Routine Urine Cultures Among Patients With Simple, Uncomplicated Pyelonephritis

Opposing authors provide succinct, authoritative discussions of controversial issues in emergency medicine. Authors are provided the opportunity to review and comment on opposing presentations. Each topic is accompanied by an Editor's Note that summarizes important concepts. Participation as at authoritative discussant is by invitation only, but suggestions for topics and potential authors can be submitted to the section editors.

Editor's Note: *Urine cultures can provide information on the microbiological cause and optimal treatment for patients diagnosed with acute pyelonephritis, but the need for routine cultures for patients with simple, uncomplicated pyelonephritis is unclear. In this Clinical Controversies series our pro and con discussants present opposing viewpoints of the benefits and drawbacks of routine urine cultures among patients with simple, uncomplicated pyelonephritis.*

URINE CULTURES IN ACUTE PYELONEPHRITIS: KNOWING WHAT YOU ARE UP AGAINST

Stephen Y. Liang, MD, MPHS
Divisions of Emergency Medicine and Infectious Diseases
Washington University School of Medicine
Saint Louis, MO

Michael J. Durkin, MD, MPH
Division of Infectious Diseases
Washington University School of Medicine
Saint Louis, MO

In the United States, annual rates of acute pyelonephritis in adults approach 15 to 17 cases per 10,000 women and 3 to 4 cases per 10,000 men, the majority of which are treated in ambulatory settings such as the emergency department (ED).[1] Urinary pathogen identification through microbiologic culture and in vitro antibiotic susceptibility testing optimizes diagnosis and management of acute pyelonephritis and is supported by international clinical practice guidelines.[2] A properly collected, noncontaminated urine culture provides meaningful and objective data not only to guide antibiotic therapy for the patient but also to track regional antibiotic resistance rates.

Urinary pathogen identification in the context of acute pyelonephritis aids the delivery of patient-centered care. When a causative microorganism is isolated, urine culture confirms the presence of a bacterial infection, identifies potential pharmacologic treatment options, and establishes the basis for tailoring antibiotic therapy to a unique episode of infection. Because microbiologic culture results may not be available for 48 to 72 hours, most ED antibiotic regimens directed against acute pyelonephritis are empiric. Selecting a safe empiric antibiotic to treat acute pyelonephritis can be challenging. Increasing antibiotic resistance rates are a serious problem in ED patient populations.[3-6] Greater than 20% of urinary *Escherichia coli* isolates are now resistant to trimethoprim-sulfamethoxazole.[7] Between 2003 and 2012, ciprofloxacin resistance increased from 4% to 12%; in the elderly, ciprofloxacin resistance is nearly 30%.[7] Furthermore, infections caused by extended-spectrum β-lactamase–producing Enterobacteriaceae (ESBL) are an underrecognized but important cause of acute pyelonephritis in the ED, even in community settings.[4,5] Advancing age, a history of recurrent or resistant urinary tract infection, recent antibiotic or other health care–related exposure, and various medical comorbidities are associated with a greater risk of acute pyelonephritis caused by an antibiotic-resistant organism.[3,4,8] Yet a surprising number of ED patients with ESBL infections lack these traditional risk factors.[5]

Blindly selecting empiric antibiotics without follow-up culture data places patients at a real risk of adverse events. Individuals treated with an empiric antibiotic without activity against a urinary pathogen (pathogen-drug mismatch) identified in culture are more likely to have persistence or relapse of infection, often requiring additional care, including return ED visits.[6,8,9] Earlier discovery of pathogen-drug mismatch followed by revision of an inadequate antibiotic regimen can only enhance and expedite treatment success. In integrated health care settings in which timely ambulatory follow-up is ensured, treatment of acute pyelonephritis with a narrow-spectrum oral antibiotic (eg, trimethoprim-sulfamethoxazole, a β-lactam) with close monitoring of the patient and urine culture results could be considered. The advantages of this approach include avoiding the collateral damage of

fluoroquinolones (eg, *Clostridium difficile* infection) and reducing selection pressure for future antibiotic-resistant organisms. Obtaining a urine culture in the setting of acute, uncomplicated pyelonephritis promotes targeted, patient-focused care.

Antibiograms for urinary pathogens including *E coli* are only as accurate and reliable as the microbiologic culture and antibiotic susceptibility data on which they are built. Sampling bias favoring hospitalized patients with severe infection or selected ambulatory patients with a history of antibiotic-resistant infection can paint a confusing picture when a hospital antibiogram is used to decide empiric therapy for uncomplicated pyelonephritis in the ED. Increasing evidence suggests that ED-specific antibiograms may differ significantly from inpatient antibiograms.[10,11] Antibiograms reflective of the heterogenous ambulatory population an ED cares for not only increase confidence in empiric ED antibiotic prescribing but also yield important and timely insights into community antibiotic resistance patterns. Obtaining urine cultures for a wide spectrum of patients presenting with acute pyelonephritis ensures an accurate characterization of the constantly evolving epidemiology of urinary tract infections and ultimately helps refine population-based treatment strategies and guidelines.

Although urine cultures may not change management for the majority of ED patients found to have a susceptible urinary pathogen, antibiotic resistance should be a concern for all emergency health care professionals. In a study of 10 academic US EDs participating in the EMERGEncy ID NET, greater than 45% of patients with acute pyelonephritis caused by a fluoroquinolone-resistant pathogen and 75% with ESBL infection initially received an empiric antibiotic lacking in vitro activity.[4] Of patients with ESBL infection who were discharged home from the ED, nearly 78% were prescribed a nonactive oral antibiotic. In an era of increasing antibiotic resistance, urine cultures obtained in the ED can significantly influence downstream antibiotic therapy for these patients.

We acknowledge that there are limitations with urine cultures. Periurethral contamination of urine specimens and inappropriate culturing of patients with abdominal pain from a separate cause can lead to false-positive results, triggering unnecessary antibiotic therapy. Standard urine culture techniques may fail to detect a significant number of fastidious and emerging urinary pathogens in clearly symptomatic patients.[12] Urinary pathogens deemed resistant by in vitro testing may not reveal the entirety of in vivo antibiotic activity. Several antibiotics achieve significantly higher concentrations in urine compared with serum, increasing their efficacy in treating urinary tract infections.[13] Innovative rapid molecular techniques for urinary pathogen identification and antibiotic susceptibility testing may in time render conventional urine culture obsolete.[14]

The fundamental questions of what urinary pathogen is responsible for a patient's infection and what antibiotic can effectively eradicate it with the least disruption to the human microbiome are worthy of asking if we are to be responsible stewards of increasingly finite antibiotic resources and hope to stem the tide of antibiotic resistance. For now, urine culture continues to provide meaningful answers to these questions.

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URINE CULTURES IN PYELONEPHRITIS: AN OVERSTATED REQUIREMENT

Brit Long, MD
Department of Emergency Medicine
San Antonio Uniformed Services Health Education Consortium
Fort Sam Houston, TX

Alex Koyfman, MD
Department of Emergency Medicine
The University of Texas Southwestern Medical Center
Dallas, TX

Michael D. April, MD, DPhil
Department of Emergency Medicine
San Antonio Uniformed Services Health Education Consortium
Fort Sam Houston, TX

Pyelonephritis involves infection of the upper urinary tract, including the renal parenchyma and pelvis. This disease process is distinct from simple cystitis, or bladder infection, and requires distinct management strategies. The Infectious Diseases Society of America guidelines for urinary tract infections in adult women recommend obtaining urine cultures for pyelonephritis, with initial empiric treatment adjusted according to the uropathogen isolated.[1] However, the guidelines fail to incorporate consideration of patient clinical status.[1] For patients with severe pyelonephritis and toxic appearance, we agree that intravenous antibiotics, hospital admission, and cultures of blood and urine are necessary. Conversely, we argue that urine cultures are not necessary for patients with simple pyelonephritis in the absence of severe toxicity, recent antimicrobial use, and recent hospitalization.[2,3]

Our position principally arises from the predictability of the infectious organisms resulting in pyelonephritis. Enterobacteriaceae species such as *Escherichia coli* account for greater than 80% of pyelonephritis infections.[2,3] The Infectious Diseases Society of America guidelines recommend fluoroquinolones as the mainstay of empiric antibiotic treatment for pyelonephritis.[1] Multiple studies highlight that the majority of *E coli* organisms are susceptible to these agents, with resistance rates less than 5%.[4,5] Non–*E coli* organisms in these studies exhibited similar susceptibility to fluoroquinolones. Although these guidelines suggest that β-lactam agents are less effective in treating pyelonephritis, the literature suggests that failure rates for treatment with cefdinir approximate 1%.[5]

Another argument against the routine collection of urine cultures among these patients is the limited utility of the resulting sensitivity data. Urine cultures report an organism and minimum inhibitory concentration, which is a measurement of reported in vitro microbe blood resistance to an antibiotic. This measure does not consider patient factors, in vivo medication levels and effects, or urinary drug concentrations.[6,7] In vivo resistance assesses microbe resistance at the site of activity (ie, the upper urinary tract in pyelonephritis). Antimicrobials possess greater in vivo activity than predicted by urine culture minimum inhibitory concentration, an in vitro evaluation.[7,8] One study highlighting this discordance between in vitro and in vivo activity examined patients with acute pyelonephritis and found that cefuroxime is effective in patients according to clinical improvement, regardless of whether the urine culture minimum inhibitory concentration was consistent with microbe susceptibility or resistance to this antibiotic.[9] This study demonstrated that urine culture minimum inhibitory concentration does not equate to antimicrobial inefficacy.[9]

These issues related to urine culture testing similarly speak to the limitations of using these data at the population level by constructing antibiograms with culture data to drive antibiotic choices.[6,7] The Infectious Diseases Society of America guidelines recommend use of these data inasmuch as they recommend using an antimicrobial with less than 20% in vitro resistance (<10% for fluoroquinolones).[1] Yet, to reiterate, in vitro resistance does not accurately portray clinical antimicrobial activity and so may overestimate uropathogen antibiotic resistance.[6,7] A study evaluating ciprofloxacin for pyelonephritis in a setting with high resistance (approximately 15%) found clinical cure rates to be statistically equivalent at 3 days in individuals with predicted susceptible versus resistant organisms, with no increase in the incidence of complications.[10] Ultimately, fluoroquinolones and cephalosporins such as ceftriaxone and cefdinir are effective in simple pyelonephritis because of antimicrobial concentrations and efficacy at the site of infection.[2,9] Reliance on antibiogram data to drive therapeutic decisions may hence lead to the unnecessary selection of more expensive agents with less favorable adverse effect profiles. Meanwhile, urine culture testing comes at increased population costs, ranging from $13 to $247, depending on the region and location; the cost-effectiveness of these expenditures is unclear.

The increased cost of urine culture testing is justifiable despite its limitations in patients at high risk for resistant organisms or poor outcomes. Such patients include those older than 60 years or who have hematologic disease, neurologic disease, chronic renal disease, urinary tract infection history, urinary catheter, and recent hospitalization or antimicrobial use (<3 months).[1] Yet for