



## A Review of Urinary Tract Infection and Asymptomatic Bacteriuria Management Initiatives Across Kentucky

On behalf of the Kentucky Antimicrobial Stewardship Innovation Consortium (KASIC)

The management and treatment of urinary tract infections (UTI) and asymptomatic bacteriuria (ASB) are common stewardship targets for institutions across the state of Kentucky. The KASIC Advisory Board members in Kentucky provide UTI initiatives that were implemented in their own institutions to serve as a framework for antimicrobial stewardship programs (ASP) hoping to implement a new initiative related to UTIs/ASB.

### Introduction

Promoting antimicrobial stewardship in the management of UTIs/ASB is a common practice for antimicrobial stewardship programs (ASP) across the state and nation. Due to the high volume of patients admitted with the diagnosis of UTI, a significant percentage of hospitals' antimicrobial utilization stems from the management of UTIs/ASB.<sup>1,2</sup> With such high numbers of UTIs being diagnosed for inpatients, ASPs often place a special emphasis on antimicrobial stewardship related to UTIs/ASB. However, the sheer volume of UTIs diagnosed within hospitals lends not only to inappropriate diagnoses of UTIs but inappropriate exposure to unneeded antimicrobials (e.g. ASB).<sup>3,4</sup>

For well-established ASPs, there have been a multitude of various strategies for the holistic management of UTIs/ASB. The strategies employed have ranged from updating urinalysis orders and subsequent workflows, to altering the reporting of urine cultures available to providers.<sup>4,5</sup> The available literature paired with UTI guidelines from the Infectious Diseases Society of America (IDSA) provides a blueprint for how ASPs should focus their efforts to provide guideline-concordant therapy while mitigating exposure to inappropriate antibiotics.<sup>6,7,8</sup> However, consolidating the vast amount of information available can be particularly difficult for new ASPs with limited access to resources and no formalized training in infectious diseases.

The purpose of this document is to summarize UTI/ASB initiatives put in place by well-established ASPs. The document will provide a framework of ideas for ASPs needing to implement stewardship initiatives related to UTIs/ASB. In addition to summarizing UTI/ASB initiatives, this document will provide pertinent primary literature, guidelines, and relevant KASIC pearls (see end of document) along with standardized definitions pertaining to urinalysis components and UTIs/ASB.

## Methods

The Kentucky Antimicrobial Stewardship Innovation Consortium (KASIC) was created in 2022 to help support antimicrobial stewardship optimization across the Commonwealth. The KASIC Advisory Board members represent 10 institutions or organizations that have well-established ASPs and are involved with antimicrobial stewardship activities across the state. KASIC requested the Advisory Board fill out a survey to describe stewardship initiatives for the management of UTIs/ASB at their respective institutions. The survey included two sections to be filled out, the first was diagnostic stewardship and the second was antimicrobial stewardship. Additionally, the respondents were asked to give their opinion on the success of the initiative.

## Results

Four institutions from the KASIC Advisory Board responded to the survey. The narrative review is listed in Table 1. Three of the four institutions implemented an initiative addressing diagnostic stewardship and all four institutions implemented an initiative addressing antimicrobial stewardship. The initiatives related to diagnostic stewardship included updates to urinalysis ordering and urine culture ordering. The initiatives related to antimicrobial stewardship included multiple initiatives, with the most common initiatives being provider and staff education, prospective audit and feedback, and microbiology lab changes (Table 2).

**Table 1. Narrative Overview of Institutional Responses**

<b>Institution</b>	<b>High-Level Narrative Review</b>
Institution 1	<ul style="list-style-type: none"><li>- Update to urinalysis order to prompt providers to select certain criteria before a urine culture reflex will be performed and removal of stand alone urine culture orders</li></ul>
Institution 2	<ul style="list-style-type: none"><li>- Culture comment on positive urine cultures to prompt treatment only on certain patients (urinary symptoms, pregnancy, or those undergoing urological procedure)</li><li>- Urine culture results updated with higher cefazolin MIC breakpoint for uncomplicated UTIs</li><li>- Asymptomatic bacteriuria provider reports to track treatment of ASB</li><li>- Updated order set to act as a guideline for treating patients with sepsis based on disease state, which includes urinary source</li></ul>
Institution 3	<ul style="list-style-type: none"><li>- Update to the procedure for ordering urinalysis and the criteria for performing a urine culture as a stand-alone or as a reflex from urinalysis</li></ul>
Institution 4	<ul style="list-style-type: none"><li>- Required &gt;10 WBC in the urinalysis in order for reflex to urine culture</li><li>- Provider and staff education on updated UTI guidelines</li></ul>

**Table 2. Categorical Responses for UTI Initiative Survey**

	Institution 1	Institution 2	Institution 3	Institution 4
Initiatives Addressing Diagnostic Stewardship	Green	Red	Green	Green
- Change to Urinalysis Ordering	Green	Red	Green	Red
- Change to Urine Culture Ordering	Green	Red	Green	Green
Initiatives Addressing Antimicrobial Stewardship	Green	Green	Green	Green
- Guideline Creation	Green	Green	Red	Red
- Provider and Staff Education	Green	Green	Green	Green
- Data Tracking and/or Analysis	Green	Green	Green	Red
- Clinical Decision Support	Green	Red	Green	Green
- Prospective Audit and Feedback	Green	Green	Green	Green
- Microbiology Lab Changes	Green	Green	Green	Green

Green = “yes”, Red = “no”

### Updates to Urinalysis and Urine Culture Ordering

Three of the four institutions implemented initiatives that changed the process for ordering urinalysis and urine cultures. Institution 1 implemented an initiative that required providers to select if a patient had urinary symptoms or was categorized within a special population when a urinalysis was ordered. If the urinalysis resulted with pyuria ( $\geq 10$  WBC) and one of the selections was made, then the urinalysis was reflexed to culture. An additional component of the initiative was that standalone urine cultures were no longer an option for providers to order.

Institution 3 implemented an initiative that targeted urinalysis and urine culture orders. When ordering urinalysis, providers were required to select if a patient was experiencing urinary symptoms or was experiencing sepsis of unknown origin to allow the urinalysis to reflex to culture. If one of the two selections was not made by the provider, then the urinalysis would reflex to microscopy. Another component of the initiative allowed providers to denote whether a patient was pregnant or undergoing a urological procedure and would result in a direct urine culture being ordered. Like institution 1, this initiative also implemented a step to remove stand-alone urine culture orders and removed the urine culture orders from order sets that did not pertain to sepsis or septic shock.

Finally, institution 4 addressed urine culture reflex criteria from ordering a urinalysis. For a UA to be reflexed to a urine culture there must be  $> 10$  WBC on the UA.

### Updates to Microbiology Results and Workflows

Institution 2 implemented multiple initiatives in conjunction with their microbiology department. The first initiative was to implement a comment on urine cultures to provide suggestions for when to treat or withhold antimicrobial therapy. The comment states, “Colonization of the urinary tract without infection is common. Treatment is discouraged unless the patient is symptomatic, pregnant, or undergoing an invasive urologic procedure.”

Institution 2 also implemented another initiative with their microbiology lab to include higher cefazolin minimum inhibitory concentrations (MICs) for urine culture results and a comment to denote that uncomplicated UTIs can be treated with cefazolin or oral cephalosporins in the setting of uncomplicated UTIs. The Clinical and Laboratory Standards Institute (CLSI) recommends utilizing higher cefazolin MIC breakpoints for *E. coli*, *Proteus mirabilis*, and *Klebsiella pneumoniae* when treating uncomplicated UTIs. Cefazolin is noted to have a susceptible breakpoint for  $\leq 2$   $\mu\text{g}/\text{mL}$  for Enterobacterales outside of the urinary tract, but is  $\leq 16$   $\mu\text{g}/\text{mL}$  for the three urinary pathogens in uncomplicated UTIs. Not only does this allow cefazolin to be used for treating common urinary organisms with elevated MICs in uncomplicated UTIs, but this can be inferred to use other oral cephalosporins (cefdinir, cefpodoxime, cefuroxime, and cephalexin).

### **Data Tracking**

Institution 2 implemented an initiative based on data tracking in hopes of influencing provider practices. The institution created an asymptomatic bacteriuria report that was presented to providers and leadership on a regular basis. The antimicrobial stewardship program at this health system tracked recommendations made to stop antibiotics that were initiated for ASB. The number of recommendations were tracked along with the providers' de-identified responses to the recommendations in aggregate. Due to multiple hospitals within the system, each facility had separate reports and could compare their antibiotic prescribing trends for ASB over time and between hospitals.

### **Guideline Creation**

Institution 1 created a guideline to assist with their UA and urine culture initiative. This guideline covered the diagnosis of ASB and UTI and outlined the updated algorithm for obtaining a urine culture on patients. This guideline served to update providers on the new workflow but also informed them on the most recent definitions for ASB and UTI to avoid outdated definitions of these disease states.

Institution 2 created a guideline within the electronic health record through an order set on the treatment of sepsis. This guided providers through the correct selection of antibiotics based on a specific source of sepsis, including urinary sources. This resource assisted providers in selecting appropriate regimens for suspected UTIs given local susceptibility and resistance patterns. Additionally, by limiting therapy options, unnecessarily broad antibiotics could potentially be avoided as they were not readily available to order through the order set.

### **Education and Prospective Audit and Feedback**

Each institution participated in various methods of education and prospective audit and feedback. However, zero institutions implemented specific initiatives that only pertained to these two categories.

## **Discussion**

The findings demonstrate UTI/ASB initiatives across the state of Kentucky vary between ASP programs. There are two categories that well-established programs focus on, diagnostic stewardship related to the urinalysis and urine culture, and antimicrobial stewardship.

Diagnostic stewardship related to urinalysis and urine culture ordering is a common practice for ASP programs and is a feasible starting point for programs looking to implement new stewardship activities. This approach was done by multiple institutions within Kentucky and has also shown benefit in previous studies. One specific initiative that could be considered is updating the workflow of only reflexing urine culture from certain criteria on an initial urinalysis. One study determined that by only reflexing urine cultures when white blood cells were at least 5/hpf, 93% of the reflexed cultures were positive, as opposed to only a 20% positivity rate when all urinalyses were reflexed.<sup>9</sup> This intervention alone can have a positive impact on the number of unneeded reflex tests and ultimately lead to cost savings for institutions.<sup>10</sup>

While the creation of guidelines and provider education can necessitate a more active role from ASPs, there are initiatives that can be implemented to take a more passive approach for stewardship programs. One example of a passive initiative could be creating cascade reporting rules for bacteria from the urine. Cascade reporting involves releasing tailored therapy options in the susceptibility report for bacteria. The emphasis is placed on displaying narrow spectrum agents, while suppressing more broad-spectrum agents in hopes of directing providers to utilize narrower therapy.<sup>11</sup> This method was utilized by multiple responding institutions in Kentucky and previous literature has demonstrated this can be an effective initiative to decrease broad-spectrum antibiotic use, even when specifically utilized for UTIs.<sup>11,12</sup>

Certain passive initiatives such as cascade reporting can demonstrate positive effects, however other passive initiatives may have mixed results. Nudge commenting stewardship initiatives have demonstrated mixed results across the literature. One study from Belk and colleagues demonstrated positive results by implementing a microbiology nudge comment that discouraged use of antibiotics for possible asymptomatic bacteriuria, which resulted in less antibiotic days of therapy after implementation.<sup>13</sup> However, another study demonstrated no de-escalation improvement from a microbiology nudge comment to encourage use of first-generation cephalosporins for UTIs caused by susceptible bacteria.<sup>14</sup>

## Conclusion

UTI/ASB stewardship initiatives varied across the state of Kentucky. New or under resourced ASPs may consider implementing an initiative tied to either diagnostic stewardship or antimicrobial stewardship to improve UTI/ASb management at their local institution.

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## Appendix

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### Additional Resources Available for Institutions

- Deconstructing the urinalysis: A novel approach to diagnostic and antimicrobial stewardship (<https://pmc.ncbi.nlm.nih.gov/articles/PMC8486290/>)
- Optimal Urine Culture Diagnostic Stewardship Practice—Results from an Expert Modified-Delphi Procedure (<https://academic.oup.com/cid/article/75/3/382/6446183>)
- The Five Ds of Outpatient Antibiotic Stewardship for Urinary Tract Infections (<https://journals.asm.org/doi/10.1128/cmr.00003-20>)

### Guidelines

- IDSA 2019 Clinical Practice Guideline Update for the Management of Asymptomatic Bacteriuria (<https://www.idsociety.org/practice-guideline/asymptomatic-bacteriuria/>)
- IDSA 2025 Guideline Update on Complicated Urinary Tract Infections (<https://www.idsociety.org/practice-guideline/complicated-urinary-tract-infections/>)
- IDSA 2010 Clinical Practice Guideline Update for the Treatment of Acute Uncomplicated Cystitis and Pyelonephritis in Women (<https://www.idsociety.org/practice-guideline/uncomplicated-cystitis-and-pyelonephritis-uti/>)
- Guidelines for the Prevention, Diagnosis, and Management of Urinary Tract Infections in Pediatrics and Adults - A WikiGuidelines Group Consensus Statement (<https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2825634>)



## Reading the Pee Leaves: Understanding Urinalysis

A urinalysis (UA) is a frequently ordered test that examines multiple biomarkers in the urine. Antibiotics are often initiated in response to a “positive” UA. Is this appropriate? How does a UA relate to, or not relate to, urinary tract infections (UTI)?

### What is in a urinalysis?

A UA comprises of two components: dipstick and microscopic analysis. The dipstick provides a rapid, point of care chemical analysis of the urine while microscopic analysis requires additional lab processing.<sup>1</sup> These analyses provide a snapshot of urologic conditions (e.g. renal calculi or UTI) and systemic diseases affecting the kidneys (e.g. diabetes).<sup>1,2</sup> As a result, competing etiologies can alter the results of a UA. Some components of a UA, such as ketones, bilirubin, or urobilinogen have no correlation to UTI.<sup>2</sup> Other UA components that may suggest infection are described below.

**Table 1: Components of a Urinalysis<sup>2-8</sup>**

Test	Usual Range	Dipstick or Microscopic	Comments
<b>pH</b>	4.5 – 8.0	Dipstick	pH ↑ with urea-splitting bacteria (e.g. <i>Proteus mirabilis</i> ), but ↑ also caused by vegan diet, respiratory or metabolic alkalosis, renal tubular acidosis
<b>Nitrites</b>	Absent	Dipstick	Produced by bacteria that reduce nitrate (e.g. <i>Escherichia coli</i> , <i>P. mirabilis</i> ), but some UTI pathogens (e.g. <i>Enterococcus</i> spp) do not reduce nitrate. Exposure to phenazopyridine; exposure of dipstick to air can also cause presence.
<b>WBC</b>	< 5	Microscopic	Both indicate <b>pyuria</b> , which may suggest urinary tract inflammation from infection, but also seen in patients with catheters, urinary stones, polycystic kidney disease, inflammatory diseases, chronic kidney disease, etc.
<b>Leukocyte esterase</b>	Absent	Dipstick	
<b>RBC</b>	< 5	Microscopic	Hematuria may be seen in UTIs, but is uncommon. Other causes include sickle cell disease, polycystic kidney disease, malignancy, trauma, anticoagulation
<b>Epithelial cells</b>	< 5	Microscopic	Presence suggest contamination and puts others UA findings into question
<b>Bacteria</b>	Absent	Both	Presence may suggest bacteriuria or contamination during collection
<b>WBC Casts</b>	Absent	Microscopic	Indicates inflammation of kidney tubules which includes pyelonephritis but also glomerulonephritis, interstitial nephritis, and other renal inflammatory processes

### Should antibiotics be started if the UA is “positive” or “abnormal?”

While several components may suggest presence of bacteria and/or inflammation, a “positive” or “abnormal” UA, in the absence of urinary tract symptoms, is NOT an indication for antibiotics. Exceptions include pregnant patients and those who are undergoing urological procedures where mucosal bleeding is expected.<sup>9</sup>

**Key Takeaway:** A urinalysis is limited by multiple competing etiologies that may skew its results, and a positive urinalysis is NOT an indication for empiric antibiotics in the absence of UTI signs or symptoms for most patients.

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## Don't Lose Your Head: Bacteriuria and Altered Mental Status

Many patients, family members, and practitioners attribute non-specific symptoms such as altered mental status (AMS) to urinary tract infections. As such, elderly patients are often given antibiotics for asymptomatic bacteriuria or [pyuria](#).<sup>1,2</sup> Asymptomatic bacteriuria (ASB) and AMS is common in the elderly and therefore frequently overlap.<sup>3</sup> Complicating the issue is concern that a true UTI exists, but patients with AMS are unable to verbalize urinary symptoms. Should we err on the side of caution and give antibiotics to all elderly patients with AMS and bacteriuria?

### What do the guidelines say?

The Infectious Diseases Society of America (IDSA) asymptomatic bacteriuria guideline addresses elderly patients that present with cognitive impairment, delirium, or a fall WITHOUT local genitourinary symptoms or systemic signs and symptoms of infection (e.g. fever, hemodynamic instability). The recommendation is to undergo careful observation rather than antimicrobial treatment. Other causes of AMS should be explored before antibiotics. Patients who fail to improve may be trialed on antibiotics.<sup>3</sup>

### What are outcomes in patients with AMS and ASB who are treated with antibiotics?

In a prospective cohort study of older delirious inpatients with asymptomatic bacteriuria, no difference in functional recovery occurred between 68 patients who received antibiotics and 22 patients who did not receive antibiotics.<sup>4</sup> However, screening and treating asymptomatic bacteriuria in elderly patients can be harmful. In a prospective study, 50 institutionalized elderly women were randomly assigned to receive or not receive treatment for asymptomatic bacteriuria. Most women had a history of Alzheimer's disease (73-79%) and were confused (69-79%). While the no antibiotic group had more persistence of bacteriuria, the treated group experienced more recurrent infections as well as increased incidence of antimicrobial resistance. The treatment group also had more adverse drug effects including rash, candidiasis, and diarrhea.<sup>5</sup>

### Are we missing true UTIs?

AMS occurring with no other systemic signs of infection in sepsis due to urinary tract infections is rare. A retrospective study examined the incidence of bacteremia from a presumed urinary source in hospitalized adults with asymptomatic bacteriuria and altered mental status. Of the 5059 patients, 1.8% developed bacteremia from a presumed urinary source. This number drops to 0.7% when excluding patients with signs of systemic infection.<sup>6</sup>

**Key Takeaways:** Bacteriuria in elderly patients with altered mental status is not always a urinary tract infection. In patients without systemic signs of infection (e.g. fever, hypotension, leukocytosis), initially monitor off antibiotics while treating alternative causes of altered mental status.

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## Urinary Tract Infection: Are Men Really that Complicated?

[Urinary tract infections \(UTIs\)](#) are one of the most commonly diagnosed bacterial infections and affect women more frequently than men. Lower rates of UTIs in men is thought to be due to a protective effect from a longer urethra. Similarly, when men do develop a UTI, it has historically been thought that the UTI was more complicated and required longer durations of treatment. However, are men really that complicated and do they need longer durations of antibiotics?

### What do guidelines recommend?

Hot off the presses, the 2025 Infectious Diseases Society of America (IDSA) complicated urinary tract infection (cUTI) guideline provides updated definitions intended to guide management. A key update is the inclusion of afebrile men in the classification for uncomplicated UTI, where the infection is confined to the bladder and no systemic signs of infection are present. The IDSA cUTI guideline notes that specific antibiotic choice and duration of therapy may still differ between men and women with uncomplicated UTI (uUTI) and that these will be addressed in the forthcoming uUTI guideline.<sup>1</sup>

The 2024 UTI WikiGuideline suggest standard recommended antibiotics and durations for cystitis, pyelonephritis, and febrile UTI, irrespective of biological sex.<sup>2</sup>

### What is the evidence?

Evidence is limited in cystitis and uncomplicated UTI as many trials excluded men. However in a recent double-blind, randomized controlled trial in afebrile men with UTI, 7 days of ciprofloxacin or trimethoprim-sulfamethoxazole was found to be non-inferior to 14 days for resolution of UTI symptoms (93.1% vs 90.2%) and recurrence (9.9% vs 12.9%).<sup>3</sup>

For pyelonephritis and complicated UTI, men made up 39.1% of patients in a randomized controlled trial that found 5 days of levofloxacin to be non-inferior to 10 days of ciprofloxacin.<sup>4</sup> Additionally, in studies demonstrating non-inferiority of 7 days to 14 days for uncomplicated gram-negative bacteremia, men comprised approximately 50% of patients included and urinary source was the majority source (~50-70%).<sup>5-7</sup>

**Key Takeaway:** Males sex alone does not make a urinary tract infection complicated and longer durations of treatment are not routinely needed.

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## ***Staphylococcus aureus* in a urine culture**

Isolation of *S. aureus* on urine culture is uncommon, representing <5% of positive urine cultures.<sup>1</sup> When it is isolated, it may represent colonization or specimen contamination. However, there are situations where isolation is clinically relevant.

### ***S. aureus* on urine culture may indicate invasive infection outside of the urinary tract**

Urine cultures positive for *S. aureus* may be a result of invasion of the pathogen and translocation from blood to urine. The proportion of concurrent bacteremia in patients with *S. aureus* on urine cultures varies widely between studies. A retrospective study of 2,054 patients with *S. aureus* on urine culture found 7% of patients also had *S. aureus* bacteremia.<sup>2</sup> Additionally, a review reported *S. aureus* is isolated on urine culture in up to 39% of patients with *S. aureus* bacteremia and has been associated with increased mortality.<sup>3</sup>

### ***S. aureus* on urine culture may indicate urinary tract infection (UTI)**

True *S. aureus* UTI is very rare and should be a diagnosis of exclusion after systemic disease has been ruled out.<sup>1</sup> Patients with indwelling urinary catheters or invasive urologic procedures are more likely to have UTI due to *S. aureus* than the general population.<sup>4</sup> A retrospective study of 102 patients with *S. aureus* on urine culture, most of whom were catheterized, found 33% of the cohort had symptoms of UTI.<sup>4</sup>

### **Key take-aways**

- *S. aureus* on urine culture may represent the following clinical scenarios:
  - Asymptomatic colonization or contamination during collection process
  - Invasive *S. aureus* infection outside of the urinary tract
  - *S. aureus* UTI (least common)
- **It is prudent to perform blood cultures in patients with *S. aureus* isolated on urine culture to rule out systemic infection, especially those at high risk of invasive disease.**

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## Pre-op Pee, Let it Be

Preoperative [asymptomatic bacteriuria \(ASB\)](#) is a risk factor for postoperative complications including surgical site infections. Therefore, screening with urinalysis and urine culture has been a common practice for many surgeons, especially in orthopedics. Does identification and treatment of preoperative ASB improve outcomes?

### What do the guidelines say?

The Infectious Diseases Society of America (IDSA) guidelines recommends AGAINST screening for and treating ASB in patients undergoing nonurological surgery.<sup>1</sup>

### What is the evidence?

In one study, patients with preoperative ASB undergoing hip arthroplasty were randomized to treatment or non-treatment of preoperative ASB. No difference in prosthetic joint infection (PJI) within one year of surgery was detected. In patients that did develop prosthetic joint infection, no organisms cultured from the PJI matched the organisms from preoperative urine culture.<sup>2</sup>

In cohort study of patients undergoing total or hip arthroplasty with preoperative ASB, no difference in 1- year PJI rates were detected between patients who were treated and those that were not treated. No organisms isolated from a PJI matched the organisms from preoperative urine culture.<sup>3</sup>

### What happens when screening for preoperative ASB is stopped?

A pre-post study of 2,754 patients undergoing orthopedic or spinal procedures evaluated the impact of institutional guidance to stop ordering preoperative urine cultures. This study found a 86.6% reduction of urine cultures from the 12 months prior (1141 urine cultures) to the 12 months post intervention (153 urine cultures). The surgical site infection (SSI) rate did not differ between pre (1.2%) and post groups (0.7%).<sup>4</sup>

In another pre-post study of 4,663 patients undergoing total joint arthroplasty or spinal fusion, preoperative urinalysis were reduced from 99% (499/502) in pre-intervention procedures to only 3% (126/4161) in pre-intervention procedures. Urine cultures were reduced from 18.7% (94/502) to 0.7% (31/4161). There were no differences in rates of catheter associated urinary tract infections and surgical site infections between the pre and post groups.<sup>5</sup>

**Key Takeaways:** Screening and treatment of preoperative ASB with urinalysis and/or urine culture does NOT reduce risk for surgical site infections in nonurological surgeries. Stopping preoperative screening for ASB reduces waste and is an important diagnostic stewardship opportunity.

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## Higher Cefazolin Urine Breakpoint

Antibiotics need to achieve therapeutic concentrations at the site of infection to work. Many antibiotics will concentrate in the urine, but the Clinical Laboratory Standards Institute (CLSI) does not differentiate most breakpoints based on site of infection, however cefazolin for uncomplicated urinary tract infections (UTIs) is an exception. The 2025 IDSA guidelines define uncomplicated UTIs as infections limited to the bladder without systemic signs of infection (e.g. fever).<sup>1</sup> How should a higher urine cefazolin breakpoint be used?

### What does CLSI recommend?

For uncomplicated UTI due to *E. coli*, *K. pneumoniae*, and *P. mirabilis*, the CLSI recommends a cefazolin [breakpoint](#) of 16 µg/mL, which is 3fold dilutions higher than the non-urinary breakpoint of 2 µg/mL.<sup>2</sup> This breakpoint may also act as a surrogate for oral cephalosporins including cefaclor, cefdinir, cefpodoxime, cefprozil, cefuroxime, cephalexin, and loracarbef. This higher cefazolin urine breakpoint may overcall resistance to [cefuroxime, cefpodoxime, and cefdinir, which may be susceptible if tested individually](#).

### What concentrations do cephalosporins achieve in the urine?

Cephalosporins in general reach high concentrations in the urine.<sup>3</sup> For example, the average urine cefazolin concentration was ~290 µg/mL obtained 8 hours after a single 500 mg cefazolin IM dose in 10 volunteers with varying renal function.<sup>4</sup> The average urine cephalixin concentration was ~ 1290 µg/mL obtained 4-6 hours after a single 1 g PO cephalixin dose given with and without food to 6 volunteers.<sup>5</sup>

### What antimicrobial stewardship benefits are there with the higher urine breakpoint?

A higher breakpoint will decrease the % of isolates categorized as resistant thereby increasing the role of empiric and definitive cefazolin and narrow spectrum oral cephalosporins (e.g. cephalixin) in the treatment of uncomplicated UTIs.<sup>6</sup> This can aid in preserving the activity of broader spectrum agents like ceftriaxone which are often used empirically in more complicated infections such as complicated UTIs and complicated intra-abdominal infections and lower the [risk for C. difficile infection](#).

### How can this be implemented?

The Food and Drug Administration did not endorse the higher urine breakpoints recommended by CLSI due to a lack of clinical outcomes data.<sup>7</sup> However, some have argued that it is unlikely that these studies will be done and they are not critical due to known PK-PD profiles and cephalosporin abilities for concentrating in the urine.<sup>3</sup> Microbiology labs can implement the CLSI breakpoints over FDA breakpoints if they are able (e.g. have the correct concentration of [wells](#) on their susceptibility panels, resources to validate, etc) and chose to do so.<sup>3</sup>

**Key Takeaway:** Using higher urine breakpoints for cefazolin allows for more frequent use of narrow-spectrum antibiotics for uncomplicated UTIs, which reduces risk of resistance and *C. difficile* infections.

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## Ceftriaxone Guided IV to PO

The Clinical and Laboratory Standards Institute (CLSI) recommends cefazolin, a first generation cephalosporin, as a surrogate for oral cephalosporins in uncomplicated urinary tract infections caused by *Escherichia coli*, *Klebsiella pneumoniae*, and *Proteus mirabilis*.<sup>1</sup> However the CLSI notes that cefazolin may overcall resistance to 2<sup>nd</sup> and 3<sup>rd</sup> generation oral cephalosporins such as cefuroxime, cefpodoxime, and cefdinir.<sup>1</sup> In practice, susceptibility testing for specific oral cephalosporins is not often performed. Clinicians may be tempted to use ceftriaxone as a surrogate to predict oral 2<sup>nd</sup> and 3<sup>rd</sup> generation cephalosporin activity. Is this safe?

### How well does ceftriaxone predict oral 2<sup>nd</sup> and 3<sup>rd</sup> generation cephalosporin susceptibility?

In a study of 312 ceftriaxone-susceptible Enterobacterales isolates from clinical blood cultures, susceptibilities to cefuroxime, cefdinir, cefpodoxime, and cefixime were 89%, 86%, 90%, and 94%, respectively.

When [inducible AmpC organisms](#) were excluded and only ceftriaxone-susceptible *E. coli*, *K. pneumoniae*, *K. oxytoca* and *P. mirabilis* were examined, 95%, 96%, 92%, and 98% of isolates were susceptible to cefuroxime, cefdinir, cefpodoxime, and cefixime, respectively.<sup>2</sup>

Another study of 88 *E. coli*, *K. pneumoniae*, *K. oxytoca*, *P. vulgaris* and *P. mirabilis* isolates assessed the use of ceftriaxone as a surrogate for cefpodoxime. The categorical agreement rate between ceftriaxone and cefpodoxime was high at 97%.<sup>3</sup>

**Key Takeaway:** Ceftriaxone susceptibility does not guarantee susceptibility to oral 2<sup>nd</sup> and 3<sup>rd</sup> generation cephalosporins, but high agreement (> 90%) has been seen with *E. coli*, *K. pneumoniae*, *K. oxytoca* and *P. mirabilis* isolates. Consult your microbiology lab for oral cephalosporin susceptibility availabilities.

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## Aminopenicillins for Enterococcal Cystitis: Teaching an Old Dog New Tricks

*Enterococcus* species are common pathogens for urinary tract infections (UTIs), especially among hospitalized patients.<sup>1</sup> *Enterococcus* infections can be difficult to manage due to [intrinsic resistance to multiple antibiotics](#).<sup>1</sup> Aminopenicillins (i.e. amoxicillin and ampicillin) can achieve high enough concentrations in the urine to potentially overcome resistance. Is it possible to leverage the high urinary concentrations of aminopenicillins to teach an old dog new tricks in the treatment of Enterococcal UTIs?

### **Aminopenicillin Breakpoints for *Enterococcus* spp. and Urinary Concentrations**

Per Clinical and Laboratory Standards Institute (CLSI), *Enterococcus* spp. with an ampicillin minimum inhibitory concentration (MIC) of 16 mcg/mL or higher are resistant to aminopenicillins. This breakpoint is set based on achievable **systemic** concentrations with typical dosing regimens of aminopenicillins.<sup>1</sup>

Aminopenicillins concentrate well in the urine and reach levels that far exceed the MIC range of ampicillin-resistant *Enterococci*. Ampicillin MICs in resistant strains typically range from 64-512 mcg/mL.<sup>1</sup> Contrast that with urinary concentration of 1500-3300 mcg/mL from a single 1 g parenteral dose of ampicillin. Even a **single** 500 mg dose of oral amoxicillin produces urinary concentration of 115-1850 mcg/mL.<sup>1</sup>

### **Aminopenicillins to Treat *Enterococcus* Cystitis Irrespective of Susceptibilities**

Some hospitals no longer routinely test and report antibiotic susceptibilities on Enterococcal isolates in urine culture, but instead display a comment encouraging use of aminopenicillins for treatment of Enterococcal cystitis.<sup>1,2</sup> In one institution where VRE is mostly ampicillin resistant, clinical cure for VRE UTIs were similar between patients treated with aminopenicillins (82.2%) vs non-aminopenicillins (81.6%), p=0.9.<sup>2</sup> At another site, high clinical cure rate (88%) were seen among patients who received ampicillin for ampicillin-resistant VRE urinary tract infections.<sup>3</sup>

**Key Takeaway:** Aminopenicillins (ampicillin/amoxicillin) achieve urinary concentrations high enough to overcome resistance and are still a treatment option for Enterococcal **cystitis** irrespective of antibiotic susceptibility testing. Increasing utilization of aminopenicillins for Enterococcal cystitis helps to preserve alternative agents that are broader spectrum, more expensive, or more difficult to administer such as linezolid and daptomycin.

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