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After 180 Years, Is it Time for Something Better for Diagnosing UTI's?

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Abstract

Urinary Tract Infections (UTI) are a common source of outpatient encounters for all ages of patients, along with emergency department visits and hospital admissions. Standard urine culture (SUC) has been the mainstay for diagnosis and treatment options for over 100 years, yet 25% of female patients develop recurrent, persistent urinary tract infections. New technologies are now available that quickly provide increased ability to detect organisms along with improved susceptibility information. We discuss the clinical validity and utility data available for Multiplex polymerase chain reaction (M-PCR) coupled with pooled antibiotic susceptibility testing (P-AST) for managing urinary tract infections.

Mini Review

Urinary Tract Infections (UTI) are a common source of outpatient encounters, emergency department visits, and hospital admissions [1,2]. Young and healthy people suffering from a UTI, while symptomatically aggravating, are unlikely to progress to serious complications [3]. However, older adults' patients suffer from UTIs symptoms ranging from mild to severe, which may lead to delirium, sepsis, or mortality [4,5]. Effective treatment of UTI based on timely and accurate diagnosis is essential to keep elderly patients out of emergency rooms and hospitals. The Standard Urine Culture (SUC) has been the gold standard test for UTI diagnosis for over one hundred years, and has played a significant clinical role in managing patients with suspected UTI. Testing by SUC can often provide informative and actionable clinical information. However, SUC has limitations, particularly for providing complete information for the clinical management of older patients suffering from recurrent, persistent, or other complicated UTIs. These limitations include the inability to detect all relevant organisms causing the infection, producing results quickly enough to avoid empirical treatment and generating efficacious treatment recommendations [6-8]. Given the hospitalization and morbidity rates associated with UTIs in the elderly population, failure to identify a UTI, or adequately treat it, may have significant ramifications.

Novel advanced diagnostic testing methods such as multiplex polymerase chain reaction (M-PCR) coupled with pooled antibiotic sensitivity testing (P-AST) can provide clinically relevant microbiological data missed by SUC. Furthermore, the clinical need for these tests' stems from the ability of these technologies to not only identify organisms but also provide optimal treatment options in a timely manner [9]. Four peer-reviewed published papers prospectively or retrospectively validated M-PCR/P-AST testing methods as a more useful diagnostic tool for managing complicated or recurrent UTI in the elderly [8,10-12]. A study by Wojno K et al. established the clinical value (or analytical validity) of using M-PCR to detect bacteria in urine. This study reported the results of 582 consecutive elderly patients with an average age of 77 years presenting to urologists with symptoms of a lower UTI. The authors compared the identification of bacterial organisms by M-PCR and SUC when tests were run in parallel on the same samples. The M-PCR detected uropathogens in 326 patients (56%, 326/582), while SUC detected uropathogens in 217 patients (37%, 217/582). M-PCR and SUC agreed in 74% of cases (431/582), and disagreed in 26% of cases (151/582): M-PCR was positive while SUC was negative in 22% of cases (130/582), and SUC was positive while PCR was negative in 4% of cases (21/582). The study identified polymicrobial infections, defined as 2 or more organisms present in a sample, in 175 patients (30%, 175/582), with M-PCR detecting 166 and SUC detecting only 39 (6.7%, 39/582). M-PCR identified polymicrobial infections in 67 cases (12%, 67/582) for which SUC results were negative. Additionally, M-PCR identified several microbes including Gram-positive bacterium, A. *schaalii, A. omnicolens, C. riegelii, M. tuberculosis, M. hominis and Gram-negative bacterium, P. agglomerans, P. stuartii, and U. urealyticum* missed by standard urine culture [8].

The publication concluded that SUC has limitations, including the inability to detect slow-growing, fastidious, or non-aerobic microorganisms, and SUC has a profound detection bias for fast-growing Gram-negative aerobic organisms. Significantly, SUC had difficulty identifying most of the microorganisms that make up a polymicrobial infection. Similarly, the article by Vollstedt A. et al summarized results from a prospective trial comparing the detection levels of M-PCR and SUC of bacteria in UTI-symptomatic patients. The study enrolled 2,511 patients with UTI symptoms and an average age of 73 years from 37 urology clinics across the United States. M-PCR and SUC identified bacteria in 62.7% (1,575/2,511) and 43.7% (1,098/2,511) of cases, respectively. M-PCR detected 6 organisms which SUC failed to detect, including five Gram-positive bacteria (*A. schaalii, A. omnicolens, C. riegelii, M. genitalium, and M. hominis*) and one Gram-negative bacterium (*U. urealyticum*), affecting 590 samples. Between the two testing methods, the study detected a total of 861 polymicrobial infections, with M-PCR detecting 834 (96.9%) and SUC detecting only 167 (19.5%). Polymicrobial detections made up 34.3% (861/2,511) of the total patients, and 53.0% of M-PCR positive cases (834/1575). SUC did not detect A. schaalii, which was the most common bacterium [53.0% (442/834)] detected in polymicrobial infections by M-PCR. The bacterial species detected by SUC but not detected by M-PCR, including Enterobacter species, the Enterococcus species, and several other rarely detected species, were detected in very small subsets of patients by SUC (0.9%, 0.2%, and 0.9%, of all patients, respectively). The M-PCR mix did not include primers for the missed species in the M-PCR assay at the time of the study [10].

This analysis has also showed the identity of microbes identified by M-PCR and the susceptibility results generated by P-AST takes an average of 29.7 hours (9 hours less than SUC) to provide physicians with urine pathogen and antibiotic susceptibility results. The difference in turnaround time improved a median of 19 hours (34.5 hours and 53.7 hours, for M-PCR/P-AST and SUC, respectively) for patients with both positive pathogen identification and susceptibility results [10]. These two publications show the superior ability of M-PCR to quickly detect all relevant uropathogens in the sample, especially Gram-positive bacteria, along with more polymicrobial infections in patients with UTI symptoms [8,10].

A second paper by Vollstedt A. et al. focused on bacterial interactions in affecting susceptibility patterns. The study used a novel pooled antibiotic sensitivity testing method (P-AST) which assess the functional antibiotic sensitivity for a pooled sample. This assay measures optical density with a spectrophotometer, setting a threshold value to measure growth of organisms in a 'pool', or polymicrobial mixture. The benefit of the 'pooled' approach is that it allows real-world antibiotic sensitivity assessment of the polymicrobial community from the patient's UTI. The average age of the patients were 74.9 years. This study analyzed 758 UTI-symptomatic patients with polymicrobial bacterial infections and antibiotic susceptibility results. By comparing results from these polymicrobial samples against monomicrobial bacterial samples from 594 UTI-symptomatic patients, the analyses revealed the odds of resistance to ampicillin ($p = 0.005$), amoxicillin/clavulanate ($p = 0.008$), five different cephalosporins ($p<0.05$), vancomycin ($p = <0.0001$), and tetracycline ($p = 0.010$), increased with each additional bacterial species present. In contrast, the odds of resistance to piperacillin/tazobactam decreased by 75% for each additional species present (95% CI 0.61, 0.94, $p = 0.010$). Additionally, the comparison revealed 44 situations for which 13 pairs of bacterial species exhibited statistically significant interactions, which caused susceptibility patterns to change as measured by the Highest Single Agent Principle or Union Principle statistical analysis models [11]. These findings align with the results reported by De Vos et al, who examined the interactions between 72 bacterial isolates from elderly people with UTI symptoms. They measured the impact of species-to-species interactions on antibiotic efficacy. They assessed organism's growth in response to two commonly used antibiotics for UTIs (trimethoprim-sulfamethoxazole and nitrofurantoin). Using media conditioned by donor isolates they observed that clinical isolates often protected each other from the antibiotics: 25% of tested species-to-species interactions showed greater than a 3.5-fold increase in tolerance for trimethoprim-sulfamethoxazole but decreases of the same magnitude only occurred in 12% of patient results [12].

Therefore, M-PCR is able to quickly detect all relevant uropathogens, especially Gram-positive bacteria, along with more polymicrobial infections in patients with UTI symptoms, [8,11] whereas the 'pool' approach used in the P-AST testing allows real-world antibiotic sensitivity assessment of the polymicrobial community from the patient's UTI.

Does the improved performance of M-PCR/P-AST lead to better clinical outcomes? The study by Daly A. et al. addressed this question and shows the M-PCR/P-AST results are associated with better outcomes. The study used existing data from 66,381 patients seen for UTIs by primary care providers in the patient home or assisted living locations. The clinical outcomes measured in the study were numbers of hospital admission and/or emergency department utilization. Daly et al. divided patients into two non-overlapping cohorts. Physicians treated patients in cohort one (N=34,414) based upon the results from SUC. Physicians treated the other cohort (N=31,967) based upon the results from the M-PCR/P-AST assay. The patients in the two cohorts had similar demographics, comorbidities, Charlson/Deyo Index Scores, number of provider visits, and enrollment locations. The analysis detected a 13.7% reduction in hospital admissions and/or emergency department utilization associated

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with the use of the M-PCR/P-AST assay compared with the use of traditional SUC. The 13.7% reduction in hospitalization when normalized to 34,414 patients in the SUC cohort would result in 156 fewer patients attending the ED/hospitalizations and/or ED utilization from a UTI [13]. Another study has shown that the savings of keeping patients out of the hospital for a UTI can be as high as $64,000 per patient when considering the dollars paid by the patient and insurance [14]. Thus, the cost avoidance for 156 patients is as high as $10,000,000. The cost of testing using M-PCR/P-AST for the target population suffering from UTI's is well below the cost associated with adverse effects that result in ED or hospitalization.

For over a century, health care providers have accepted SUC as a tool to manage UTIs to identify both the bacteria and the appropriate treatment options. The diagnostic tool is well accepted, as is the notion that E. coli is the leading cause of UTI's. Some may argue, therefore, that the pathogenic nature of bacteria uniquely identified by M-PCR is unknown as researchers have yet to perform Koch's postulate studies on these species. Yet, though SUC has been accepted for over a century, 25% of UTI symptomatic women develop recurrent UTI's despite SUC providing definitive bacterial identification and antibiotic recommendations [15-17]. There is growing evidence of the pathogenic nature of the organisms uniquely identified by M-PCR. For example, A. schaalii, found to be involved in 53% of all M-PCR detected polymicrobial UTIs [10], was recently acknowledged as an uropathogen in older adults and young children [18]. Beyond missing critical pathogens, SUC fails to detect more than 2 organisms in an infection and does not consider bacterial interactions that impact susceptibility results. More than one in two patients (56.1%) who tested positive for UTIs were diagnosed with a polymicrobial infection based on M-PCR, and the odds of patients' resistance to most antibiotics increased with each additional bacterial organism present, possibly due to bacterial interactions [11]. Additionally, specific combinations of bacteria either increase susceptibility or increase resistance, depending upon the specific pair of organisms and the antibiotic the pair is exposed to. Therefore, the P-AST methodology may detect the effects of these interactions, compared with the antibiotic susceptibility performed on isolates as in SUC [11].

What are the cumulative effects of SUC failure? Those with recurrent UTI's are prophylactically prescribed antibiotics for recurrent UTI's. As these patients age, the prophylactic use of antibiotic for UTI results in inappropriate antibiotic use, i.e. antibiotics being prescribed at a dose higher then recommended and for longer periods of time then recommended. In fact, some antibiotics are prescribed for life [19]. Indeed, studies show that 55% of antibiotics prescribed for UTI's are inappropriate in the long-term home setting [20]. For older women, prophylactic antibiotic use was found to be associated with an increased risk of UTI related hospitalizations [21]. These patients may benefit from the M-PCR/P-AST test, which provide physicians with comprehensive and sensitive bacterial identification results from M-PCR along with susceptibility results from a pooled setting. As a result, therapeutic guidance may lead to more effective antibiotic selections. UTIs are a significant source of morbidity for the elderly. While conventional urine cultures remained the mainstay of diagnosing these patients for the last 180 years, evidence shows advanced diagnostic tests such as M-PCR/P-AST can identify pathogens not detected by SUCs, generates results more quickly, and provides antibiotic susceptibility results from real-world polymicrobial community [8,10-12]. Further evidence shows the detection and\treatment of these pathogens based on M-PCR/P-AST may lead to decreased hospital utilization as compared to patients who were managed using SUC [13].

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