Community acquired urosepsis

January 17, 2017 by Josh Farkas

contents

- Diagnosis (#diagnosis)
- Imaging (#imaging)
- Management
  - Resuscitation (#resuscitation)
  - Antibiotics: general principles (#antibiotics: general principles)
  - Antibiotics: what to use (#antibiotics: what to use)
  - Decompression & source control (#decompression)
- Checklist (#checklist)
- Podcast (#podcast)
- Questions & discussion (#questions & discussion)
- Pitfalls (#pitfalls)

Diagnosis

What is urosepsis?

- Bladder infection (cystitis) by itself rarely causes sepsis.
- Urosepsis nearly always results from infection that ascends to the kidneys (pyelonephritis), often spilling into the bloodstream causing bacteremia.

Urinalysis

- Urinalysis is sensitive
  - Urosepsis is nearly always accompanied by pyuria (>10 WBC per high power field).
  - Absence of pyuria largely excludes urosepsis (unless the patient is neutropenic or an obstruction is present).
• urinalysis is *nonspecific*
  • Abnormal urinalysis is common among healthy elderly patients due to *colonization* with bacteria (asymptomatic bacteriuria). Anyone with a chronic indwelling *foley* catheter is nearly guaranteed to have a positive urinalysis as well. Therefore, an abnormal urinalysis by itself doesn't necessarily mean anything.
  • Remember: bacteria in the *bladder* doesn't cause sepsis. Rather, sepsis usually reflects bacteria spreading up to the kidneys.

**additional supporting evidence**

• Diagnosing urosepsis requires additional clinical information *beyond* an abnormal urinalysis. For example:
  - (a) Clinical history suggestive of urosepsis (e.g. urgency, frequency, dysuria, suprapubic or flank pain, hematuria).
  - (b) Imaging evidence (e.g. CT scan reveals pyelonephritis).
  - (c) Abnormal urinalysis with *diligent exclusion* of all other common sources of infection (e.g. normal CXR, unremarkable CT of the abdomen/pelvis, no other localizing signs/symptoms).

**blood cultures**

• The utility of blood cultures has been questioned, as they will generally match the urine culture results.\(^1\)
  - Blood cultures will be most useful in patients who initially appear to have urosepsis, but later are diagnosed with something else (e.g. endocarditis or ascending cholangitis). Unfortunately, studies usually *exclude* such patients due to retrospective inclusion of only patients with a *final* diagnosis of pyelonephritis.
  - When possible, blood cultures should be obtained prior to antibiotics.

**complications to look for**

• (1) Most important complication is obstruction
  • 10% of patients have urinary obstruction, which requires immediate drainage to achieve source control.\(^2\) Obstruction causes pressure and bacteria to back up into the glomeruli, leaking into systemic circulation and exacerbating sepsis. If obstruction is detected, urology should be consulted immediately for stent placement (or, if that isn't an option, percutaneous nephrostomy drainage by interventional radiology).
  • (2) Less common complications
    • Perinephric or prostate abscess (which may require surgical or percutaneous drainage).
    • Emphysematous pyelonephritis or, less commonly, emphysematous cystitis (which may require surgical resection).

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**Abdominal CT, 240 mAs**

![Abdominal CT Scan Graph](https://emcrit.org/ibcc/urosepsis/)

**Brenner DJ and Heil EJ, NEJM 2007; 357:2277**
imaging in older urosepsis patients

- Stone-protocol CT scan is a good choice. This provides immediate and definitive imaging, which will help motivate and guide intervention (most urologists won't come into the hospital at 2 AM for a positive ultrasound).
- The only risk involved in this non-contrast CT scan is radiation exposure, which isn't a major issue among older patients.
- Beyond imaging the genitourinary tract, a stone-protocol CT will also image the abdomen. This may help avoid missing other diagnoses that can masquerade as pyelonephritis (e.g. cholecystitis, diverticulitis).

imaging in younger urosepsis patients

- Younger patients are at higher risk from harm due to radiation. They are also less likely to have an unusual presentation or anatomic complication.
- Bedside ultrasonography to exclude hydronephrosis may be adequate in these patients. This isn't quite as easy as it looks. If images are suboptimal or interpretation is unclear, there should be a low threshold to obtain a formal study or second opinion from a more experienced clinician.

resuscitation

This is similar to resuscitation of other septic patients. The only difference here is that patients with urosepsis may tend to recover a bit faster than those with other sources of sepsis. Therefore, patients who are requiring only low-dose vasopressors don't necessarily need a central line. Especially with the use of metabolic resuscitation, patients can often be liberated from low-dose vasopressors quickly.

antibiotics: general principles

Urosepsis is somewhat unique among infections because a causative organism is nearly always cultured. This allows for de-escalation of antibiotics within 2-3 days of admission. Initial therapy should be sufficiently broad to cover any likely pathogen.
what are we targeting?


<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Female outpatient rates</th>
<th>Male outpatient rates</th>
<th>Female inpatient rates</th>
<th>Male inpatient rates</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Escherichia coli</em></td>
<td>81.6%</td>
<td>74.0%</td>
<td>84.5%</td>
<td>71.0%</td>
</tr>
<tr>
<td><em>Klebsiella</em> species</td>
<td>2.6%</td>
<td>6.0%</td>
<td>3.4%</td>
<td>7.3%</td>
</tr>
<tr>
<td><em>Proteus</em> species</td>
<td>1.2%</td>
<td>2.2%</td>
<td>1.9%</td>
<td>1.5%</td>
</tr>
<tr>
<td><em>Enterobacter</em> species</td>
<td>1.3%</td>
<td>1.9%</td>
<td>1.9%</td>
<td>0%</td>
</tr>
<tr>
<td><em>Pseudomonas</em> species</td>
<td>0.5%</td>
<td>1.9%</td>
<td>1.2%</td>
<td>1.5%</td>
</tr>
<tr>
<td><em>Citrobacter</em> species</td>
<td>0.3%</td>
<td>2.2%</td>
<td>0.4%</td>
<td>2.9%</td>
</tr>
<tr>
<td><em>Enterococcus</em> species</td>
<td>1.0%</td>
<td>4.4%</td>
<td>1.5%</td>
<td>4.4%</td>
</tr>
<tr>
<td><em>Staphylococcus saprophyticus</em></td>
<td>2.8%</td>
<td>0.9%</td>
<td>0%</td>
<td>2.9%</td>
</tr>
<tr>
<td><em>Staphylococcus aureus</em></td>
<td>0.2%</td>
<td>0.6%</td>
<td>0.4%</td>
<td>1.5%</td>
</tr>
<tr>
<td>Other</td>
<td>8.5%</td>
<td>5.9%</td>
<td>4.8%</td>
<td>7.0%</td>
</tr>
</tbody>
</table>

Czaja CA et al. 2007. PMID 17593908

- The vast majority of urosepsis is due to gram-negative rods (mostly *E. coli*).³
- Occasionally the culprit is a gram-positive (mostly enterococci, but occasionally staph saprophyticus).
- *Pseudomonas* is possible, albeit unlikely. Some other series have reported rates of pseudomonas between 2-5%.⁴⁻⁶

**urine gram stain**

- Some hospitals are able to perform STAT gram stains on urine, which can be extremely helpful.
  - Gram-positive detected: May tailor therapy to focus on enterococcus and Group B streptococci.
  - Gram-negative detected: Focus on gram-negative coverage.
- The regimens below are designed in the absence of a urine gram stain (realistically, gram stain usually isn’t immediately available).

**urine nitrites**

- Nitrites are generated by gram-negative enteric pathogens, but not gram-positives.⁷,⁸
  - In urinary tract infection with gram-positives, nitrites are detected only rarely (~5% of cases).
  - In urinary tract infection with gram-negatives, nitrites are commonly detected (~40% of cases).
- Therefore:
  - Positive nitrites has a likelihood ratio for gram-negative infection of ~8.
  - Negative nitrites has a likelihood ratio for gram-negative infection of ~0.6 (this provides little useful information).
- Given that the prevalence of gram-negative infection is ~95% to begin with, a positive urinary nitrite result results in post-test probability of gram-negative infection >99%. This might be useful in determining the necessity of covering for gram-positive pathogens, if a urinary gram stain isn’t available.

**favorable pharmacology**

- Several factors are working in our favor here:
  - In the absence of obstruction, the flow of urine tends to clear bacteria from the kidneys and bladder.
  - Drugs which are excreted unchanged by the kidney will be concentrated in the urine. This can allow for clinical cure, even if the organism is "resistant" at drug concentrations which are achieved in the blood (although this shouldn't be relied upon in septic patients who may have bacteremia).⁹
  - Unlike an abscess or socked-in lung consolidation, tissue penetration isn’t a huge problem here.
  - These factors shouldn’t lead us to be sloppy in antibiotic selection. However, at the same time, not every drug-resistant organism must be treated with meropenem (more on this below).¹⁰

antibiotics: what to use

[back to contents/ at top]
lack of consensus!

Above are treatment recommendations from common sources. These recommendations vary widely. Some of this variability may reflect irregularities in the definition of "complicated" versus "uncomplicated" pyelonephritis.

Below is one attempt at antibiotic selection, based on available evidence (as cited). Please be aware that this doesn't represent a universal consensus. Furthermore, this won't necessarily apply perfectly to every geographic locale, depending on your antibiogram.

**common error #1: using a fluoroquinolone**

- Fluoroquinolones are poor drugs for use in critically ill patients for several reasons, as explored [here](https://emcrit.org/pulmcrit/uoroquinolone-critical-illness/).
- Over-use of fluoroquinolones in the community has led to increasing antibiotic resistance (e.g. ciprofloxacin resistance among E. coli is reaching 15%).
- Fluoroquinolones simply are no longer adequate coverage for urosepsis.

**common error #2: using a 3rd generation cephalosporins (ceftriaxone or ceftazidime)**

<table>
<thead>
<tr>
<th>Source</th>
<th>Antibiotic recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>UpToDate* Acute complicated UTI** (including pyelonephritis)</td>
<td>Carbapenem (e.g. meropenem) PLUS MRSA coverage (vancomycin, doxycycline, or linezolid)</td>
</tr>
<tr>
<td>Sanford Guide 2018 Uncomplicated pyelonephritis in men/women</td>
<td>Low risk of resistant GNB: Ciprofloxacin or Levofoxacin, High risk of resistant GNB: Meropenem</td>
</tr>
<tr>
<td>Hopkins Antibiotic Guide* Acute uncomplicated pyelonephritis</td>
<td>Depending on local antibiogram may use any of the following: Ciprofloxacin, Levofoxacin, Ceftalexan, Gentamicin, Tobramycin, Piperacillin-Tazobactam (with or without aminoglycosides), Meropenem</td>
</tr>
</tbody>
</table>

*Accessed on file 12/14/18.
**UpToDate defines "complicated" UTI in a unique fashion, to include what some other references term "uncomplicated" pyelonephritis.

- Ceftriaxone or ceftazidime are suboptimal for urosepsis, mostly for two reasons:
  - **1) Main problem:** *AmpC inducible beta-lactamase*
    
    - Many species of gram-negative organisms have *inducible* beta-lactamases (AmpC-type). These bacteria may appear to be sensitive to an antibiotic *in vitro*, but *in vivo* the bacteria will up-regulate its beta-lactamases and become resistant. The main offenders here highlighted in pink above.
    
    - Based on the antibiogram, it may appear that ceftriaxone or ceftazidime has very good gram-negative coverage. However, accounting for the many species which may have AmpC beta-lactamases, this coverage actually isn't terrific.
  
  - **2) Enterococcus:** Commonly used cephalosporins don't cover enterococcus (the only cephalosporin with enterococcal activity is ceftaroline).
  
  - **3) Pseudomonas:** Pseudomonas isn't a major uropathogen, so this may not be a huge problem. Ceftazidime will cover pseudomonas.

**common error #3: over-use of vancomycin**

https://emcrit.org/ibcc/urosepsis/
Methicillin-resistant staph aureus (MRSA) is an extremely uncommon cause of community-acquired urosepsis. For example, the table shown above reported staph aureus in 0.25% of cases admitted from the community. The vast majority of these cases are presumably *methicillin*-sensitive staph aureus, leaving the incidence of methicillin-resistant staph aureus well below 0.25%

Incidentally, if staph aureus is detected in the urine this should trigger suspicion of some other infectious process (e.g. endocarditis with hematogenous seeding of the kidneys).

If a resistant gram-positive pathogen is involved in urosepsis, the most likely culprit is *vancomycin-resistant enterococci (VRE)*. Vancomycin won't help with this. So if you want to use an agent that covers resistant gram-positives, the most logical choices are either linezolid or daptomycin (drugs that will cover both MRSA and VRE). None of these agents are really needed for community-acquired urosepsis, but at least linezolid or daptomycin would make more sense than vancomycin.

preferred option #1: piperacillin-tazobactam

- Piperacillin-tazobactam checks all the boxes:
  - Excellent gram-negative coverage including pseudomonas.
  - Coverage of community-acquired enterococci (*enterococcus faecalis*).
  - Adequate coverage for AmpC enterobacteriaceae (may not be ideal for them, but emerging evidence suggests that it's OK).  
  - The main limitation of piperacillin-tazobactam is that it can miss extended-spectrum beta-lactamase (ESBL) gram-negatives. Some reports indicate that ESBL are being seen increasingly in the community, particularly in certain geographic locales. Fortunately, piperacillin-tazobactam may often be adequate for ESBL species, especially urinary tract infection with ESBL E. Coli.
- **Role:** Overall, piperacillin-tazobactam is a solid choice for urosepsis in locations with a low rate of ESBL gram-negatives.

preferred option #2: meropenem

- Meropenem has excellent coverage for *enterococcus faecalis* and gram-negatives (including pseudomonas, AmpC or ESBL enterobacteriaceae).
- **Role:**
  - 1) Severe penicillin allergy: Meropenem has no cross-allergy with penicillins, and is safe to use even in patients with a history of anaphylaxis to penicillins.
  - 2) Superior to piperacillin-tazobactam in locales with high rates of ESBL gram-negatives.

alternative option: cefepime

- Antibiotic spectrum of cefepime:
  - Better gram-negative coverage compared to ceftriaxone (cefepime covers gram-negatives with AmpC beta-lactamase and pseudomonas).
  - Lacks any enterococcal coverage.
- **Role:**
  - 1) Would be a good choice for patient with gram-negative infection (e.g. urine gram stain shows gram-negative bacilli, or urinalysis is positive for nitrites).
  - 2) Can be used in patients with penicillin allergy (cefepime's side chain doesn't cross-react with penicillins).

decompression

Foley catheter placement

- Should be placed for measurement of urine output.
- In some cases (e.g. urosepsis due to prostatic hypertrophy), the foley may also help by decompressing the infection.

source control in cases with obstruction (e.g. an obstructing stone)

- Source control requires relief of the obstruction. Decompression may be done by urology (e.g. stent placement) or interventional radiology (percutaneous nephrostomy tube placement).
- Sometimes decompression releases bacteria into the blood, causing patients to deteriorate. Thus, patients should ideally receive antibiotics and hemodynamic stabilization immediately, **before** intervention.
community-acquired urosepsis

- **Diagnostic tests**
  - Urinalysis & urine culture
  - Blood cultures x 2 (don’t repeat if already done at another hospital)
  - Procalcitonin
  - Imaging: Stone protocol CT (>35YO) or renal ultrasonography (<35YO)
    - Obstruction = STAT urology consult.

- **Resuscitation**
  - Fluid, early vasopressors, adjunctive therapies as per usual.

- **Antibiotics**
  - Piperacillin-tazobactam monotherapy generally adequate.
  - Meropenem may be used if PCN-allergy or high local rate of ESBL organisms.

going further:

- [Urosepsis](https://lifeinthefastlane.com/ccc/urosepsis/), (Chris Nickson, LITFL)
References


The Internet Book of Critical Care is an online textbook written by Josh Farkas (@PulmCrit), an associate professor of Pulmonary and Critical Care Medicine at the University of Vermont.