Pediatric Antimicrobial Stewardship: Focusing on What Matters

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ashp Certification Resources

ashp MIDYEAR 2016 Clinical Meeting & Exhibition

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

Dellit TH et al. *Clin Infect Dis*. 2007;44:159-177. Barlam TF et al. *Clin Infect Dis*. 2016;62:e51-77.
Newland JG et al. *Infect Control Hosp Epidemiol*. 2014;35(3):265-271.

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

Gerber JS et al. *Pediatrics*. 2010;126:1067-1073. Schulman J et al. *Pediatrics*. 2015;135:826-833.

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

Logan LK. *Clin Infect Dis*. 2012;55(6):852-9. ; Patel SJ et al. *J Pediatr Infect Dis*. 2016;doi:10.1093/jpids/piw032. Pant C et al. *Infect Control Hosp Epidemiol*. 2016;37(1):104-106. Argamany JR et al. *Am J Infect Control*. 2015;43(5)435-40.

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

Barlam TF et al. Clin Infect Dis. 2016;62:e51-77.

Core Strategies in Pediatrics

2016 IDSA/SHEA Recommendation #1:

Preauthorization and/or prospective audit and feedback are recommended

Strong recommendation, moderate-quality evidence

Barlam TF et al. *Clin Infect Dis*. 2016;62:e51-77.

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

Barlam TF et al. *Clin Infect Dis*. 2016;62:e51-77.

Where to Start: Janowski et al

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

	Initiate	Discontinue @ 72 hours	Continue @ 72 hours
Total, n	200	110	90
Agree, n (%)	186 (93)	104 (94.5)	67 (74.4)
Agree Unanimously, n (%)	171 (91.9)	-	-

- Time better spent on targeted 72 hour review

Janowski AB et al. *J Pediatr Infect Dis Soc.* 2016;5(3):342-5.

Preauthorization

24/7 Pager

(PharmD, MD, Fellows)

Approval by Service-Level Pharmacists

Computerized Alerts with Pre-Approved Indications

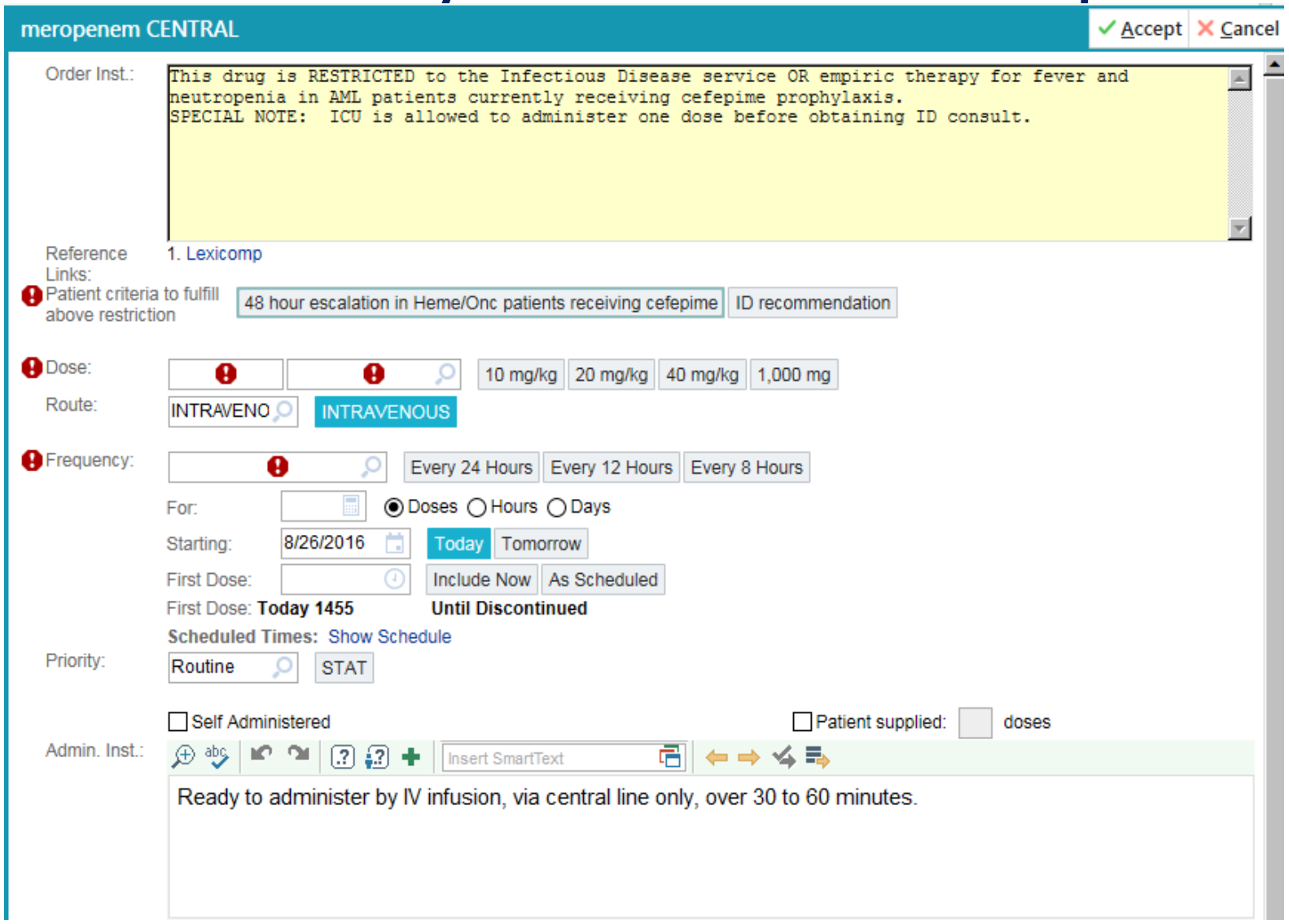
9-5 Pager or ID Consult Only (initial doses permitted)

Restricted Antimicrobials

Generic name	Trade name	Restriction / Preapproved indications	Comments
Antimicrobial Locks	NA	Infectious Disease, Intestinal failure/Short Bowel Syndrome (ethanol)	ID approval required
Aztreonam	Azactam®	Cystic fibrosis, Infectious Disease, Hematology/Oncology	Alternative therapy for gram negative pathogens with an abdominal source as in combination with metronidazole (Hematology/Oncology)
Botulism Immune Globulin	BabyBIG ®	Infectious Disease	
Cefepime	Maxipime®	Patient with Cystic fibrosis, Ophthalmology for globe injuries, Fever and neutropenia, Infectious Disease	ID approval for Hematology/Oncology patients not meeting criteria for fever and neutropenia
Cefotaxime	Claforan®	Children <1 month of age	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
Ceftazidime	Fortaz®	Infectious Disease and Cystic Fibrosis	
Cidofovir	Vistide ®	Infectious Disease	
Ciprofloxacin	Cipro®	Patient with Crohn's (GI only), BMT prophylaxis, PCN allergy – UTI only, Infectious Disease	-Otic and Ophthalmic formulations are NOT restricted -Class restriction includes all *non-formulary* products (i.e. moxifloxacin (Avelox®))
Ganciclovir	Cytovene®	Immunocompromised patient (CMV disease or prophylaxis), Transplant Services, Infectious Disease	
Foscarnet	Foscavir®	Infectious Disease, Documented viral resistance	
Immune Globulin	IVIG ®	Immunodeficiency disease, Guillian Barre, Kawasaki, BMT, ITP, Hypogammaglobulinemia, Neurology, Cardiomyopathy	Approved within certain indications (See CMC policy 7.10.07)
Levofloxacin	Levaquin®	Infectious Disease, Stem cell transplant patient (Heme/Onc only), PCN allergy Immunocompromised patient - sepsis	Class restriction includes all *non-formulary* products (i.e. moxifloxacin (Avelox®))
Linezolid	Zyvox®`	Infectious Disease	

Example from Children's Health System, Children's Medical Center Dallas

Formulary Restriction Example



Example from Children's Health System, Children's Medical Center Dallas

Patient Case #1

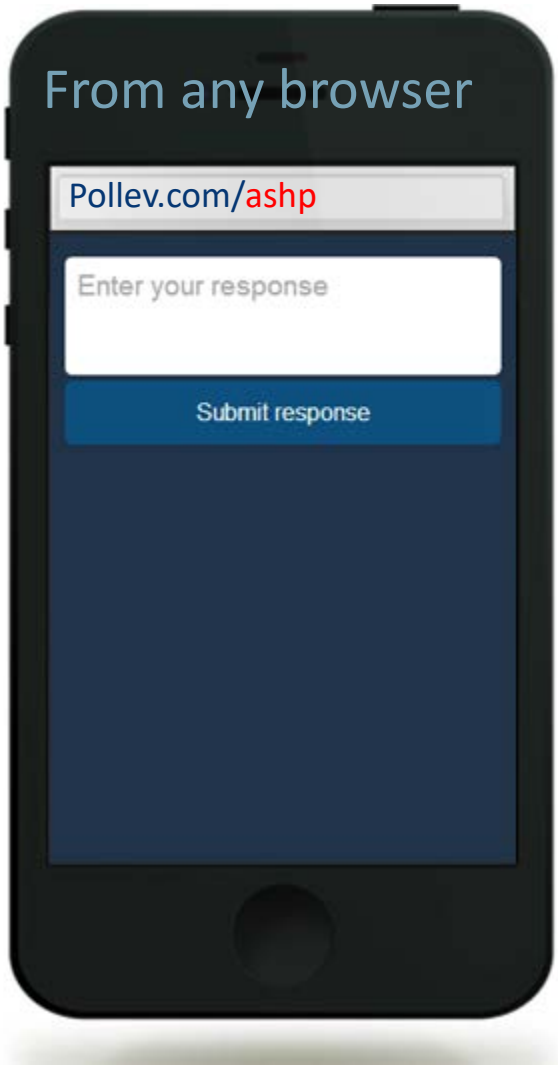
Ben – 5 months

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



How to vote via text message

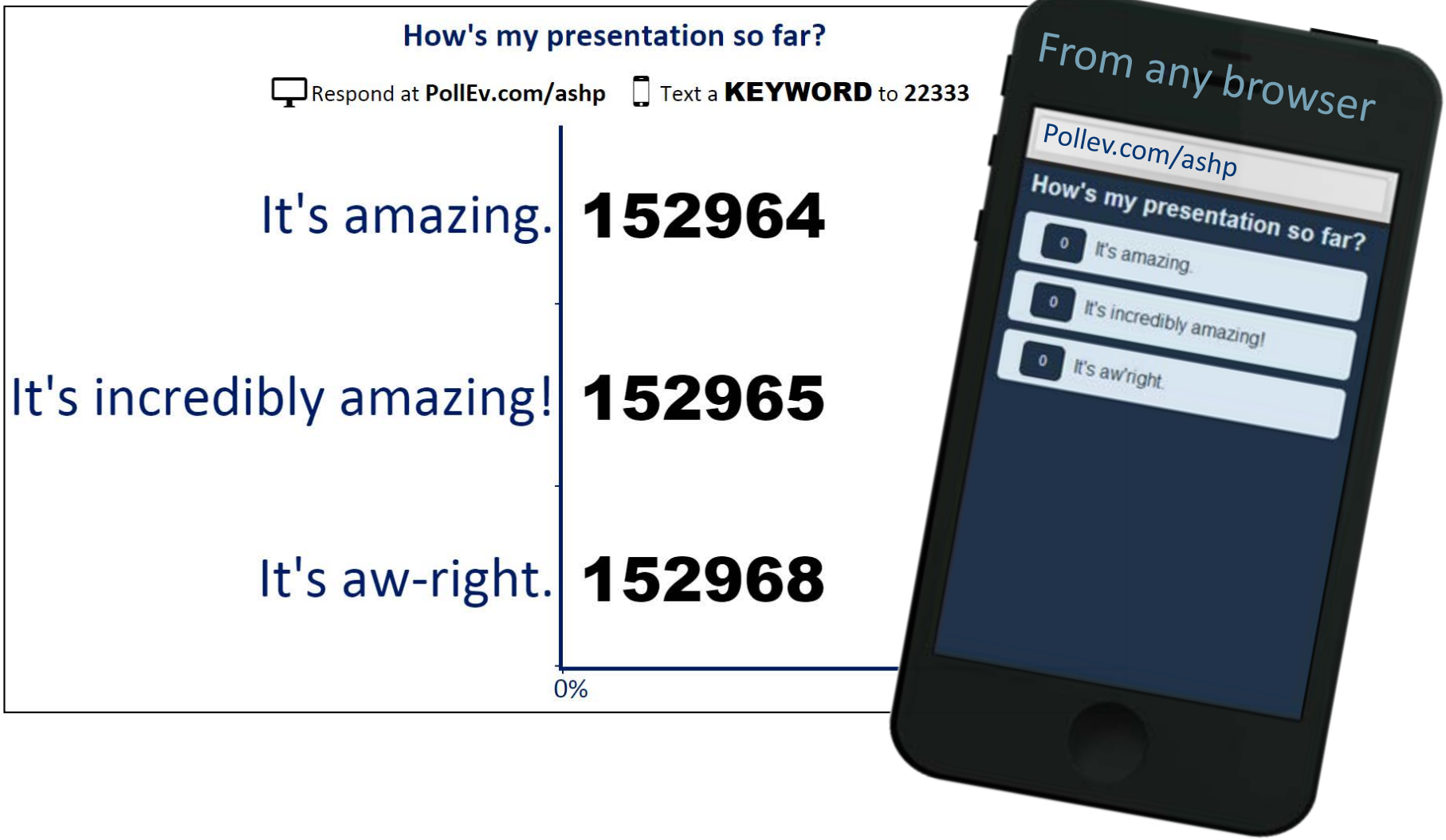
How's my presentation so far?

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

It's amazing.	**152964**
It's incredibly amazing!	**152965**
It's aw-right.	**152968**

0%

How to vote via the web



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*

Question #1

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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***

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

Newland JG et al. *J Pediatr Infect Dis*. 2012;1:179-186.

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

Bessesen et al. *Hosp Pharm*. 2015;50(6):477-483. Nguyen-Ha et al. *Pediatrics*. 2016. 137(5):e20150316.

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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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

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)

Hurst AL et al. *Pediatr Infect Dis J.* 2016; 35(10):1104-10.

Handshake Stewardship Results

Antibiotic consumption in DOT/1000 pt days/month

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

Hurst AL et al. *Pediatr Infect Dis J.* 2016; 35(10):1104-10.

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

Component	Description	Examples
Drug choice	Therapy appropriately narrow or broad	De-escalate to ampicillin from cefepime for a pan-susceptible *E.coli* bacteremia
	Need (or lack of) for duplicate therapy considered	Assess need for "double coverage" for directed therapy of Gram-negative organisms
Dose	Dose is optimized based on PK/PD properties	Prolonged infusion beta-lactam, evaluate dosing per MIC
Duration	Ensure duration is sufficient but minimum effective	10 days adequate for some bacteremias (vs. ≥ 14 days)

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/mm^3, 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

MacDougall C. J Pediatr Pharmacol Ther. 2011;16(1):23-30. Tamma PD et al. JAMA Pediatr. 2013;167:903-10.
Park SH et al. J Antimicrob Chemother. 2014;69:779-785.

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

MacDougall C. *J Pediatr Pharmacol Ther*. 2011;16(1):23-30.

Question #3

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MacDougall C. *J Pediatr Pharmacol Ther*. 2011;16(1):23-30.

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**."

Dellit TH et al CID.2007;44(2):159-77.

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

Question #4

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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

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

GerberJS et al. *Infect Control Hosp Epidemiol.* 2013;34(12): 1252-8.

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

Gerber JS et al. *Infect Control Hosp Epidemiol.* 2013;34(12): 1252-8.

Kronman MP et al. *J Pediatr Infect Dis Soc*. 2015;4(4):e100-8.

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)

Sandora T et al. *JAMA Pediatr.* 2016;170(6):570-6.

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

Probability of stewardship associated recommendation

- 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

The Joint Commission. Prepublication requirements: new antimicrobial stewardship standard. June 22, 2016. https://www.jointcommission.org/assets/1/6/HAP-CAH_Antimicrobial_Prepub.pdf

Centers for Disease Control and Prevention core elements of hospital antibiotic stewardship programs 2014. http://www.cdc.gov/getsmart/healthcare/pdfs/core-elements.pdf

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

Question #5

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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

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

Goff D et al. *Clin Infect Dis.* 2012;55(4):587-92.

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

Adibe OO et al. *Am J Surg.* 2008;195(2):141-3.
Zaoutis T et al. *Pediatrics*. 2009; 123(2):636-42.
Keren et al. *JAMA Pediatr.* 2015 ;169(2):120-8.

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

Barlam TF et al. *Clin Infect Dis*. 2016;62:e51-77.

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 ($p < 0.01$)

Boggan JC et al. *Pediatrics.* 2012;130(2):e615-21.

Pediatric Antibiograms: 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

Tamma PD et al. *Infect Control Hosp Epidemiol*. 2013;34(12):1244-51.

Hindler JF et al. *Clin Infect Dis*. 2007;44:867-73.

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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D Conduct an MUE of fluoroquinolone use within the institution

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

Goldman J et al. *Infect Dis Clin North Am*. 2015(29):503-11.

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?

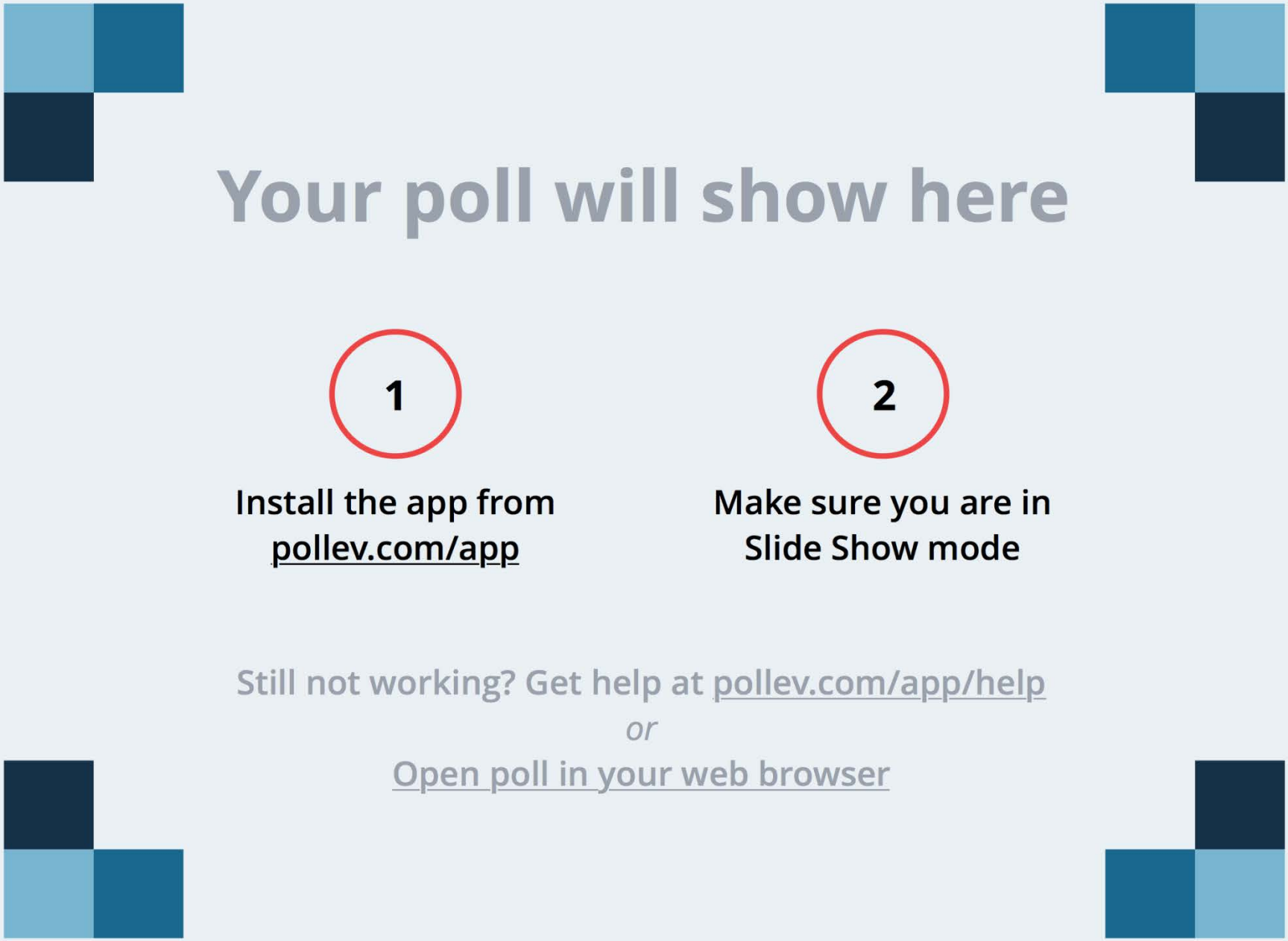
A Preauthorization requirement

B Guideline with education

C 48-hour time out task

D Prospective audit with feedback

Question #7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B **Guideline with education**

C 48-hour time out task

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 KR et al. *Pediatr Crit Care Med.* 2016;17(3):187-193.

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

Lee KR et al. *Pediatr Crit Care Med.* 2016;17(3):187-193.

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%

Holzmann-Pazgal G et al. *Am J Infect Control.* 2015;43(11):1255-1257.

Smith MJ et al *Pediatrics.* 2012;129(5):e1326-e1333.

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%)

Watson JR et al. Pediatr Emerg Care. 2016; doi:10.1097/PEC.0000000000000688.

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

Intervention	Feasibility	Considerations
Formulary restriction/ preauthorization		Could restrict Cipro and TMP/SMX upon ordering
Guideline with education		Develop UTI guideline as a collaborative group
Prescriber led review for appropriateness		Without a designated provider may be difficult
48 hour time out		Depends on EMR and personnel

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

Intervention	Feasibility
Formulary restriction/ preauthorization	
Guideline with education	
Prescriber led review for appropriateness	
48 hour time out	

Application

Stewardship in Appendicitis

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

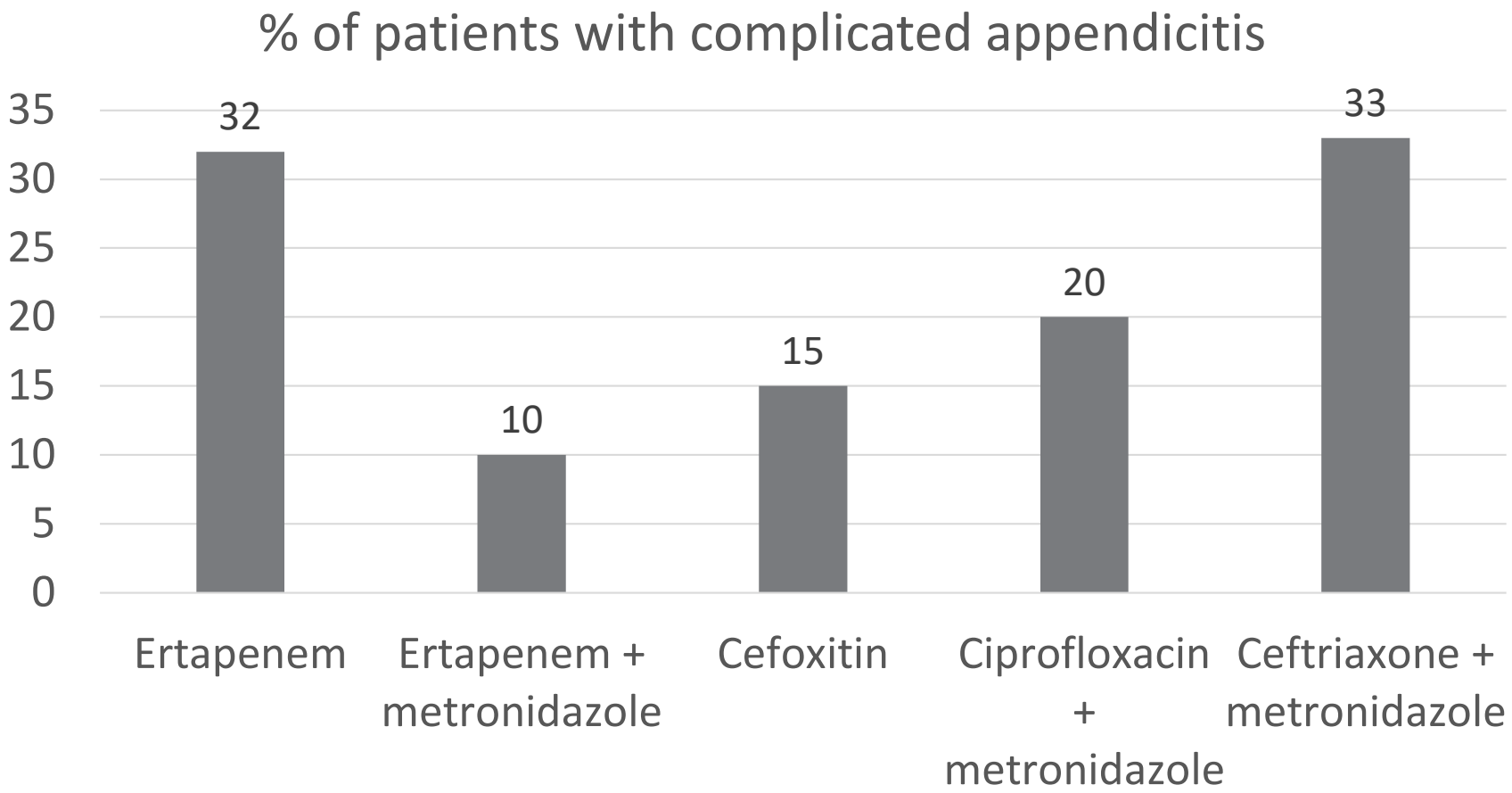
Data to Evaluate - Appendicitis

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



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

Gupta N et al. *Clin Infect Dis* 2011;53(1):60-67. Paterson DL. *Clin Infect Dis* 2004;38(suppl 4):S341-345.
Barlam TF et al. *Clin Infect Dis*. 2016;62:e51-77.

Appendicitis Antibiotic Choice

Author	Antibiotics	Outcomes
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

Hurst AL et al. *J Pediatr Infect Dis Soc*. 2015;doi:10.1093/jpids/piv082.

Kronman MP et al. *Pediatrics*. 2016;138(1):doi:10.1542/peds.2015-4547.

Appendicitis Antibiotic Choice Continued

Author	Antibiotics	Outcomes
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)

Lee JY et al. *J Pediatr Pharmacol Ther*. 2016;21(2):140-5.

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

Rice HE et al. *Arch Surg*. 2001;136:1391-1395. Fraser JD et al. *J Ped Surg*. 2010;45:1198-1202.
Kronman MP et al. *J Pediatr Infect Dis Soc*. 2015;4(4):e100-8. Sawyer RG et al. *N Engl J Med*. 2015;372:1996-2005.

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

Meyers R et al. *J Pediatr Pharmacol Ther*. 2013;18(2):166-7.

GRAM-NEGATIVE AEROBES	total isolates	ampicillin	ampicillin-sulbactam	cefazolin	cefuroxime	ceftriaxone	cefepime	piperacillin-tazobactam	meropenem	gentamicin	ciprofloxacin	TMP/SMX	nitrofurantoin
E. cloacae	38					88	97		100	100	100	68	26
E. coli	434	44	52	78	94	95	96	92	100	97	90	69	92
H. influenzae	24	34	100										
K. pneumoniae	66		63	80		93	93	84	98	95	96	72	89
P. aeruginosa	61						91	88	90	86	93		

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)

Hoberman et al. *Pediatrics*. 1999;104:79-86.

Finnell SM et al. *Pediatrics*. 2011;128:e749-e770.

Barlam TF et al. *Clin Infect Dis*. 2016;62:e51-77.

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

The Joint Commission. Prepublication requirements: new antimicrobial stewardship standard. June 22, 2016. https://www.jointcommission.org/assets/1/6/HAP-CAH_Antimicrobial_Prepub.pdf

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

Barlam TF et al. *Clin Infect Dis*. 2016;62:e51-77.

The Joint Commission. Approved: new antimicrobial stewardship standard. Jt Comm Perspect. 2016; 36:1,3,4,8. https://www.jointcommission.org/assets/1/6/New_Antimicrobial_Stewardship_Standard.pdf.

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

Lee KR et al. *Pediatr Crit Care Med.* 2016;17(3):187-193.

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 ($p = 0.017$)

Mertz D et al. *J Antimicrob Chemother.* 2009;dkp131.

Dunn K et al. *Int J Clin Pharm.* 2011.33(2);208=14.

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)

Question #8

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D Length of therapy (LOT)

Tracking Antibiotic Use & Resistance

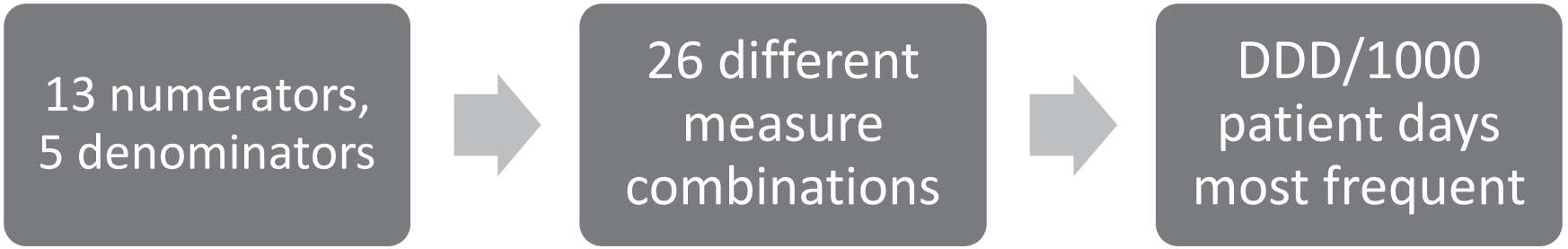
- IDSA/SHEA 2016 Guidelines rec #21: every ASP must measure antibiotic use
  - DOT/1000 patient days is the preferred metric (2016)
- CDC Antimicrobial Use and Resistance (AUR) module
  - Days present: time in which any patient is at risk for antimicrobial exposure
    - Number of patients present for 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

Barlam TF et al. *Clin Infect Dis*. 2016;62:e51-77.

Centers for Disease Control and Prevention. Antimicrobial use and resistance module. January. 2016.http://www.cdc.gov/nhsn/pdfs/pscmanual/11pscaurcurrent.pdf

Measuring Antimicrobial Use in Pediatrics: Systematic Review

- 79 studies included to review existing measures of antimicrobial use



- 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

Fortin E et al. *J Antimicrob Chemother*. 2014;69:1447-1456.

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

Morris A. *Curr Treat Options Infect Dis*. 2014;(6):101-12.

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

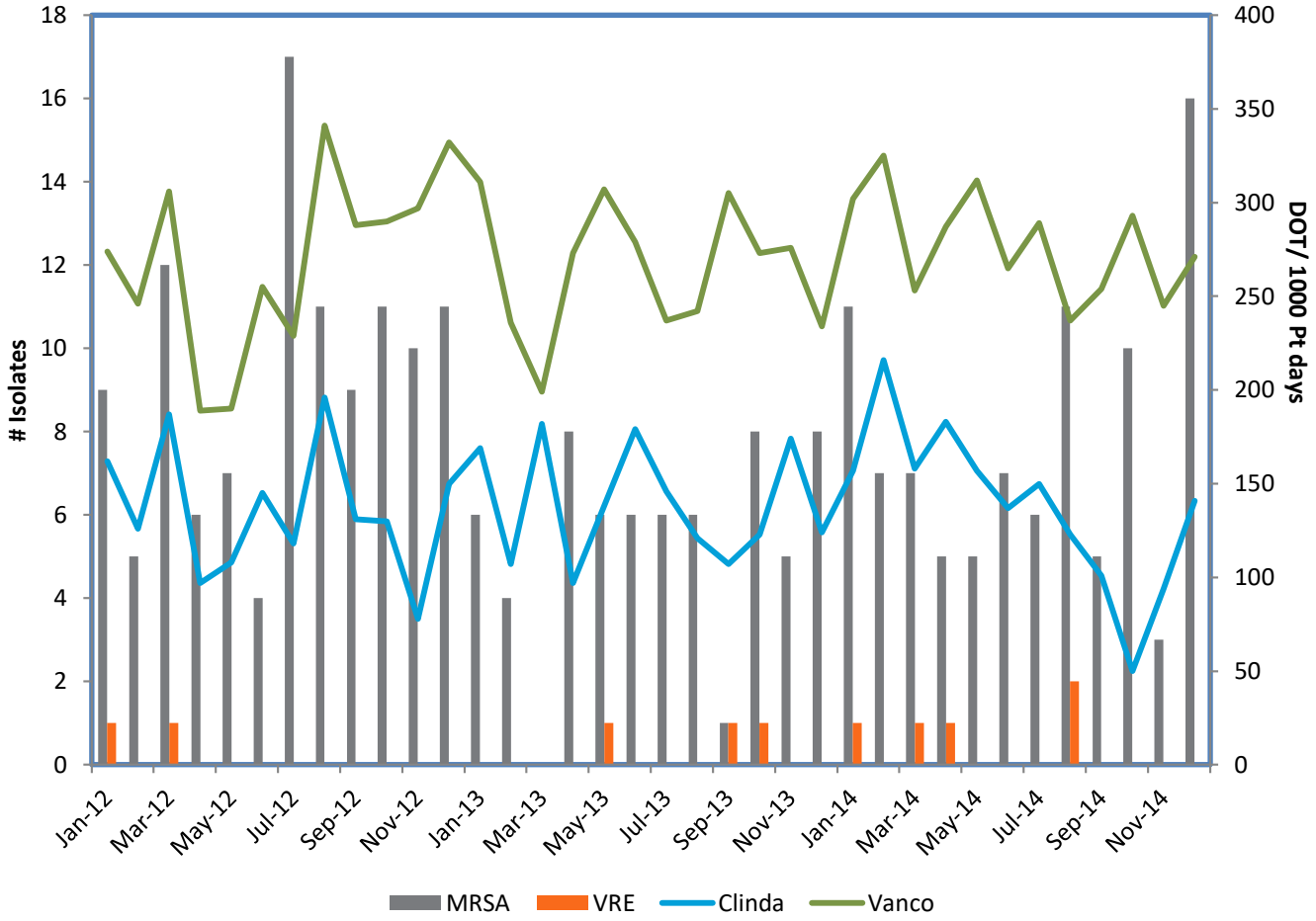
Examples

July 2014		
Drug Name	**Location**	**DOT/1000**
PIPERACILLIN/TAZOBACTAM	6C	377.66
PIPERACILLIN/TAZOBACTAM	4C	316.52
PIPERACILLIN/TAZOBACTAM	6D	316.11
SULFAMETHOXAZOLE/TRIMETHOPRIM	6D	308.51
SULFAMETHOXAZOLE/TRIMETHOPRIM	6C	265.96
CEFTRIAXONE	12C	221.03
CEFTRIAXONE	7C	215.05
CLINDAMYCIN	5C	187.27
VANCOMYCIN (SYSTEMIC)	12C	184.55
CEFTRIAXONE	5C	183.52

August 2014		
Drug Name	**Location**	**DOT/1000**
SULFAMETHOXAZOLE/TRIMETHOPRIM	6C	494.74
PIPERACILLIN/TAZOBACTAM	4C	271.05
PIPERACILLIN/TAZOBACTAM	6D	248.07
SULFAMETHOXAZOLE/TRIMETHOPRIM	6D	244.99
CEFTRIAXONE	11C	177.78
VANCOMYCIN (SYSTEMIC)	11C	157.78
VANCOMYCIN (SYSTEMIC)	6D	155.62
SULFAMETHOXAZOLE/TRIMETHOPRIM	5C	155.39
CLINDAMYCIN	4C	154
CLINDAMYCIN	5C	146.25

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

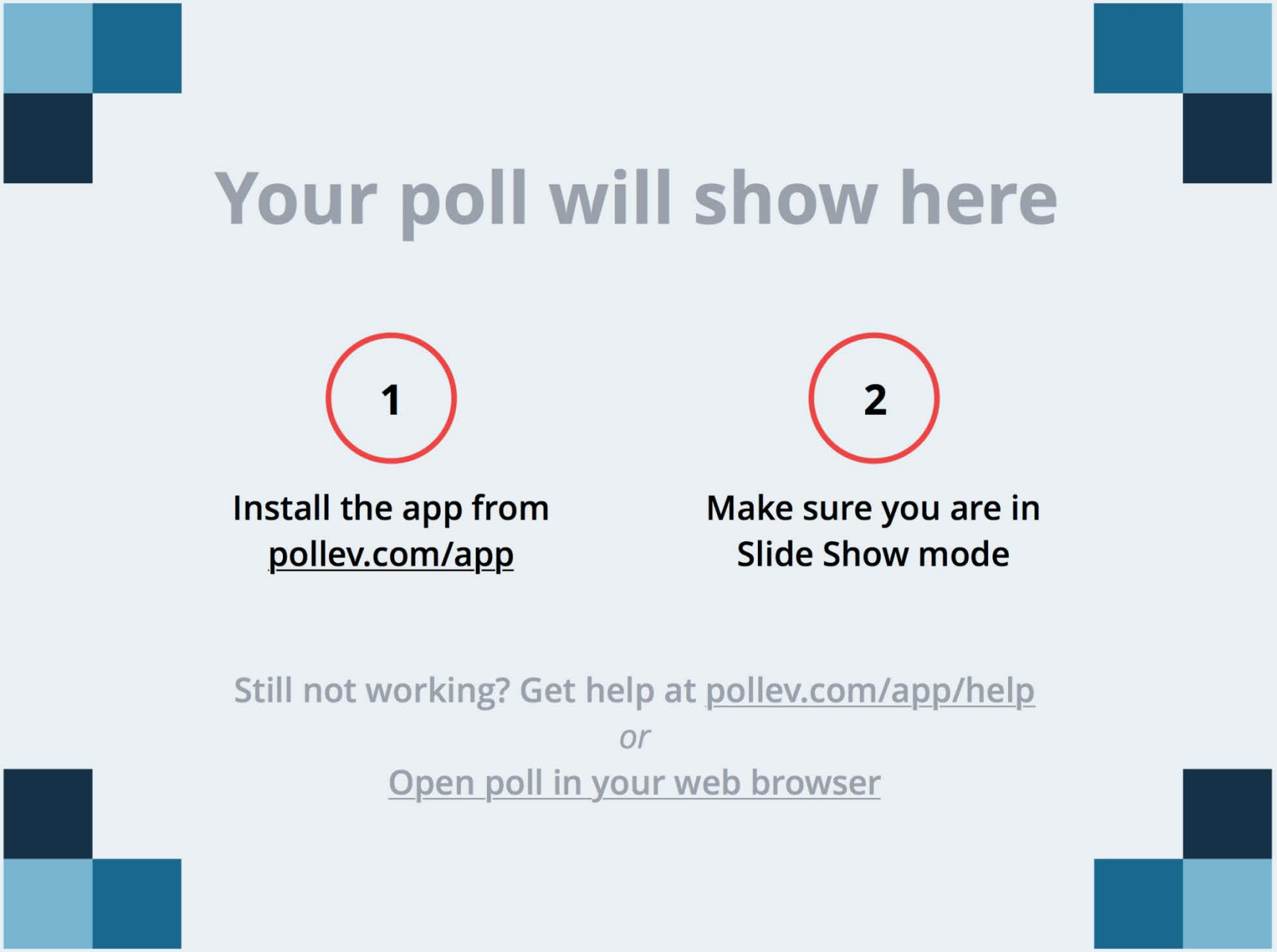
Morris A. *Curr Treat Options Infect Dis*. 2014;(6):101-12.

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

Question #9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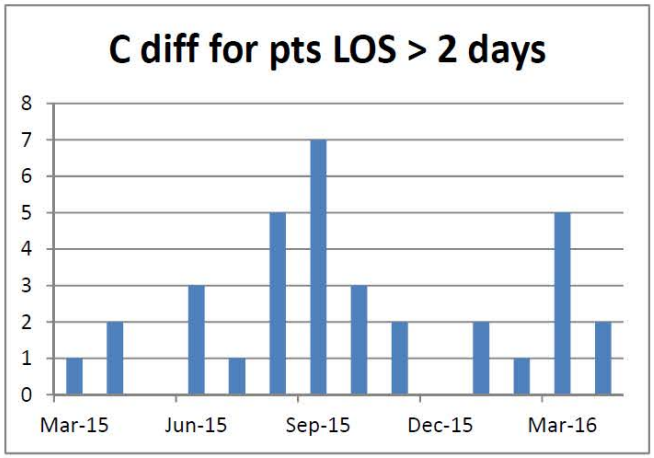
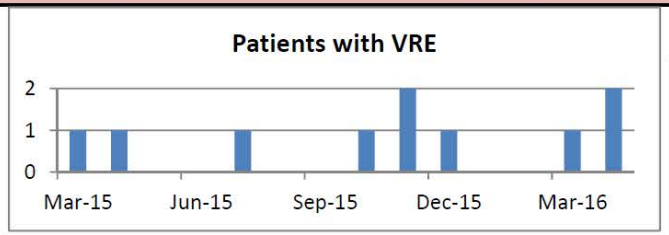
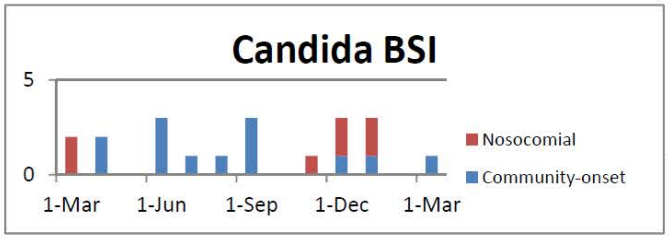
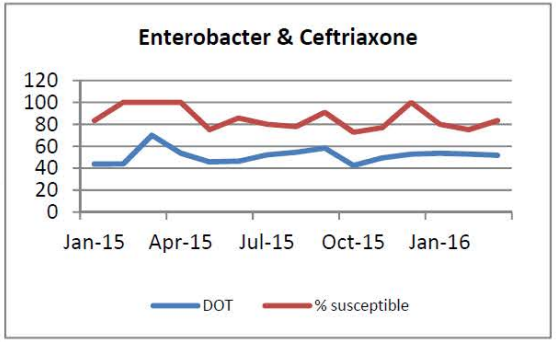
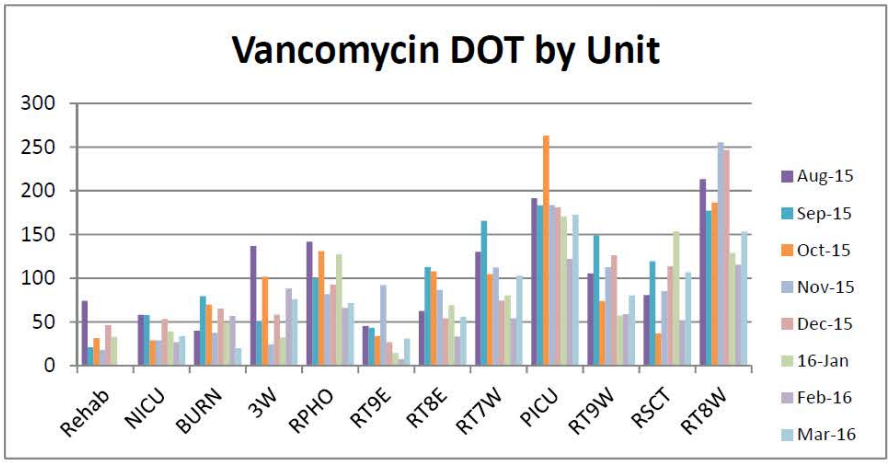
Pediatric Antimicrobial Stewardship Dashboard - Riley Hospital for Children - May 2016

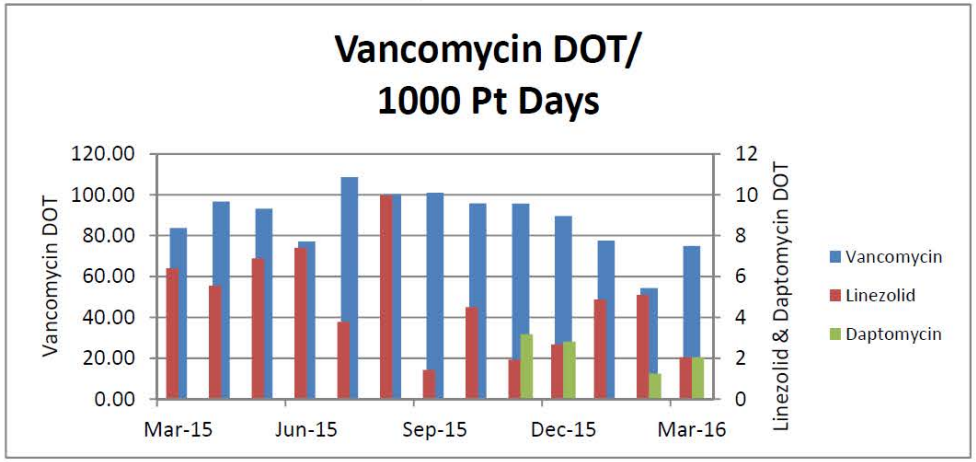


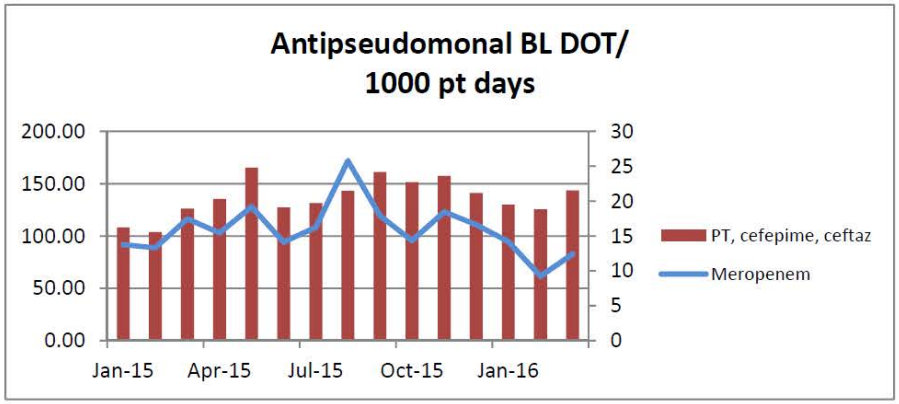


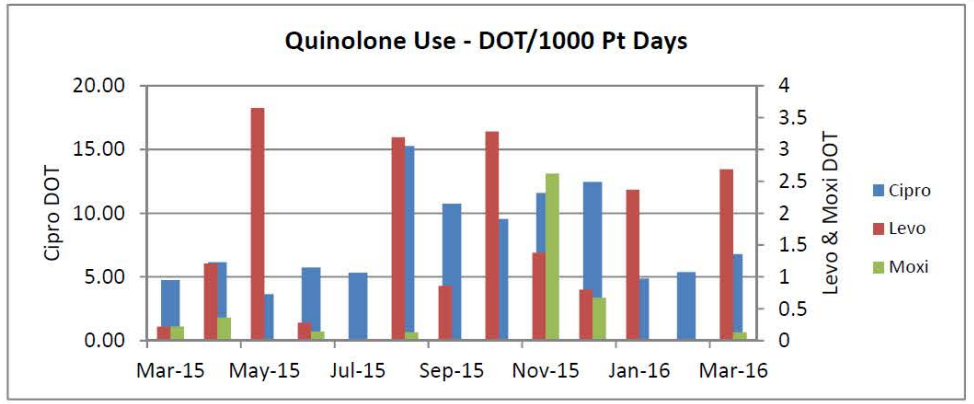












Additional Metrics: SAAR

- 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

Centers for Disease Control and Prevention. Antimicrobial use and resistance module. January. 2016. http://www.cdc.gov/nhsn/pdfs/pscmanual/11pscaurcurrent.pdf

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

Centers for Disease Control and Prevention. Antimicrobial use and resistance module. January. 2016. http://www.cdc.gov/nhsn/pdfs/pscmanual/11pscaurcurrent.pdf

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

Hersh et al. *Pediatrics*. 2015; 135(1):33-9.

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?

Barlam TF et al. *Clin Infect Dis*. 2016;62:e51-77.

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?