Pediatric Antimicrobial Stewardship: Focusing on What Matters

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Children’s Medical Center Dallas
Dallas, Texas
Disclosure

• Faculty have nothing to disclose.
Learning Objectives

• Define major goals for antimicrobial stewardship in the pediatric population and evaluate progress in achieving those goals.
• Apply antimicrobial stewardship principles in the evaluation of a patient case and recommend evidence-based alterations to antimicrobial therapy.
• Design pediatric antimicrobial stewardship interventions that target specific antimicrobial agents, infectious diseases, or pathogens, and outline the roles of antimicrobial stewardship team members and metrics used to assess effectiveness of the interventions.
Antimicrobial Stewardship in Pediatrics

2007 IDSA & SHEA Guidelines
2016 IDSA & SHEA Guidelines

2011 survey of Children’s Hospital Association hospitals:
38% formal antimicrobial stewardship programs (ASPs)
36% plans to implement

Challenges for Pediatric Patients

- Diagnostic uncertainty
- Subspecialties
- Special populations
- Sparse data
- Fear factor
- Resource limitations
Variability in Antibiotic Consumption

• Gerber et al: Pediatric Health Information System (PHIS) hospitals
  – 38 – 72% of patients receive antibiotics
  – 368 – 601 DOT/1000 patient days

• Schulman et al: California NICUs
  – Parenteral rates of antibiotic use: 2.4 – 97.1%

• Limitations
  – “Appropriateness” is the holy grail
  – SHARPEC study

Convincing the Skeptics

Less antibiotic resistance

- MRSA is common
- 63 reports of children with CRE 2002-2010
- 7% of Enterobacteriaceae produce ESBL in a Texas children’s hospital
- NICU: 23% of GNB resistant to ≥ 1 tested agent

Less *Clostridium difficile* infection

- 2001-2010:
  - Incidence 1.2 vs. 11.6 per 1000 discharges
  - Mortality 3.1% vs 8.8%
- 2003 → 2012
  - ↑ 2.4 → 5.8 per 1000 discharges
  - Highest in HSCT & IBD

Peer Pressure

**Regulatory**
- Centers for Medicare & Medicaid Services (CMS)
- The Joint Commission (TJC)

**Children’s Hospital Specific**
- US News & World Report Rankings
- Vermont Oxford Network NICU initiative
The Team

Pharmacists
- ID
- Pediatric & Specialists

Physicians
- ID
- Subspecialists

Leadership
Microbiology
Infection Prevention
Informatics
Data Analyst

2016 IDSA/SHEA Recommendation #1:

Preauthorization and/or prospective audit and feedback are recommended

Strong recommendation, moderate-quality evidence
Core Strategies in Pediatrics

Preauthorization
- Approval required prior to dispensing
- Most useful at initiation of therapy (empirically)

Prospective audit with feedback
- Real-time review & optimizing antibiotic use
- Time-intensive
- Useful when more information is available

Where to Start: Janowski et al

- Retrospective chart review
- 200 randomly selected courses of piperacillin/tazobactam
- Initiation & continuation evaluated by 3 reviewers

<table>
<thead>
<tr>
<th></th>
<th>Initiate</th>
<th>Discontinue @ 72 hours</th>
<th>Continue @ 72 hours</th>
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<tbody>
<tr>
<td>Total, n</td>
<td>200</td>
<td>110</td>
<td>90</td>
</tr>
<tr>
<td>Agree, n (%)</td>
<td>186 (93)</td>
<td>104 (94.5)</td>
<td>67 (74.4)</td>
</tr>
<tr>
<td>Agree Unanimously, n (%)</td>
<td>171 (91.9)</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

- Time better spent on targeted 72 hour review

Preauthorization

24/7 Pager (PharmD, MD, Fellows)

Approval by Service-Level Pharmacists

Computerized Alerts with Pre-Approved Indications

9-5 Pager or ID Consult Only (initial doses permitted)
## Restricted Antimicrobials

<table>
<thead>
<tr>
<th>Generic name</th>
<th>Trade name</th>
<th>Restriction/Preapproved indications</th>
<th>Comments</th>
</tr>
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<tbody>
<tr>
<td>Antimicrobial Locks</td>
<td>NA</td>
<td>Infectious Disease, Intestinal failure/Short Bowel Syndrome (ethanol)</td>
<td>ID approval required</td>
</tr>
<tr>
<td>Aztreonam</td>
<td>Azactam®</td>
<td>Cystic fibrosis, Infectious Disease, Hematology/Oncology</td>
<td>Alternative therapy for gram negative pathogens with an abdominal source as in combination with metronidazole (Hematology/Oncology)</td>
</tr>
<tr>
<td>Botulism Immune Globulin</td>
<td>BabyBIG®</td>
<td>Infectious Disease</td>
<td></td>
</tr>
<tr>
<td>Cefepime</td>
<td>Maxipime®</td>
<td>Patient with Cystic fibrosis, Ophthalmology for globe injuries, Fever and neutropenia, Infectious Disease</td>
<td>ID approval for Hematology/Oncology patients not meeting criteria for fever and neutropenia</td>
</tr>
<tr>
<td>Cefotaxime</td>
<td>Claforan®</td>
<td>Children &lt;1 month of age</td>
<td>Uses beyond neonates requires ID approval due to nationwide shortage For patients on TPN or receiving calcium infusions 1 dose may be given prior to obtaining ID approval</td>
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<tr>
<td>Ceftazidime</td>
<td>Fortaz®</td>
<td>Infectious Disease and Cystic Fibrosis</td>
<td></td>
</tr>
<tr>
<td>Cidofovir</td>
<td>Vistide®</td>
<td>Infectious Disease</td>
<td></td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>Cipro®</td>
<td>Patient with Crohn’s (GI only), BMT prophylaxis, PCN allergy – UTI only, Infectious Disease</td>
<td>-Otic and Ophthalmic formulations are NOT restricted -Class restriction includes all non-formulary products (i.e. moxifloxacin (Avelox®)</td>
</tr>
<tr>
<td>Ganciclovir</td>
<td>Cytovene®</td>
<td>Immunocompromised patient (CMV disease or prophylaxis), Transplant Services, Infectious Disease</td>
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<tr>
<td>Foscarnet</td>
<td>Foscavir®</td>
<td>Infectious Disease, Documented viral resistance</td>
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<tr>
<td>Immune Globulin</td>
<td>IVIG®</td>
<td>Immunodeficiency disease, Guillain Barre, Kawasaki, BMT, ITP, Hypogammaglobulinemia, Neurology, Cardiomyopathy</td>
<td>Approved within certain indications [See CMC policy 7.10.07]</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>Levaquin®</td>
<td>Infectious Disease, Stem cell transplant patient (Heme/Onc only), PCN allergy Immunocompromised patient - sepsis</td>
<td>Class restriction includes all non-formulary products (i.e. moxifloxacin (Avelox®)</td>
</tr>
<tr>
<td>Linezolid</td>
<td>Zyvox®</td>
<td>Infectious Disease</td>
<td></td>
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Formulary Restriction Example

This drug is RESTRICTED to the Infectious Disease service OR empiric therapy for fever and neutropenia in ANL patients currently receiving cefepime prophylaxis. SPECIAL NOTE: ICU is allowed to administer one dose before obtaining ID consult.

Dose: 10 mg/kg, 20 mg/kg, 40 mg/kg, 1,000 mg
Route: INTRAVENOUS
Frequency: Every 24 Hours, Every 12 Hours, Every 8 Hours
For: Doses
Starting: 8/26/2016
First Dose: TODAY 1455
Priority: Routine
Admin. Inst.: Ready to administer by IV infusion, via central line only, over 30 to 60 minutes.

Example from Children’s Health System, Children’s Medical Center Dallas
Patient Case #1

Ben – 5 months

Presents with sepsis likely secondary to UTI

Staff wants to use meropenem....
Time for a Poll

How to vote via the web or text messaging

From any browser

Enter your response

Submit response

From a text message

To: 22333

152964
How to vote via text message

How's my presentation so far?

- Respond at PollEv.com/ashp
- Text a **KEYWORD** to 22333

<table>
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Question #1
Which of the following statements provides the best stewardship targeted rationale for appropriate use of meropenem in this infant?

A. The patient is critically ill
B. *E. coli* isolates are 100% susceptible to meropenem
C. A penicillin allergy is documented in the chart
D. The patient has a history of UTI due to MDR *E. coli*
Your poll will show here

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Prospective Audit with Feedback

• ID specialist (PharmD ± MD) reviews therapy for optimization
• Targeted antibiotic list, positive blood cultures, etc.
• Newland et al: intervened on 20% of reviewed antibiotics
  – 17% decrease in days of therapy for targeted antibiotics
  – 7% decrease in days of therapy for all antibiotics

Dedicated ID Pharmacists

Bessesen et al.: ID PharmD improved: initiation & modification of therapy, IV to PO

Ward or Service-Based Pharmacists

Nguyen-Ha et al.: Service pharmacists ↓ caspofungin, vancomycin, & meropenem use via day 3 audits

Question #2
Which of the following is an antimicrobial stewardship strategy described by the team at Colorado Hospital Colorado that involves rounding daily with each pediatric service?

A. Collaborative stewardship
B. Community stewardship
C. Handshake stewardship
D. Subspecialty stewardship
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B. Community stewardship
C. Handshake stewardship
D. Subspecialty stewardship
A Similar Approach: Handshake Stewardship

- Children’s Hospital Colorado
- No preauthorization
- Daily review of ALL antimicrobials
  - 24- & 72-hr antimicrobial reports
  - Shared by stewardship MD and PharmD
- Round daily with ALL services
  - Communicate recommendations
  - Field questions/touch base (even if no changes)

Handshake Stewardship Results

Antibiotic consumption in DOT/1000 pt days/month

<table>
<thead>
<tr>
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<th>Pre</th>
<th>Post</th>
<th>Difference</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>All antimicrobials</td>
<td>942</td>
<td>839</td>
<td>103 (10.9%)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>All antibacterials</td>
<td>750</td>
<td>673</td>
<td>77 (10.3%)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>105</td>
<td>78</td>
<td>27 (25.7%)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>PICU all antimicrobials</td>
<td>1587</td>
<td>1357</td>
<td>230 (14.5%)</td>
<td>0.03</td>
</tr>
<tr>
<td>Heme/onc/BMT all antimicrobials</td>
<td>2205</td>
<td>1855</td>
<td>350 (15.9%)</td>
<td>0.03</td>
</tr>
</tbody>
</table>

Frontline Pharmacist Feedback

• Pharmacists responsible for evaluating antibiotics daily

• ASP PharmD reviews daily
  – Positive blood cultures
  – Restricted agents
  – Specific initiatives

• Education & support provided by ASP Pharm.D.
### Example Review Components

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<th>Component</th>
<th>Description</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug choice</td>
<td>Therapy appropriately narrow or broad</td>
<td>De-escalate to ampicillin from cefepime for a pan-susceptible <em>E.coli</em> bacteremia</td>
</tr>
<tr>
<td></td>
<td>Need (or lack of) for duplicate therapy considered</td>
<td>Assess need for “double coverage” for directed therapy of Gram-negative organisms</td>
</tr>
<tr>
<td>Dose</td>
<td>Dose is optimized based on PK/PD properties</td>
<td>Prolonged infusion beta-lactam, evaluate dosing per MIC</td>
</tr>
<tr>
<td>Duration</td>
<td>Ensure duration is sufficient but minimum effective</td>
<td>10 days adequate for some bacteremias (vs. ≥ 14 days)</td>
</tr>
</tbody>
</table>
Patient Case #2: CLABSI

- 3-year old with a CVC for home nafcillin for osteomyelitis
  - Weight = 16 kg
- Admitted with fever, fatigue, irritability
  - WBC 22.4K cells/mm³, 83% neutrophils
  - SCr 0.35 mg/dL
- Patient initiated on antimicrobial therapy
  - Vancomycin 240 mg IV every 6 hr
  - Ceftazidime 800 mg IV every 8 hr, infused over 4 hours
- Blood cultures (central & peripheral) positive at 6 & 12 hours
  - Gram Stain: Gram-negative bacilli
  - CVC removed!
Patient Case #2 Continued

- **PCR-based rapid diagnostic test:** *Enterobacter spp.*
  - Discontinue vancomycin
  - Change ceftazidime to cefepime 800 mg IV q 8 hours
    - Avoid AmpC induction

- **Medical resident would like to add tobramycin**
  - ID & susceptibilities confirmed
  - Rec against addition of tobramycin
    - Similar mortality
    - ↓ incidence of AKI

- **Planned duration:**
  - 14 days from first negative culture
  - Recommend 10 days from first (-)
  - Longer duration doesn’t protect against relapse; possible ↑ ADE

---

**Question #3**
Which antibiotic is least likely to induce production of AmpC beta-lactamases by *Enterobacter cloacae*?

- **A** Cefepime
- **B** Ceftriaxone
- **C** Imipenem/cilastatin
- **D** Piperacillin/tazobactam

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Framing Antimicrobial Stewardship

“to optimize clinical outcomes while minimizing unintended consequences of antimicrobial use, including toxicity, the selection of pathogenic organisms, and the emergence of resistance.”

Ideal Targets & Strategies in Pediatrics

- Current literature (Disease states, antibiotics)
- Institution-specific usage and disease data
- Get in line with new regulations
- Low-hanging fruit & pharmacy-driven initiatives
Question #4
Which of the following is among the top 4 disease states for which antibiotics are prescribed in hospitalized children?

A. Cystic fibrosis
B. Meningitis
C. Osteomyelitis
D. Urinary tract infection
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A. Cystic fibrosis
B. Meningitis
C. Osteomyelitis
D. Urinary tract infection
Disease-Specific Targets

• Retrospective evaluation of antibiotic use at 32 freestanding children’s hospitals

• Highest-use conditions
  – 1% of conditions
  – 10% of antibiotic use

Pneumonia  Appendicitis  Cystic Fibrosis  Skin & Soft-tissue Infection

Surgical Targets

• Gerber et al: 43% of all DOT in surgical patients
• Kronman et al: retrospective evaluation of surgical inpatients
  – 82.9% of patients received antimicrobials
  – Most common: cefazolin, vancomycin, piperacillin/tazobactam
  – Biggest opportunities:

  | Vancomycin: cardiothoracic & neurosurgical | Broad-spectrum antipseudomonals: GI surgery patients |

Surgical Site Infection Prophylaxis

- Goal: reduction in surgical site infections
- Variability in selection & use despite guidelines
- Sandora et al 2016
  - Retrospective database study (PHIS)
  - Large variability by procedure within and among institutions
  - Prophylaxis indicated: 72% of patients received
  - Prophylaxis NOT indicated: 40% of patients received
  - *C. difficile* infection OR: 3.34 [1.66-6.73] (p <0.001)

Pediatric ASP Recommendations & Clinical Diagnoses

• Retrospective evaluation of ASP recommendations
• Reviews with recommendations
  – 20% in year 1
  – 14% by year 5
• 45% of recommendations: “stop therapy”
• Diseases with highest adjusted probability of recommendation:
  – Ear, nose, & throat infections (0.26)
  – Community-acquired pneumonia (0.26)
  – Genitourinary infections (0.22)
  – Respiratory infections (0.21)

Goldman JL et al. Infect Control Hospital Epidemiol. 2015:36(6); 673-680.
Probability of Pediatric ASP Recommendations for Specific Antimicrobials

- 3rd-generation cephalosporins
  - Ceftazidime
  - Ceftriaxone/cefotaxime

- Combination therapy with additional agents
  - Gentamicin
  - Clindamycin

- Fluoroquinolones
  - May still want to evaluate due to spectrum & potential for collateral damage
  - Same with carbapenems

Goldman JL et al. Infect Control Hospital Epidemiol. 2015:36(6); 673-680.
Guideline Endorsements/ Regulatory Perspective

• The Joint Commission
  – New Antimicrobial Stewardship Standard
  – 8 elements of performance

• Centers for Medicare and Medicaid Services
  – Proposed antimicrobial stewardship rule

• CDC core elements

• U.S. News & World Report Survey

Question #5
Which of the following initiatives could be considered “low-hanging fruit”?

A. Development of a guideline for management of early-onset sepsis in the NICU
B. Implementation of batch preparation for intravenous daptomycin
C. Publication of a system-wide antibiogram with unit-specific data
D. Initiation of daily prospective audit with feedback in each pediatric unit
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Low Hanging Fruit

• “Most obtainable” targets with limited resources
• Stems from community hospital experiences
• Often associated with favorable financial impact
• Examples
  – Intravenous-to-oral conversions
  – Batch preparation of IV antimicrobials
  – Formulary restriction & therapeutic substitution
  – Dose optimization

IV-to-Oral Conversions

• Acute osteomyelitis = huge opportunity
  – Zaoutis et al: multicenter retrospective evaluation showed no association between early IV to PO transition and failure rate
  – Keren et al: multicenter comparison of PO vs extended IV therapy (via PICC)
    – No increased risk of treatment failure; more ADE and re-admissions in PICC group

• Appendicitis: Adibe et al
  – Decreased postoperative IV antibiotic use by converting to oral therapy

• Or focus on highly bioavailable anti-infectives

Getting Beyond Low Hanging Fruit

• Something everyone can(and should)have...

Antibiogram 😊

2016 IDSA/SHEA Rec #15

Develop stratified antibiograms to assist ASPs in developing guidelines for empiric therapy

Can expose important susceptibility differences

Weak recommendation, low-quality evidence

Pediatric-Stratified Antibiograms

• Pediatric-specific antibiogram for *E. coli* (patients ≤ 12 years)

• Compared with at-large institutional antibiogram
  – More resistant to ampicillin & TMP/SMX (p <0.005)
  – Less resistant to amoxicillin/clavulanate & ciprofloxacin (p <0.005)

• Case scenarios presented to prescribers
  – Acute UTI treatment
  – Effective antibiotic choices increased with pediatric antibiogram use in both infants and adolescents (p <0.01)

Pediatric Antibiotics: Do They Exist?

- Tamma et al: Survey to determine pediatric susceptibility trends

- Clinical and Laboratory Standards Institute (CLSI) recommends at least 30 isolates
  - May need to go back 2 years

Question #6
Senior leadership approaches the ID Clinical Pharmacist at a 450-bed institution to identify an antimicrobial stewardship intervention that can be developed as they begin efforts towards starting a formalized ASP program at the institution. Which of the following would be best to initiate at this time?

A. Antimicrobial formulary restriction program
B. Provide didactic education for medical staff
C. Develop guidelines for all infectious related diagnoses
D. Conduct an MUE of fluoroquinolone use within the institution
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Where to Start?

• Assessment of antibiotic use within institution
  – Direct efforts towards minimizing unnecessary use
  – Common issues
  – Use benchmarking if available
  – MUE “deep dives” driven by usage data

• Consider available resources

• What aligns with goals & desires of leadership, physicians, other stakeholders

Choosing Initiatives

• Don’t be paralyzed by indecision
  – You can’t fix it all at once!
• You probably already have some ideas
• Which fruit is ripe for picking?
• Make use of associated adult hospitals
  – Extended-infusion beta-lactams
  – Development of patient or staff education video
Question #7
Which of the following would the best initial approach to improve the management of urinary tract infections at an institution with limited resources?

A. Preauthorization requirement
B. Guideline with education
C. 48-hour time out task
D. Prospective audit with feedback
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D. Prospective audit with feedback
Guideline Use: Initial Broad Sweep?

- ASP implemented at children’s hospital (1.5 FTE)
- Initial review of ICU antibiotic use:
  - Infection management inconsistency
  - Excessive broad-spectrum agent use
- Guideline development & implementation
  - Empiric therapy only
  - Education → retrospective review → feedback
- Guidelines also posted in order entry area
- Prospective audit for some antibiotics started at month 6

Lee et al: Guideline Implementation

- Stratified guideline recommendations by unit
  - PICU, NICU, & Cardiac ICU
- Antibiotic + “additional” recommendations
- Focus on broad-spectrum agents
  - Meropenem
  - Piperacillin/Tazobactam
  - Cefepime
- Decrease in broad-spectrum antibiotic use
- Decrease in antibiotic expenditures

Additional Guideline Impacts

• Vancomycin use in a NICU
  – 118 bed, level II – IV NICU
  – Pre- and post education and guideline intervention
    – Necrotizing enterocolitis
    – Empiric late-onset sepsis
  – NICU staff pharmacists & physicians
  – Vancomycin use past 72 hours reduced

• CAP guideline intervention
  – 263 bed tertiary care
  – 97 bed NICU/26 bed PICU
  – CAP and sepsis order sets for clinicians

• Outcome
  – Increased ampicillin use by 44%
  – Decreased ceftriaxone use by 26%

What if...

• I don’t have an Infectious Disease Service?
• I don’t have an ID trained Pharmacist?
• I am connected to an adult facility?
• We only have remote services?
• I don’t have an electronic medical record (EMR)?
• I am in a teaching institution?
• I don’t have a full time clinical pharmacy staff?
• Prescribers are not employees of our hospital?
Steps in the “Real World”

Step 1: Identify Target

- Retrospective review of diagnosis and antibiotics for pediatric patients at the institution aged 2 – 24 months
  - Urinary tract infection associated with highest DOT/1000 patient days
  - Most commonly prescribed antibiotics
    - Sulfamethoxazole/Trimethoprim
    - Ciprofloxacin
  - Median duration
    - 14 days (IQR 10 – 16)
- Collection of specimen
  - Clean catch (79%)
  - Catheterization (20%)
  - Undocumented method (0.6%)

Let’s Get To it!

• Step 2: What outcome do you want to impact?
  – Decrease length of treatment/ antibiotic duration
  – Reduce fluoroquinolone use
  – Improve adherence to established guideline

• Step 3: Determine approach that best fits institution
  – Formulary restriction/Preauthorization
  – Guideline with education
  – Prescriber led review for appropriateness
  – 48 hour time out
## UTI Stewardship Initiative

- **Curry Hospital for Women and Children**
  - 15 bed PICU
  - 45 bed general pediatrics ward
  - 65 bed NICU
  - (2) Centralized staff pharmacists
  - (1) Clinical Pharmacy Specialist
  - (0) Pediatric infectious disease service or physician

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<tbody>
<tr>
<td>Formulary restriction/ preauthorization</td>
<td>YES!</td>
<td>Could restrict Cipro and TMP/SMX upon ordering</td>
</tr>
<tr>
<td>Guideline with education</td>
<td>YES!</td>
<td>Develop UTI guideline as a collaborative group</td>
</tr>
<tr>
<td>Prescriber led review for appropriateness</td>
<td>MAYBE NOT</td>
<td>Without a designated provider may be difficult</td>
</tr>
<tr>
<td>48 hour time out</td>
<td>MAYBE NOT</td>
<td>Depends on EMR and personnel</td>
</tr>
</tbody>
</table>
UTI Stewardship Initiative

- Gotham Children’s Medical Center
  - 650-bed free standing children’s hospital
  - (60) Decentralized clinical pharmacists
  - (8) Clinical Pharmacy Specialists
  - (1) ID Clinical Specialist, Pharmacist
  - Pediatric infectious disease service

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Feasibility</th>
</tr>
</thead>
<tbody>
<tr>
<td>Formulary restriction/preauthorization</td>
<td>YES!</td>
</tr>
<tr>
<td>Guideline with education</td>
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<td>YES!</td>
</tr>
</tbody>
</table>
Application
Stewardship in Appendicitis

What are some focus areas that we could dive into to optimize treatment of appendicitis at our institution?
Data to Evaluate - Appendicitis

1. Are patients receiving timely perioperative prophylaxis?
   • What antibiotics are being used for perioperative prophylaxis?

2. Are patients with uncomplicated disease receiving prolonged antibiotic therapy?
   • What antibiotics are being used and at what doses?

3. Is IV therapy being used for the entire duration of therapy?
   • Is a minimum effective duration being utilized? For how long do patients receive antibiotics?
Evaluation of Antibiotic Use

% of patients with complicated appendicitis

- Ertapenem: 32%
- Ertapenem + metronidazole: 10%
- Cefoxitin: 15%
- Ciprofloxacin + metronidazole: 20%
- Ceftriaxone + metronidazole: 33%

Fabricated data
Opportunities - Appendicitis

**Ertapenem Use**
- Unless local susceptibilities drive use, reserve for resistant isolates
- Use of carbapenems associated with carbapenem resistance
- More expensive than other options

**Ciprofloxacin Use**
- Dig deeper – related to “penicillin allergies”?
  - Clarify/skin testing (#13)
- Collateral damage
  - ESBLs
  - CRE
  - MRSA
  - C. difficile
  - Candida

# Appendicitis Antibiotic Choice

<table>
<thead>
<tr>
<th>Author</th>
<th>Antibiotics</th>
<th>Outcomes</th>
</tr>
</thead>
</table>
| Hurst AL et al  | Ceftriaxone + metronidazole vs. cefoxitin OR ertapenem | - Shorter time to afebrile in CTX + met  
- No difference in abscess rate or LOS  
- Cost savings with CTX + met |
| Kronman MP et al| “Extended spectrum” (ES) versus “narrower spectrum”  | - Adjusted analysis: no difference in treatment failure  
- ES moderately associated with treatment failure, only statistically significant for complicated disease |

## Appendicitis Antibiotic Choice Continued

<table>
<thead>
<tr>
<th>Author</th>
<th>Antibiotics</th>
<th>Outcomes</th>
</tr>
</thead>
</table>
| Lee JY et al  | Ceftriaxone + metronidazole vs “other” | • Similar postoperative length of stay  
• Postop abscess rate 8% vs 4% (p=0.57)  
• 30-day readmission 3% vs 11% (p = 0.19) |

Opportunities Beyond Coverage

• Double anaerobic coverage
  – 12.8% of children receive (1.5 – 49.5%)
  – Potential risks (Candidemia, ADE) + cost

• Conversion to oral therapy
  – Rice et al: no increase in complications
  – Fraser et al: no increase in abscess formation, ↓ LOS

• Shortest effective duration
  – Sawyer et al (adults) no difference in time to primary composite outcome
    – 4 days post source control vs 2 days resolution of all systemic inflammatory response syndrome (SIRS) criteria

Stewardship in Urinary Tract Infections

What are some focus areas that we could dive into to optimize treatment of urinary tract infections at our institution?

*Translates well to ED or ambulatory setting*
Local Susceptibility-Driven Empiric Coverage

• Meyers et al:
  – Evaluated susceptibilities of bacteria causing UTI in children over a 2-year period
  – 94% of *E. coli* isolates susceptible to cefazolin
  – Ceftriaxone used empirically 42% of time
  – Resistance to cefazolin predicted by underlying urinary tract abnormalities

• Riley Hospital for Children evaluation:
  – Similar 18-month evaluation
  – *E. coli* isolates 91.9% susceptible to cefazolin
    – 93% in patients with no known risk factors

<table>
<thead>
<tr>
<th>GRAM-NEGATIVE AEROBES</th>
<th>total isolates</th>
<th>ampicillin</th>
<th>ampicillin-sulbactam</th>
<th>cefazolin</th>
<th>cefuroxime</th>
<th>ceftriaxone</th>
<th>cefepime</th>
<th>piperacillin-tazobactam</th>
<th>meropenem</th>
<th>gentamicin</th>
<th>ciprofloxacin</th>
<th>TMP/SMX</th>
<th>nitrofurantoin</th>
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</thead>
<tbody>
<tr>
<td><strong>E. cloacae</strong></td>
<td>38</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>88</td>
<td>97</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>68</td>
<td>26</td>
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<tr>
<td><strong>E. coli</strong></td>
<td>434</td>
<td>44</td>
<td>52</td>
<td>78</td>
<td>94</td>
<td>95</td>
<td>96</td>
<td>92</td>
<td>100</td>
<td>97</td>
<td>90</td>
<td>69</td>
<td>92</td>
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<tr>
<td><strong>H. influenzae</strong></td>
<td>24</td>
<td>34</td>
<td>100</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>K. pneumoniae</strong></td>
<td>66</td>
<td>63</td>
<td>80</td>
<td></td>
<td></td>
<td></td>
<td>93</td>
<td>93</td>
<td>84</td>
<td>98</td>
<td>95</td>
<td>72</td>
<td>89</td>
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<tr>
<td><strong>P. aeruginosa</strong></td>
<td>61</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

Fabricated data
Additional Opportunities

• Use oral therapy when possible
  – Initial cefixime vs cefotaxime: similar outcomes, lower cost

• Avoid treating colonization/contamination
  – Positive UA, symptoms, >50,000 colony-forming units

• Narrow therapy once susceptibilities available

• Avoid quinolones where possible
  – Associated with high rates of *C. diff* infection (ASP Guideline Rec #5)

• Minimum effective duration (7-10 days)

Make it Count Twice!

• TJC: The hospital’s antimicrobial stewardship program uses organization-approved multidisciplinary protocols (for example, policies and procedures)

• Examples:
  – Appendicitis pathway
  – UTI pathway
  – Dosing & antimicrobial usage guidelines

Starting an Initiative

• Multidisciplinary team on board
  – Key stakeholders
  – Engage leadership if necessary
  – Consider different ages & special populations
    – “Adult” considerations

• Hospital resources
  – Quality & safety experts
  – Lean methodology
  – Other quality improvement methodologies
Next Steps

• Evaluate current state
  – What should be measured?
  – What are the (measurable) goals?
  – What are possible unintended consequences?

• What will need to happen in order to get started?
  – Computer changes
    – Submit necessary forms or requirements
  – Education
    – Who will be impacted?
  – Evaluate possible barriers
Education

• Rec #2: Do not rely solely on didactic education for stewardship
• Should go along with active interventions
• Never pass up a chance!
• The Joint Commission standards
  – Educate practitioners upon hire and periodically thereafter
  – Educate patients & families regarding appropriate use of antimicrobials

Let’s Go!

• Determine realistic start date
• Engage learners for help
• Seek feedback & gather follow-up data
  – Review together as a multidisciplinary group
  – Determine frequency of follow-up monitoring
  – Some outcomes may need to wait longer
• Repeat review as necessary
• Guideline implementation
  – Educate → review → make changes → educate

Low Hanging Fruit Implementation

• Checklists of tasks
• Pharmacy or prescriber level
• Prescribers (Mertz et al)
  – Implemented a checklist for IV-to-PO conversation
  – Shortened duration of IV therapy without impacting treatment outcomes
• Pharmacists (Dunn et al)
  – Stickers placed in chart if patients met criteria for switch
  – Post-intervention:
    – Reduction in IV therapy (p = 0.02)
    – Timeliness of transition improved (p = 0.017)

Question #8
Which of the following, normalized per 1000 patient days, is currently preferred for measuring antibiotic consumption in pediatrics?

A. Cost per course of therapy
B. Days of therapy (DOT)
C. Defined daily dose (DDD)
D. Length of therapy (LOT)
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C. Defined daily dose (DDD)
D. Length of therapy (LOT)
Tracking Antibiotic Use & Resistance

- IDSA/SHEA 2016 Guidelines rec #21: every ASP must measure antibiotic use
  - DOT/1000 patient days is the preferred metric (2016)
- CDC Antimicrobial Use and Resistance (AUR) module
  - Days present: time in which any patient is at risk for antimicrobial exposure
    - Number of patients present for each day of a calendar month by location
  - Recommended as denominator for surveillance of MDR organisms
  - Can be standardized by admission days between for comparison among institutions

Measuring Antimicrobial Use in Pediatrics: Systematic Review

- 79 studies included to review existing measures of antimicrobial use

13 numerators, 5 denominators → 26 different measure combinations → DDD/1000 patient days most frequent

- Positive correlation between proportion of exposed patients & antimicrobial-days/patient-days
- Correlation to resistance rates
  - Doses/patient-days $r = 0.80$
  - Agent-days/patient-days $r = 0.55$

Utilization Data

• Defined daily dose/1000 patient days (DDD/1000)
  – Developed in the 1970s by the WHO
  – 2007 IDSA inaugural ASP guidelines
  – “use in pediatrics results in uninterpretable data”

• Days of therapy/1000 patient days (DOT/1000)
  – Deemed more clinically relevant
  – Still lends itself to say less is more → monotherapy
  – Broadly applicable to pediatrics

• Where to get data
  – EMR
  – Surveillance tools

Data Mining/Surveillance Tools

• Antimicrobial stewardship targeted software
  – Several providers/vendors on the market
• Can provide real-time tracking and reporting
  – Facilitate IV-to-oral conversions
  – Antibiotic time outs
  – Best practice alerts
• Consult local IT department
  – May have tools that they can build in the absence of vendors
• Pediatric-specific rules & functions needed
## Examples

### July 2014

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Location</th>
<th>DOT/1000</th>
</tr>
</thead>
<tbody>
<tr>
<td>PIPERACILLLIN/TAZOBACTAM</td>
<td>6C</td>
<td>377.66</td>
</tr>
<tr>
<td>PIPERACILLLIN/TAZOBACTAM</td>
<td>4C</td>
<td>316.52</td>
</tr>
<tr>
<td>PIPERACILLLIN/TAZOBACTAM</td>
<td>6D</td>
<td>316.11</td>
</tr>
<tr>
<td>SULFAMETHOXazole/TRIMETHOPRIM</td>
<td>6D</td>
<td>308.51</td>
</tr>
<tr>
<td>SULFAMETHOXazole/TRIMETHOPRIM</td>
<td>6C</td>
<td>265.96</td>
</tr>
<tr>
<td>CEFTRIAXONE</td>
<td>12C</td>
<td>221.03</td>
</tr>
<tr>
<td>CEFTRIAXONE</td>
<td>7C</td>
<td>215.05</td>
</tr>
<tr>
<td>CLINDAMYCIN</td>
<td>5C</td>
<td>187.27</td>
</tr>
<tr>
<td>VANCOMYCIN (SYSTEMIC)</td>
<td>12C</td>
<td>184.55</td>
</tr>
<tr>
<td>CEFTRIAXONE</td>
<td>5C</td>
<td>183.52</td>
</tr>
</tbody>
</table>

### August 2014

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Location</th>
<th>DOT/1000</th>
</tr>
</thead>
<tbody>
<tr>
<td>SULFAMETHOXazole/TRIMETHOPRIM</td>
<td>6C</td>
<td>494.74</td>
</tr>
<tr>
<td>PIPERACILLLIN/TAZOBACTAM</td>
<td>4C</td>
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<tr>
<td>PIPERACILLLIN/TAZOBACTAM</td>
<td>6D</td>
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<tr>
<td>SULFAMETHOXazole/TRIMETHOPRIM</td>
<td>6D</td>
<td>244.99</td>
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<td>CEFTRIAXONE</td>
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<td>VANCOMYCIN (SYSTEMIC)</td>
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<td>VANCOMYCIN (SYSTEMIC)</td>
<td>6D</td>
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<td>SULFAMETHOXazole/TRIMETHOPRIM</td>
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<td>155.39</td>
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<tr>
<td>CLINDAMYCIN</td>
<td>4C</td>
<td>154</td>
</tr>
<tr>
<td>CLINDAMYCIN</td>
<td>5C</td>
<td>146.25</td>
</tr>
</tbody>
</table>

Example from Children’s Health System, Children’s Medical Center Dallas
Vancomycin & Clindamycin Use and VRE/MRSA
Combined ICU
2012 - 2014

Example from Children’s Health System, Children’s Medical Center Dallas.
Utilization Data: Inherent Issues

• Doesn’t account for spectrum of activity
• Common pediatric scenarios w/dual therapy:
  – Ampicillin + gentamicin for early-onset sepsis
  – Ceftriaxone + metronidazole for appendicitis
• Doesn’t take into account dosing regimen
  – Patient on 2 days of ceftriaxone 50 mg/kg/dose IV every 24 hr for bacterial meningitis = 2 DOT
  – Patients on 2 days of ceftriaxone 50 mg/kg/dose IV every 12 hr for bacterial meningitis = 2 DOT
• Other measures of appropriateness not assessed
  – Some scoring systems in development
  – Severity of illness scoring to rank patients

Question #9
Which of the following is the most critical limitation in tracking utilization data/metrics for antimicrobial stewardship programs?

- A. Inability to evaluate “appropriateness” of therapy
- B. Cumbersome calculations of patient days
- C. Lack of consensus on the appropriate metric
- D. Software limitations
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B. Cumbersome calculations of patient days
C. Lack of consensus on the appropriate metric
D. Software limitations
Pediatric Antimicrobial Stewardship Dashboard - Riley Hospital for Children - May 2016

- C diff for pts LOS > 2 days
- Patients with VRE
- Enterobacter & Ceftriaxone
- Candida BSI
- Vancomycin DOT by Unit
- Vancomycin DOT/1000 Pt Days
- Antipseudomonal BL DOT/1000 pt days
- Quinolone Use - DOT/1000 Pt Days
Additional Metrics: SAAR

• SAAR = Standardized Antimicrobial Administration Ratio
• DOT for a specific category of agents
• Ratio of observed antimicrobial use to predicted antimicrobial use
• Integrates predictive models for the 5 antimicrobial use categories defined by CDC

Additional Metrics: AbSI

- AbSI = Antibiotic Spectrum Index
- 2014 ID Week Poster
- Ranks antibiotics based on antimicrobial spectrum of activity
- Designed for benchmarking
- Limited information or experience
Benchmarking in Pediatrics

• Pediatric Health Information System (PHIS)
  – Administrative database of 47 freestanding children’s hospitals
  – Data elements included
    – Discharge diagnosis
    – Patient demographics
    – Procedures
    – Medications prescribed
  – Dedicated antimicrobial stewardship reports available

• Choosing comparable peers
• Clinical surveillance comparators: be careful

Antimicrobial Cost

• A challenge in pediatrics
  – Size matters! 500-g patient vs 54-year-old

• IDSA/SHEA 2016 Rec #22:
  – Measure cost based on administration data NOT purchasing data
  – Purchasing agreements vary between institutions
  – Shortages and pricing variations throughout the year

• CMS
  – Proposed regulation: show decline in antimicrobial expenditures
  – How?

Key Takeaways

• Key Takeaway #1
  – Antimicrobial stewardship in pediatrics requires various considerations that differ from those in adult-focused programs

• Key Takeaway #2
  – Key targets for pediatric stewardship may include diseases, such as appendicitis, cystic fibrosis, or community-acquired pneumonia; prophylaxis of surgical site infection, and third-generation cephalosporins and clindamycin

• Key Takeaway #3
  – Pediatric pharmacists can significantly impact the stewardship of antimicrobials in a variety of ways
Question?