

A Diagnostic Test Combining Molecular Testing with Phenotypic Pooled Antibiotic Susceptibility Improved the Clinical Outcomes of Patients with Non-*E. coli* or Polymicrobial Complicated Urinary Tract Infections

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Purpose: Complicated UTIs (cUTIs) cause significant morbidity and healthcare resource utilization and cost. Standard urine culture has limitations in detecting polymicrobial and non-*E. coli* infections, resulting in the under-diagnosis and under-treatment of cUTIs. In this study, patient-reported outcomes were compared between treated and untreated patients when an advanced diagnostic test combining multiplex-polymerase chain reaction (M-PCR) with a pooled antibiotic susceptibility method (P-AST) was incorporated into the patients' clinical management.

Methods: Patients who had symptoms typical of cUTI and positive M-PCR/P-AST test results were recruited from urology clinics. Symptom reduction and clinical cure rates were measured from day 0 through day 14 using the American English Acute Cystitis Symptom Score (ACSS) Questionnaire. Clinical cure was defined based on the sum of the scores of four US Food and Drug Administration (FDA) symptoms and the absence of visible blood in the urine.

Results: Of 264 patients with suspected cUTI, 146 (55.4%) had exclusively non-*E. coli* infections (115 treated and 31 untreated) and 190 (72%) had polymicrobial infections (162 treated and 28 untreated). Treated patients exhibited greater symptom reduction compared to untreated ones on day 14 for those with exclusively non-*E. coli* organisms (3.18 vs 1.64, $p = 0.006$) and polymicrobial infections (3.52 vs 1.41, $p = 0.002$), respectively. A higher percentage of treated patients than of untreated patients achieved clinical cure for polymicrobial infections on day 14 (58.7% vs 36.4%, $p = 0.049$).

Conclusion: Patients with cUTIs treated based on the M-PCR/P-AST diagnostic test had significantly improved symptom reduction and clinical cure rates compared to untreated patients among those with non-*E. coli* or polymicrobial infections.

Keywords: urinary tract infection, complicated urinary tract infection, antibiotic, clinical outcome, diagnostic testing, polymerase chain reaction

Background

Urinary tract infections (UTIs), the most common infections in the United States, account for 10.5 million physician office visits and three million emergency department (ED) visits annually, representing a major healthcare burden.^{1,2} In many cases, particularly complicated UTIs (cUTIs), patients require antimicrobials to treat the infection. When an individual has one or more risk factors that predispose to higher treatment failure and poor outcomes, such as persistence of UTI, increasing severity, or occurrence of complications such as urosepsis, recurrence, and perinephric abscess, the case is considered a cUTI.^{3–5}

Currently, the accepted UTI diagnostic test, standard urine culture (SUC), has several inherent limitations that favor the detection of *E. coli*^{6–8} over non-*E. coli* Gram-negative uropathogens such as *Pseudomonas aeruginosa* and species of *Proteus* and *Klebsiella*, as well as Gram-positive bacteria such as *E. faecalis*, *E. faecium*, and *S. aureus*, which are well-established as causes of UTIs and can lead to sepsis.^{3,6,9–11} Khasriya (2013) demonstrated that culture of the shed urothelial cells in patients with chronic lower urinary tract symptoms found large numbers of bacteria that were undetected by SUC.¹²

SUC also often misses polymicrobial cases due to the general practice of reporting samples with more than two or three organisms as contaminated or mixed flora.^{13,14} These polymicrobial infections, which have been reported in up to 39% of suspected UTI cases in elderly populations,^{14,15} have been associated with poor outcomes.¹⁶

These limitations of SUC hinder the effective diagnosis and treatment of cUTIs, especially in polymicrobial or non-*E. coli* cases, which could be underdiagnosed, left untreated, or mistreated. Indeed, Price et al found that SUC missed 50% of uropathogens in patients with severe urinary tract symptoms, and 36% of the patients continued to have symptoms even after receiving SUC-directed treatment.¹⁷

This study focuses on an advanced diagnostic test that combines multiplexed polymerase chain reaction (M-PCR) to detect bacterial and yeast uropathogens and antibiotic resistance genes with pooled antibiotic susceptibility testing (P-AST). Prior studies have shown its superiority in bacterial identification, especially for non-*E. coli* and polymicrobial UTIs.^{18–20} Furthermore, an observational retrospective study of 66,381 UTI patients revealed a 13.7% decrease (3.27% vs 3.79%, $p = 0.003$) in ED visits and hospital admissions when using this test compared to patients diagnosed via SUC.²¹

This prospective study compares the effects of the M-PCR/P-AST test on clinical outcomes for treated vs untreated patients based on responses to a validated clinical symptom score questionnaire for patients with non-*E. coli* or polymicrobial cUTIs.

Materials and Methods

Study Design and Participants

A Western IRB review and approval was obtained in accordance with the Declaration of Helsinki (20214705). Trial registration: NCT05091931. Registered 25 October 2021, <https://clinicaltrials.gov/ct2/show/NCT05091931>. The IRB determined that the study protocol met all three requirements for a partial waiver of authorization: that the use of PHI involved no more than minimal risk to the study participants, the research could not be practicably conducted without access to PHI, and the research could not practicably be conducted without the waiver. All 369 subjects gave verbal informed consent prior to enrollment.

This is an interim analysis of an ongoing observational prospective study. We included male or female patients who presented to urology clinics with symptoms and clinical presentations highly suspicious of cUTI (see [Supplemental Table 1](#) for full Inclusion and Exclusion Criteria). This analysis focused on the clinical impact of treatment decisions on polymicrobial or non-*E. coli* cases, which are less likely to be detected by SUC than by novel M-PCR/P-AST testing.

Physicians evaluated patients' clinical presentations on their first office visit (day 0) and recorded their demographics, clinical information, and antimicrobial treatment information when applicable, and collected urine samples for the M-PCR/P-AST test.

Patients completed a baseline survey on day 0 and daily surveys from day 1 through day 14. The surveys include symptom severity and antimicrobial treatment information. The symptom portion of the survey used a validated American English Acute Cystitis Symptom Score (ACSS) Questionnaire, asking patients to evaluate six typical UTI symptoms: urinary frequency, urinary urgency, dysuria, incomplete bladder emptying, suprapubic pain, and visible blood in the urine, according to each one's severity (scoring 0–3): no (0), mild (1), moderate (2), severe (3).^{22,23} Each patient's treatment was at the discretion of the treating clinician. Treatment status (treated or untreated with antimicrobials, including antibiotic and anti-fungal drugs, between day 0 and day 14) was determined based on the clinical evaluation form completed by physicians, patients' daily surveys, and medical records.

Clinical Outcomes

Clinical outcomes evaluated in this analysis included average symptom score reductions and clinical cure rates on day 7 and day 14 based on the results of the survey based on the ASCC Questionnaire. This questionnaire was designed for symptom severity evaluation for acute cystitis, which is the relevant set of symptoms for patients included in this study. The symptom scores were the sum of four typical symptom scores for UTI defined by the US Food and Drug Administration (FDA) (urinary frequency, urinary urgency, dysuria, and suprapubic pain).^{22–24} Clinical cure was defined as the four FDA symptom scores adding up to ≤ 4 , none of the four symptom scores being > 1 , and the absence of visible blood in the urine. To best investigate the clinical cure rate, only patients with a sum of the four symptom scores of > 4 or at least one of the four symptom scores > 1 on day 0 were included in the clinical outcome analysis.

M-PCR/P-AST Test (Guidance[®] UTI, Offered by Pathnostics, Irvine, CA)

As described previously,^{19,20,25} the first step of the test involves DNA extraction from the patient's urine sample using the King Fisher/MagMAX[™] automated DNA extraction instrument and the MagMAX[™] DNA Multi-Sample Ultra Kit (Thermo Fisher, Carlsbad, CA) per the manufacturer's instructions. Extracted DNA from subjects' samples was mixed with a universal PCR master mix and amplified using TaqMan technology in a Life Technologies 12K Flex 112-format Open Array System (Thermo Fisher Scientific, Wilmington, NC). Probes and primers were used to detect 26 bacteria/bacterial groups, fastidious and non-fastidious, and four yeast species.^{19,20}

As part of the M-PCR/P-AST test, 32 antibiotic-resistance genes were also tested as described previously.²⁵ In addition, fluorescence-based P-AST was performed when at least one non-fastidious bacterium is identified by M-PCR in the first step.²⁵ P-AST determines the pooled antibiotic susceptibility profile, which accounts for bacterial interactions, against 19 antibiotics that are commonly used for UTIs.¹⁸

Statistical Analysis

Patients' demographics, including age, sex, day 0 symptom scores, and the prevalence of each baseline symptom, were summarized using the mean and standard deviation (SD) for continuous variables and frequency (proportion) for dichotomized variables. For patients with non-*E. coli* or polymicrobial infections, the symptom scores were summarized by treatment status on day 0, day 7, and day 14, respectively. In addition, the changes in the symptom scores from day 0 to day 7 and from day 0 to day 14 were also summarized. The Kruskal–Wallis test was used to compare the difference in symptom scores between treated and untreated patients. The chi-square test or Fisher's exact test was used to test whether the clinical cure rates differed according to the treatment status. The analysis was performed using Statistical Analysis System (SAS) 9.4.

Results

Patients' Demographic and Clinical Information

A total of 369 patients with positive M-PCR/P-AST results were enrolled between 03/28/2022 and 02/08/2022 from any one of the 22 urology clinics located in diverse geographic and socioeconomic cities and suburban areas in the state of Michigan. Among them, 264 patients (163 female and 101 male patients) started with either a sum of the four FDA typical symptom scores of > 4 or at least one of the four FDA symptom scores of > 1 on day 0, which was the criterion for inclusion in this analysis.

The average age of the 264 patients was 68.5 years, and the majority (180, 68.2%) of them were aged ≥ 65 years. The mean baseline symptom scores based on the four FDA symptoms on day 0 were 5.5. The most frequent baseline symptoms were frequent urination (242, 91.7%) and urgent urination (239, 90.5%) (Table 1). All but one of the urine samples were collected via the midstream clean catch.

Table 1 Patients' Demographic and Clinical Information

N = 264	n	%
Age, mean (median) = 68.5 (71.1), range 23–122, SD = 15.8 (years)		
Age of 65 years or over		
No	84	31.8
Yes	180	68.2
Sex		
Female	163	61.7
Male	101	38.3
Urine collection method		
Midstream clean catch	263	99.6
Catheter collected	1	0.4
Symptom score on day 0, mean (median)	5.5 (5.0)	
Baseline symptoms		
Frequent Urination*	242	91.7
Urgent Urination*	239	90.5
Dysuria*	156	59.1
Incomplete emptying	197	74.6
Suprapubic pain*	106	40.2
Blood in urine (without menstruation)	56	21.2

Note: *The 4 FDA symptoms.

Symptom Reduction and Clinical Cure Rates in Treated and Untreated Patients with Polymicrobial cUTIs

Polymicrobial UTIs, defined as the presence of two or more organisms, were detected in 190 (72.0%) patients, including 162 that received antimicrobial treatment and 28 that did not. There was no statistically significant difference in baseline symptom scores between the two groups of patients (5.70 vs 4.86, $p = 0.054$, Table 2). The mean symptom score reduction from day 0 was significantly greater in the treated than the untreated group on day 7 and day 14 (3.04 vs 1.48, $p = 0.004$ and 3.52 vs 1.41, $p = 0.002$, respectively; Table 2). A higher clinical cure rate was achieved in treated than in untreated patients on day 14 (58.7% vs 36.4%, $p = 0.049$, Table 3).

Symptom Reduction and Clinical Cure Rates in Treated and Untreated Patients with Non-*E. coli* cUTIs

We detected 146 (55.4%) patients with exclusively non-*E. coli* bacteria and yeast infections, including 115 that received treatment and 31 that did not. The baseline symptom scores between the two groups of patients did not differ significantly

Table 2 Mean Symptom Score Reduction on Day 7 and Day 14 in Treated and Untreated Patients

	Polymicrobial (≥ 2 Organisms) (N = 190)			Non- <i>E. coli</i> (N = 146)		
	Untreated (n = 28)	Treated (n = 162)	p value	Untreated (n = 31)	Treated (n = 115)	p value
Symptom scores: Mean (SD)						
Day 0	4.86 (1.98)	5.70 (2.06)	0.054	4.87 (2.28)	5.59 (2.14)	0.083
Day 7	3.36 (2.55)	2.67 (2.22)	0.193	3.30 (2.38)	2.64 (2.15)	0.154
Day 14	3.14 (2.46)	2.28 (2.20)	0.094	3.04 (2.49)	2.45 (2.30)	0.239
Symptom score reductions: Mean (SD)						
Day 7 - Day 0	1.48 (2.20)	3.04 (2.68)	0.004	1.57 (1.77)	2.96 (2.64)	0.012
Day 14 - Day 0	1.41 (2.44)	3.52 (2.87)	0.002	1.64 (2.45)	3.18 (2.86)	0.006

Table 3 Clinical Cure on Day 7 and Day 14 in Treated and Untreated Patients

	Patients with Symptom Scores	Untreated		Treated		p value
		# of Untreated Patients	# Clinical Cure n (%)	# of Treated Patients	# Clinical Cure n (%)	
Polymicrobial cases						
Day 7	n = 182	n = 24	9 (37.5)	n = 158	85 (53.8)	0.14
Day 14	n = 172	n = 22	8 (36.4)	n = 150	88 (58.7)	0.049
Non- <i>E. coli</i> cases						
Day 7	n = 142	n = 29	11 (37.9)	n = 113	60 (53.1)	0.15
Day 14	n = 136	n = 28	10 (35.7)	n = 108	60 (55.6)	0.061

(5.59 vs 4.87, $p = 0.083$, Table 2). Among these patients, the mean symptom score reduction from day 0 was significantly greater in the treated than the untreated group on day 7 and day 14 (2.96 vs 1.57, $p = 0.012$ and 3.18 vs 1.64, $p = 0.006$, respectively; Table 2). Clinical cure rates in the treated and untreated group did not show a statistically significant difference on day 7 and day 14 (53.1% vs 37.9%, $p = 0.15$ and 55.6% vs 35.7%, $p = 0.061$, respectively; Table 3).

Discussion

For cases of non-*E. coli* or polymicrobial infections, where SUC has known shortcomings, it is important to consider alternative tests that can provide more accurate and rapid results. The M-PCR/P-AST diagnostic test reported here has been demonstrated in prior studies to be better at detecting non-*E. coli* and polymicrobial UTIs than SUC.^{19,20} There have been questions raised about the clinical value of identifying these types of organisms, and if they are associated with clinical manifestations of UTI or are incidental findings that do not cause disease. This study evaluated whether patients improved with treatment in cases where *E. coli* is absent or where there is a polymicrobial infection detected using an M-PCR/P-AST test that can identify 26 bacteria/bacterial groups and four yeast species. The P-AST component provides phenotypic results that account for bacterial interactions in polymicrobial infections.

The majority of the 264 symptomatic patients with presumed cUTI were diagnosed with non-*E. coli* (146/264, 55.4%) or polymicrobial (190/264, 72.0%) infections. These percentages are consistent with those in previous reports and further demonstrate the importance and prevalence of non-*E. coli* and polymicrobial UTIs. Due to the inherent limitations of SUC, many of these uropathogens would not have been detected, leading to under-treatment or inadequate antibiotic use, which elevates the risk of disease progression and antibiotic-resistance.

Here, both treated and untreated patients started with similar baseline symptom scores in cases with non-*E. coli* or polymicrobial infections. Mean symptom scores decreased faster on both day 7 and day 14 for non-*E. coli* and polymicrobial infection in the treated compared to the untreated group. In addition, a higher clinical cure rate was achieved in the treated than in the untreated group among patients with polymicrobial UTIs. There was a trend that more patients with non-*E. coli* infections achieved clinical cure in the treated than in the untreated group on day 14; however, the difference was not statistically significant.

One limitation of our study was that the 22 urology clinics were all located in Michigan as part of a single entity, Comprehensive Urology, which has extensive experience utilizing M-PCR/P-AST in the clinical diagnosis and management of UTIs. Further studies involving greater geographic distribution and an additional group to compare the M-PCR/P-AST test to SUC are warranted.

Conclusion

The lack of accurate and rapid directed treatment of cUTIs presents a significant healthcare problem, causing a higher risk of treatment failure, persistence, increasing severity, progression to acute pyelonephritis, recurrence and urosepsis.^{4,26} Increased ED and hospitalization visits, along with urosepsis (which is responsible for 25% of sepsis cases), causes increased healthcare cost and significant patient morbidity. These indicate a strong need for more accurate

and rapid diagnosis and better-targeted therapy for these cases. The results of this study indicate the use of this M-PCR/P-AST test for polymicrobial or non-*E. coli* cUTI cases might be beneficial, showing an association with better symptom resolution and clinical cure rates.

Abbreviations

ASCC, Acute Cystitis Symptom Score; cUTIs, Complicated UTIs; ED, emergency department; M-PCR, multiplex-polymerase chain reaction; P-AST, pooled antibiotic susceptibility method; SD, standard deviation; SUC, standard urine culture; UTIs, Urinary tract infections.

Data Sharing Statement

All relevant data are present within the manuscript text and Tables.

Ethics Approval and Consent to Participate

All patients provided verbal informed consent (Western IRB 20214705) prior to enrollment.

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Disclosure

D.B., N.L., and M.M. are employees of Pathnostics, and D.W. and X.Z. are paid consultants of Pathnostics. Dr Howard J Korman is a Scientific Advisory Board member and Consultant for Pathnostics. Dr David Baunoch has a patent US 10,160,991 issued to PATHNOSTICS, a patent US 11,053,532 issued to PATHNOSTICS, a patent US 17/178,091 pending to PATHNOSTICS, a patent US 17/335,767 pending to PATHNOSTICS, a patent US 17/830,227 pending to PATHNOSTICS, a patent PCT/US22/16816 pending to PATHNOSTICS, a patent PCT/US22/77477 pending to PATHNOSTICS. The authors report no other conflicts of interest in this work.

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