Updates on Urology Pharmacology: Focus on Antibiotics

Kristen Nichols, PharmD, BCPS (AQ-ID), BCPPS
Assistant Professor, Pharmacy Practice
Butler University College of Pharmacy and Health Sciences
I could talk about antibiotic use and resistance ALL day

Evidence-based = challenging

[MANY studies needed]
Objectives

• Design and monitor a therapeutic regimen for a patient with a urinary tract infection caused by a multi-drug resistant organism

• Describe ways to prevent or delay the development of antibiotic resistance

• Compare risks and benefits of continuous antibiotic prophylaxis

• Discuss strategies for optimal surgical prophylaxis in urologic procedures
Kevin: a 5 year old with a complex urologic tract

History of multiple UTIs
- Daily cephalexin prophylaxis at home

Culture obtained
- Cloudy urine
- Increased accidents
- Fever

Empiric therapy
- Cefixime
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<th>Extended-spectrum beta-lactamase producer</th>
</tr>
</thead>
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<tr>
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</tr>
<tr>
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Antimicrobial Resistance

Predictors of antimicrobial resistance in UTIs
- Urinary tract abnormalities (& bladder dysfunction)
- 1 course of antibiotics in past 6 months
- Antibiotic prophylaxis use
- Recent hospitalization

Multi-Drug Resistant Organism (MDRO)
- Typically resistant to ≥ 1 organism from ≥ 3 drug classes
- Resistance genes are often paired

ESBL-producing organisms
- 5-10% of UTIs in children
- Force use of second-line drugs
- Increase hospital length of stay and cost

# Antimicrobial choice

<table>
<thead>
<tr>
<th>Empiric</th>
<th>Directed</th>
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<tr>
<td>• Use local antibiogram data</td>
<td>• Use susceptibility panel</td>
</tr>
<tr>
<td>• Urinary isolates from your population ideal</td>
<td>• Most narrow option</td>
</tr>
<tr>
<td>• Consider risk factors</td>
<td>• Least likely to cause collateral damage</td>
</tr>
<tr>
<td>• Previous patient cultures</td>
<td>• Patient-specific factors</td>
</tr>
<tr>
<td></td>
<td>• Allergies</td>
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</tbody>
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Big Names in Resistance

Extended Spectrum Beta-Lactamase (ESBL)
- Hydrolyzes extended-spectrum penicillins & cephalosporins
- Most common in *E. coli* and *K. pneumoniae*
- Beta-lactamase inhibitors like tazobactam retain activity

AmpC Beta-Lactamase
- Most common in *Enterobacter cloacae, Serratia marcescens, Morganella morganii*
- Hydrolyzes piperacillin/tazobactam but not cefepime

Carbapenem-Resistant Enterobacteriaceae (CRE) & *Klebsiella Pneumoniae* Carbapenemase (KPC)
- Hydrolyzes carbapenemems
- Often resistant to other classes as well

Extended Spectrum Beta-Lactamases

Treatment Options
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Oral: Nitrofurantoin

- Only for cystitis
  - Doesn’t reach adequate tissue concentrations for pyelonephritis
  - Not for use if CrCl < 30 mL/min

- Precautions:
  - May lead to hemolytic anemia in patients who are G6PD deficient
  - Not for <1 month of age

- Liquid dosage form has to be given every 6 hours for treatment

- Macrocrystal/monohydrate formulation can be given twice daily
Oral: Fosfomycin Tromethamine

- **Only** for treatment of “uncomplicated” cystitis
  - Due to concentrations reached with oral therapy
- **Spectra of activity:**
  - Enterobacteriaceae
  - Pseudomonas
  - MRSA & VRE
- Available as a powder packet (3 grams)
- Well tolerated
  - Potential mild GI distress
- **Not FDA-approved in children**
- **Suggested dosing:**
  - <18 yo: 2 grams x 1
  - > 18 yo: 3 grams x 1
  - Principi et al used 1 gram for <1 year old
- **Has been used every other day x 6 – 21 days for complicated UTI in adults**

Oral: Fluoroquinolones

- Well-absorbed (80-100%)
- Save for when absolutely necessary
  - Many adverse effects, some serious
  - Collateral damage – rapid development of resistance
- Dose at higher end of range to avoid resistance
  - Renal adjustments needed
- Delafloxacin: new FQ (not yet FDA approved or studied in < 18 years)
Intravenous: Carbapenems

- Typically considered drugs of choice for ESBL-producing organisms
- Overuse can result in carbapenem-resistant Enterobacteriaceae
- Drug interaction: meropenem and valproic acid
- Very broad spectrum – gram-negatives, gram-positives, & anaerobes

Intravenous: Piperacillin/Tazobactam

• 80-90% of isolates will demonstrate in vitro susceptibility
• Controversial in the treatment of ESBL+ infections
  – Less effective for invasive infections
  – Majority of infections in studies demonstrating success were UTI or biliary tract infections
• High urine concentrations
• Limited data using in children

Intravenous: Aminoglycosides

- Often resistant in ESBL+ infections
- Not used alone for bacteremia
  - Potential increased mortality
  - Development of resistance
- Ok alone for uncomplicated UTI
  - Very high urine concentrations
- IV only (no oral)
- Once-daily dosing
  - Optimizes pharmacokinetic and pharmacodynamic properties
- Monitoring:
  - Nephrotoxicity
  - Ototoxicity with repeated or prolonged courses
Intravenous: Cefoxitin (?)

• Will be “susceptible” on the in vitro susceptibility panel
  – Possibly related to inoculum effect?

• VERY limited data for use in ESBL+ infections
  – None in pediatrics

• If using for carbapenem-sparing:
  – Aggressive dose
  – UTI only (or potentially when source control is very good and severity is low)
  – Resistance less like to develop in future with *E. coli* as compared to *K. pneumoniae*
  – Close monitoring

Intravesicular: Sodium oxychlorosene

- OTC as Clorpactin WCS-90
- Topical antiseptic – bladder irrigation
  - 0.025 – 0.02%
- Typically 2 x 10 minute instillations BID
  - For 3 days
- Can cause some burning
- Has also been used for prophylaxis
- Not studied or FDA-approved in children

Kevin: a 5 year old with a complex urologic tract

- History of multiple UTIs
- Daily cephalexin prophylaxis at home
- Culture obtained
  - Cloudy urine
  - Increased accidents
  - Fever
- Empiric therapy
  - Cefixime

- Ciprofloxacin 15 mg/kg PO Q12H
- Fosfomycin a reasonable option
- If bacteremic or upper tract involved → IV piperacillin/tazobactam
10 year-old with a KPC-UTI and Bacteremia

<table>
<thead>
<tr>
<th>Susceptibility</th>
<th>Klebsiella pneumoniae - Carbapenem Resistant</th>
<th>CARBAPENEM RESISTANCE GENE DETECTION - PCR-RT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>BACTERIAL SUSCEPTIBILITY MIC PANEL</td>
<td></td>
</tr>
<tr>
<td>Amoxicillin</td>
<td>&gt;=32 ug/mL</td>
<td>Resistant</td>
</tr>
<tr>
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<td>&gt;=32 ug/mL</td>
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</tr>
<tr>
<td>Cefazolin</td>
<td>&gt;=64 ug/mL</td>
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<td>4 ug/mL</td>
<td>Susceptible</td>
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<tr>
<td>IMP</td>
<td></td>
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</tr>
<tr>
<td>KPC</td>
<td></td>
<td>Detected</td>
</tr>
<tr>
<td>Levofloxacin MIC</td>
<td>&gt;=8 ug/mL</td>
<td>Resistant</td>
</tr>
<tr>
<td>Meropenem</td>
<td>&gt;=16 ug/mL</td>
<td>Resistant</td>
</tr>
<tr>
<td>NDM</td>
<td></td>
<td>Not Detected</td>
</tr>
<tr>
<td>OXA48</td>
<td></td>
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</tr>
<tr>
<td>Piperacillin/Tazobactam</td>
<td>&gt;=128 ug/mL</td>
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| Susceptibility          | Enterococcus species                       |                                             |
|-------------------------|---------------------------------------------|                                             |
|                         | BACTERIAL SUSCEPTIBILITY MIC PANEL          |                                             |
| Ampicillin              | <=2 ug/mL                                   | Susceptible                                |
| Vancomycin              | 1 ug/mL                                     | Susceptible                                |
Klebsiella pneumoniae Carbapenemase

- NO beta-lactams
- Fosfomycin (cystitis only)
- Colistin
  - Dosing guidance limited
- Combination options:
  - Double carbapenem
    - Meropenem + ertapenem
    - Recent study demonstrated improved mortality vs tigecycline, colistin, or gentamicin
  - Extended-infusion meropenem (3-4 hours) + aminoglycoside, fluoroquinolone, or colistin

## Newer Therapies

<table>
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<tr>
<th>Ceftazidime/avibactam</th>
<th>Meropenem/vaborbactam</th>
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<tr>
<td>• Approved in adults 2015</td>
<td>• Approved in adults last week</td>
</tr>
<tr>
<td>• Ceftazidime is well-studied in children</td>
<td>• Complicated UTI</td>
</tr>
<tr>
<td>• Avibactam isn’t</td>
<td>• Not yet available</td>
</tr>
<tr>
<td>– Most BLI aren’t</td>
<td>• Will be reserved for patients/isolate in true need</td>
</tr>
<tr>
<td>• Active against ESBLs and many carbapenemases</td>
<td></td>
</tr>
<tr>
<td>– No Ambler class B</td>
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https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm573955.htm
### 10 year-old with a KPC-UTI and Bacteremia

**Susceptibility**

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</tr>
<tr>
<td>Vancomycin</td>
<td>1 ug/mL</td>
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Preventing Development of Resistance: 

*Antibiotics are a shared resource – and becoming a scarce resource*
**Strategies to Save our Antibiotics**

1. Use antibiotics only when necessary
   a) Don’t treat asymptomatic bacteruria
   b) Narrowest spectrum possible
2. Avoid high-impact agents (FQs, cephalosporins) when possible
3. Limit to minimum effective duration
4. Optimize doses based on PK/PD
5. Use prophylaxis wisely
Cephalosporins

• Association with:
  – Vancomycin-resistant Enterococci (VRE)
  – ESBL-producing *K. pneumoniae*
  – Multidrug resistant *Acinetobacter*
  – *Clostridium difficile* infections

• Most data with 3rd generation cephalosporins
  – Ceftriaxone, cefotaxime (IV)
  – Cefdinir, cefixime, (oral)
  – Narrower options like cephalexin likely have less impact

Fluoroquinolones

- **Risks to patient**
  - New FDA Boxed Warning
    - Disabling and potentially irreversible adverse effects
    - Neuropsychiatric effects—CNS, peripheral neuropathy
    - Fluoroquinolone-Associated Disability
  - Musculoskeletal adverse effects
    - Tendinopathy, arthritis, arthralgia, gait abnormality

- **Risks to resistance & collateral damage**
  - Resistance to fluoroquinolones develops more rapidly than with other antibiotic classes
  - Association with:

  - ESBLs
  - MRSA
  - Carbapenem-resistant *Pseudomonas*
  - *C. diff*
  - *Candida*
  - VRE

Probability of gram-negative bacteria remaining susceptible as a function of duration of treatment days

Overview of Prophylaxis

Makes a lot of sense

• Historically a good alternative to surgery
• Association between UTI & scarring
• Some evidence does indicate decreased UTIs and renal scarring
• Makes us feel like we’re doing something

Some serious downsides

• Does it truly prevent UTIs or renal scarring? (mixed results & varied populations)
• Increase in resistance due to impact on bowel and periurethral flora
• Adverse effects to patient
• Can’t prevent everything

Antibiotic Prophylaxis

Anti-infectives are the only drugs where use in one patient can impact their efficacy in others.
UTI Prophylaxis in VUR

• Studies that demonstrate benefit of prophylaxis
  – PRIVENT trial: modest benefit (19% to 13%)
  – Swedish reflux trial: prevented renal damage

• Studies that demonstrate lack of benefit or harm
  – Clarke et al: increased infections in children who catheterize (CIC)
  – Garin et al: more recurrences in antibiotic group vs prophylaxis group
  – 2011 AAP UTI Guidelines: meta-analysis of 6 studies
  – Hari et al: prophylaxis group had an increased risk of developing UTI; similar scarring; increased resistance

RIVUR Study

- 607-patient randomized placebo-controlled study
- >90% females; median age 12 mos; mostly grade II & III

**Results:**
- Febrile or symptomatic UTI recurrence reduced by half (HR 0.5; 95% CI 0.34-0.74)
  - 14.8% vs 27.4% (missing data excluded)
  - 16 antibiotic patient-years to prevent 1 case
- Renal scarring was not impacted (11.9% vs 10.2%)
- Resistance to TMP/SMX: 63% vs 19%
  - Of patients with UTI recurrences caused by *E.coli*
- Effect lost when no initial febrile episode or bowel/bladder dysfunction
  - See figure 3 in article

The Problem with Data

- Prophylaxis should be decided on a patient-by-patient basis
  - Slant towards minimization
- Considerations:
  - Potential risk stratification?
  - Patients who are difficult to diagnose or present with severe UTI
  - Febrile on initial presentation
  - Degree of reflux/dilatation
  - Presence of bladder or bowel dysfunction

- Studied populations vary drastically
- Adherence to therapy should be considered
- Bacteria are constantly evolving
- The “holy grail” study is unlikely to be completed

Bacteria are constantly evolving.
Easterbrook et al: Updated Systematic Review 2017

11 studies → 3909 patients; 10 non-randomized

Significant heterogeneity

UTI rates: 9.9% in prophylaxis group vs 7.5% in no-prophylaxis group

Optimal peri-operative prophylaxis

Prevents infection & therefore antibiotic use

Avoids antibiotic exposure when unnecessary

Pediatric Health Information System Database Studies

- Sandora et al: evaluated variability in prophylaxis across all surgical procedures 2010 - 2013
  - Urologic procedures had greatest variability
- Chan et al: evaluated variability in prophylaxis in clean and clean-contaminated urologic procedures 2012 - 2014

Prophylaxis in Outpatient Circumcision

• Evaluated 84,226 outpatient circumcisions (>30 days to <18 years) in PHIS database

• Surgical prophylaxis did not prevent:
  – Surgical site infection (0.1% vs 0.2%)
  – Penile reoperation (0.01% vs 0.04%)
  – Hospital visit (5.5% vs 5.5%)

• Surgical prophylaxis did result in:
  – More allergic reaction (3.5% vs 2.9%, p<0.05)
  – More hospital visits (multivariate analysis)

Surgical Prophylaxis in Hypospadias Repair

- ~76% of pediatric urologists reported using antibiotic surgical site infection (SSI) prophylaxis for stented hypospadias repair
- Overall very low SSI rate

224 patients retrospectively evaluated

Pre-op antibiotics vs none (SMX/TMP while stent in place)

No difference in:
- SSI (1 vs 0)
- Complications (5.2 vs 6.7%)

Key Takeaway Points

• Resistant isolates often require use of less-studied, more harmful, or IV-only medications

• There are a variety of strategies to help delay development of resistance, including avoiding use of FQs, optimizing doses, and minimizing duration

• Continuous antibiotic prophylaxis should be limited to a small population at highest risk
  • Risks and benefits of prophylaxis should be considered
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Assistant Professor, Pharmacy Practice
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