resistance is considerably higher among inpatient isolates; 11.9% of *E. coli* isolates from 72 U.S. hospitals in 2012

**Table 4**
**Comparison of Initial Antibiotic Selection by Specialty.** Note the following abbreviations. TMP/SMX: trimethoprim/sulfamethoxazole. Pip/Tazo: piperacillin/tazobactam. PCP: primary care physician, including family medicine, internal medicine, geriatrics, and pulmonary medicine. ID: infectious diseases. URO: urology. ED: emergency medicine. Anesthesiology was excluded from this analysis given a low sample size. The most common antibiotic selected by specialty is highlighted. Note that more than 20% of the cells in this table have expected cell counts less than five, with several values at a minimum of less than one.

| Specialty | | TMP/SMX | | Nitrofurantoin | | Ciprofloxacin | | Cephalexin | | Fosfomycin | | Ceftriaxone | | Ertapenem | | Pip/Tazo | | None | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Case 1 | PCP | 9 | 23.7% | 21 | 55.3% | 2 | 5.3% | 4 | 10.5% | 0 | 0.0% | 0 | 0.0% | 0 | 0.0% | 0 | 0.0% | 2 | 5.3% |
| | ID | 6 | 31.6% | 8 | 42.1% | 2 | 10.5% | 0 | 0.0% | 2 | 10.5% | 0 | 0.0% | 0 | 0.0% | 0 | 0.0% | 1 | 5.3% |
| | URO | 11 | 52.4% | 8 | 38.1% | 0 | 0.0% | 0 | 0.0% | 0 | 0.0% | 0 | 0.0% | 0 | 0.0% | 0 | 0.0% | 2 | 9.5% |
| | ED | 1 | 11.1% | 5 | 55.6% | 1 | 11.1% | 2 | 22.2% | 0 | 0.0% | 0 | 0.0% | 0 | 0.0% | 0 | 0.0% | 0 | 0.0% |
| | | | | | | | | | *P* value 0.080 | | | | | | | | | | |
| Case 2 | PCP | 0 | 0.0% | 17 | 45.9% | 5 | 13.5% | 13 | 35.1% | 2 | 5.4% | 0 | 0.0% | 0 | 0.0% | 0 | 0.0% | 0 | 0.0% |
| | ID | 1 | 5.3% | 5 | 26.3% | 10 | 52.6% | 2 | 10.5% | 1 | 5.3% | 0 | 0.0% | 0 | 0.0% | 0 | 0.0% | 0 | 0.0% |
| | URO | 3 | 14.3% | 10 | 47.6% | 6 | 28.6% | 2 | 9.5% | 0 | 0.0% | 0 | 0.0% | 0 | 0.0% | 0 | 0.0% | 0 | 0.0% |
| | ED | 0 | 0.0% | 3 | 37.5% | 1 | 12.5% | 4 | 50.0% | 0 | 0.0% | 0 | 0.0% | 0 | 0.0% | 0 | 0.0% | 0 | 0.0% |
| | | | | | | | | | *P* value 0.017* | | | | | | | | | | |
| Case 3 | PCP | 13 | 36.1% | 1 | 2.8% | 11 | 30.6% | 6 | 16.7% | 0 | 0.0% | 2 | 5.6% | 0 | 0.0% | 1 | 2.8% | 2 | 5.6% |
| | ID | 4 | 22.2% | 0 | 0.0% | 10 | 55.6% | 3 | 16.7% | 0 | 0.0% | 1 | 5.6% | 0 | 0.0% | 0 | 0.0% | 0 | 0.0% |
| | URO | 11 | 55.0% | 1 | 5.0% | 3 | 15.0% | 1 | 5.0% | 0 | 0.0% | 1 | 5.0% | 0 | 0.0% | 0 | 0.0% | 3 | 15.0% |
| | ED | 0 | 0.0% | 2 | 25.0% | 3 | 37.5% | 1 | 12.5% | 0 | 0.0% | 1 | 12.5% | 0 | 0.0% | 0 | 0.0% | 1 | 12.5% |
| | | | | | | | | | *P* value 0.111 | | | | | | | | | | |
| Case 4 | PCP | 9 | 25.7% | 0 | 0.0% | 8 | 22.9% | 1 | 2.9% | 0 | 0.0% | 17 | 48.6% | 0 | 0.0% | 0 | 0.0% | 0 | 0.0% |
| | ID[1] | 1 | 5.6% | 0 | 0.0% | 11 | 61.1% | 1 | 5.6% | 2 | 11.1% | 2 | 11.1% | 0 | 0.0% | 0 | 0.0% | 0 | 0.0% |
| | URO | 5 | 26.3% | 0 | 0.0% | 4 | 21.1% | 1 | 5.3% | 0 | 0.0% | 7 | 36.8% | 0 | 0.0% | 2 | 10.5% | 0 | 0.0% |
| | ED | 0 | 0.0% | 1 | 12.5% | 1 | 12.5% | 1 | 12.5% | 0 | 0.0% | 4 | 50.0% | 0 | 0.0% | 0 | 0.0% | 1 | 12.5% |
| | *P* value 0.001* | | | | | | | | | | | | | | | | | | |
| Case 5 | PCP | 0 | 0.0% | 14 | 58.3% | 1 | 4.2% | 7 | 29.2% | 0 | 0.0% | 0 | 0.0% | 0 | 0.0% | 0 | 0.0% | 2 | 8.3% |
| | ID | 2 | 11.1% | 5 | 27.8% | 4 | 22.2% | 2 | 11.1% | 0 | 0.0% | 1 | 5.6% | 1 | 5.6% | 0 | 0.0% | 3 | 16.7% |
| | URO | 0 | 0.0% | 9 | 50.0% | 2 | 11.1% | 2 | 11.1% | 0 | 0.0% | 0 | 0.0% | 0 | 0.0% | 0 | 0.0% | 5 | 27.8% |
| | ED | 0 | 0.0% | 3 | 42.9% | 0 | 0.0% | 3 | 42.9% | 0 | 0.0% | 0 | 0.0% | 0 | 0.0% | 0 | 0.0% | 1 | 14.3% |
| | *P* value 0.171 | | | | | | | | | | | | | | | | | | |

[1] Not listed: one respondent chose to prescribe cefepime/ceftazidime (5.6% of infectious disease responses).
* The Chi-square statistic is significant at the 0.05 level.

were extended-spectrum beta lactamase (ESBL)-producers (Castanheira et al. 2014). Analysis of ESBL-producing bacteria in specimens in a tertiary care hospital in Rhode Island showed 80% of ESBL-producing organisms were found in patients with a UTI, with 69% of ESBL-producing *E. coli* resistant to trimethoprim/sulfamethoxazole (TMP/SMX) and 92% resistant to ciprofloxacin (Kassakian and Mermel 2014).

To combat AMR, the Joint Commission mandated that healthcare systems have antimicrobial stewardship programs that aim to reduce the use of overly broad, ineffective, and unnecessary antibiotics. Stewardship programs with computer-assisted decision support and antimicrobial de-escalation protocols have been associated with an 11-38% reduction in the prescription of antimicrobials, a $5-10 reduction in cost per patient-day, and reduced rates of ESBL *Klebsiella* (68% to 44%) and carbapenem-resistant *Pseudomonas* (61% to 41%) (Kaki et al. 2011). A key component of any antimicrobial stewardship program is utilization of narrow spectrum agents whenever appropriate. Our study found that trainees are far more likely to prescribe the narrow spectrum agent, nitrofurantoin, and adhere to UTI guidelines in their prescribing practices than attending physicians. Differences in cystitis treatment between trainees and attendings are evident despite the availability of UTI management guidelines from the IDSA, American College of Obstetricians and Gynecologists (ACOG), American Urological Association (AUA), and other professional medical societies. Although further research is needed to explore this issue, a possible cause for this discrepancy is that attending physicians developed their prescribing patterns prior to the publication of guidelines on UTI management, and, thus, became more comfortable with fluoroquinolones. Another factor may involve attendings' concerns about the adverse effects associated with narrow spectrum agents, such as TMP/SMX. Pharmaceutical marketing, antimicrobial cost, and variations in drug dosing may also contribute to UTI management practices that are independent of national and international guidelines (Lugtenberg et al. 2010; Taur and Smith 2007). As a result, adherence to updated stewardship programs may require more attention among senior physicians, as compared to their newly trained, junior colleagues.

Current approaches to antimicrobial stewardship are based on quality improvement measures, such as electronic medical record alerts and antibiograms, which are available to physicians to provide passive awareness of local resistance patterns (Kaki et al. 2011). Without improvements in UTI diagnostics, physicians will remain inaccurate in their antimicrobial use, either over- or under-prescribing antibiotics, as antimicrobial resistance rises. Unfortunately, the limited store of antibiotics available in the U.S. does not appear to be growing, especially for gram-negative uropathogens, posing a threat to the empiric treatment of UTI. Despite the financial, regulatory and intellectual property incentives for drug companies to develop novel antibiotics, 71% of these programs are limited to push incentives, leaving pharmaceutical companies the difficult task of self-financing later stages of their research (Simpkin et al. 2017). Additionally, of the drugs in development, relatively few are likely to be effective against "urgent threat" pathogens, as defined by the CDC (Simpkin et al. 2017). This crucial shortage in resources, coupled with years of limited success with stewardship programs, represents an opportunity for stewardship to be supported by an alternative approach, namely at the level of the UTI diagnostic. While rapid urinary assays for pyuria and bacteriuria have been available in the U.S. for decades, point-of-care assays to identify specific uropathogens and their antimicrobial susceptibility profiles remain under development, with several tests on the market for other applications, but not yet approved for urine specimens or analyzed for cost (Davenport et al. 2017; Waisman et al. 1999). Several national and international studies have revealed that physician approaches to antimicrobial stewardship lack personal responsibility, as 82% of physicians find the issue of resistance to be very important globally, yet only 53% find it important in their personal practices (Nicholson et al. 2018; Wester et al. 2002). Giving providers the opportunity to serve as primary diagnosticians with rapid diagnostics, rather than empiric therapists, has the potential to make antibiotic stewardship an active process and provide physicians the agency to dramatically improve antimicrobial usage.

## 5. Conclusion

In summary, rapid diagnostics have the potential to bring about a paradigm shift in the diagnosis and management of UTI. In a variety of UTI presentations, rapid IDQ and AST would improve antimicrobial accuracy and effectiveness compared to empiric therapy. Additionally, there are notable differences between trainee and attending physician management of acute cystitis. These data indicate that a rapid diagnostic has the potential to reduce the total number of antibiotics prescribed per infection and encourage the use of narrow spectrum antibiotics, particularly among senior physicians. Adapting current UTI practices to a rapid diagnostic model has the potential to improve healthcare outcomes and empower individual physician responsibility in antimicrobial stewardship.

Future studies should be aimed at gauging UTI treatment patterns within a larger sample of healthcare professionals, including physician assistants and nurse practitioners, who are frequently the primary care providers for patients with uncomplicated cystitis.

## Acknowledgements

*Financial support:* This study was supported by the Short-Term Training Program (STTP) at the David Geffen School of Medicine at the University of California, Los Angeles.

*Data analysis*: The authors thank Dr. David Goodman-Meza from the department of Infectious Disease at Ronald Reagan UCLA Medical Center for his assistance with statistical analysis.

## References

Bent S, et al. Does this woman have an acute uncomplicated urinary tract infection? Jama 2002;287(20):2701–10.
Brown P, Ki M, Foxman B. Acute pyelonephritis among adults. Pharmacoeconomics 2005; 23(11):1123–42.
Castanheira M, et al. Contemporary diversity of beta-lactamases among Enterobacteriaceae in the nine U.S. census regions and ceftazidime-avibactam activity tested against isolates producing the most prevalent beta-lactamase groups. Antimicrob Agents Chemother 2014;58(2):833–8.
Davenport M, et al. New and developing diagnostic technologies for urinary tract infections. Nature Reviews Urology 2017;14(5):296.
Food and Drug Administration, U.S.. FDA updates warnings for fluoroquinolone antibiotics on risks of mental health and low blood sugar adverse reactions; 2018.
Foxman B. Epidemiology of urinary tract infections: incidence, morbidity, and economic costs. The American journal of medicine 2002;113(1):5–13.
Foxman B, et al. Urinary tract infection: self-reported incidence and associated costs. Annals of epidemiology 2000;10(8):509–15.
Grover ML, et al. Assessing adherence to evidence-based guidelines for the diagnosis and management of uncomplicated urinary tract infection. Mayo Clin Proc 2007;82(2):181–5.
Gupta K, et al. International clinical practice guidelines for the treatment of acute uncomplicated cystitis and pyelonephritis in women: A 2010 update by the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases. Clin Infect Dis 2011;52(5):e103–20.
Kaki R, et al. Impact of antimicrobial stewardship in critical care: a systematic review. Journal of antimicrobial chemotherapy 2011;66(6):1223–30.
Kassakian SZ, Mermel LA. Changing epidemiology of infections due to extended spectrum beta-lactamase producing bacteria. Antimicrobial resistance and infection control 2014;3(1):9.
Lugtenberg M, et al. Guidelines on uncomplicated urinary tract infections are difficult to follow: perceived barriers and suggested interventions. BMC family practice 2010; 11(1):51.
MacFadden DR, et al. Predictive utility of prior positive urine cultures. Clinical Infectious Diseases 2014;59(9):1265–71.
Mach KE, Wong PK, Liao JC. Biosensor diagnosis of urinary tract infections: a path to better treatment? Trends in pharmacological sciences 2011;32(6):330–6.
Markowitz MA, et al. Lack of uniformity among United States recommendations for diagnosis and management of acute, uncomplicated cystitis. International urogynecology journal 2018:1–8.
Measuring Outpatient Antibiotic Prescribing. Centers for Disease Control and Prevention; 2017.
Nicholson A, et al. The knowledge, attitudes and practices of doctors regarding antibiotic resistance at a tertiary care institution in the Caribbean. Antimicrobial Resistance & Infection Control 2018;7(1):23.
Paterson DL. "Collateral damage" from cephalosporin or quinolone antibiotic therapy. Clinical Infectious Diseases 2004;38(Supplement_4):S341–5.
Prestinaci F, Pezzotti P, Pantosti A. Antimicrobial resistance: a global multifaceted phenomenon. Pathogens and global health 2015;109(7):309–18.
Renard J, et al. Recurrent lower urinary tract infections have a detrimental effect on patient quality of life: a prospective, observational study. Infectious diseases and therapy 2015;4(1):125–35.
Sanchez GV, et al. In vitro antimicrobial resistance of urinary Escherichia coli isolates among U.S. outpatients from 2000 to 2010. Antimicrob Agents Chemother 2012;56(4): 2181–3.
Schappert, S. and E. Rechtsteiner, Ambulatory medical care utilization estimates for 2007. Vital and Health Statistics. Series 13, Data from the National Health Survey, 2011(169): p. 1-38.
Scott V, et al. MP23-18 CLINICAL STUDY UPDATE ON A NOVEL RIBOSOMAL RNA-BASED RAPID DIAGNOSTIC METHOD TO DETECT, IDENTIFY AND ASSESS ANTIBIOTIC SUSCEPTIBILITY OF UROPATHOGENS. The Journal of Urology 2018;199(4):e288.
Simpkin VL, et al. Incentivising innovation in antibiotic drug discovery and development: progress, challenges and next steps. The Journal of antibiotics 2017;70 (12):1087.
Smith AL, et al. Treatment and prevention of recurrent lower urinary tract infections in women: a rapid review with practice recommendations. The Journal of Urology 2018;200(6):1174–91.
Stamm WE, Norrby SR. Urinary tract infections: disease panorama and challenges. The Journal of infectious diseases 2001;183(Supplement_1):S1–4.
Taur Y, Smith MA. Adherence to the Infectious Diseases Society of America guidelines in the treatment of uncomplicated urinary tract infection. Clinical infectious diseases 2007;44(6):769–74.
Wagenlehner F, et al. Social and economic burden of recurrent urinary tract infections and quality of life: a patient web-based study (GESPRIT). Expert review of pharmacoeconomics & outcomes research 2018;18(1):107–17.
Waisman Y, et al. The validity of the uriscreen test for early detection of urinary tract infection in children. Pediatrics 1999;104(4):e41.
Wester CW, et al. Antibiotic resistance: a survey of physician perceptions. Archives of internal medicine 2002;162(19):2210–6.
Zatorski C, et al. A single center observational study on emergency department clinician non-adherence to clinical practice guidelines for treatment of uncomplicated urinary tract infections. BMC Infectious Diseases 2016;16(1):638.