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

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DISCLAIMERS…

I could talk about antibiotic use and resistance ALL day

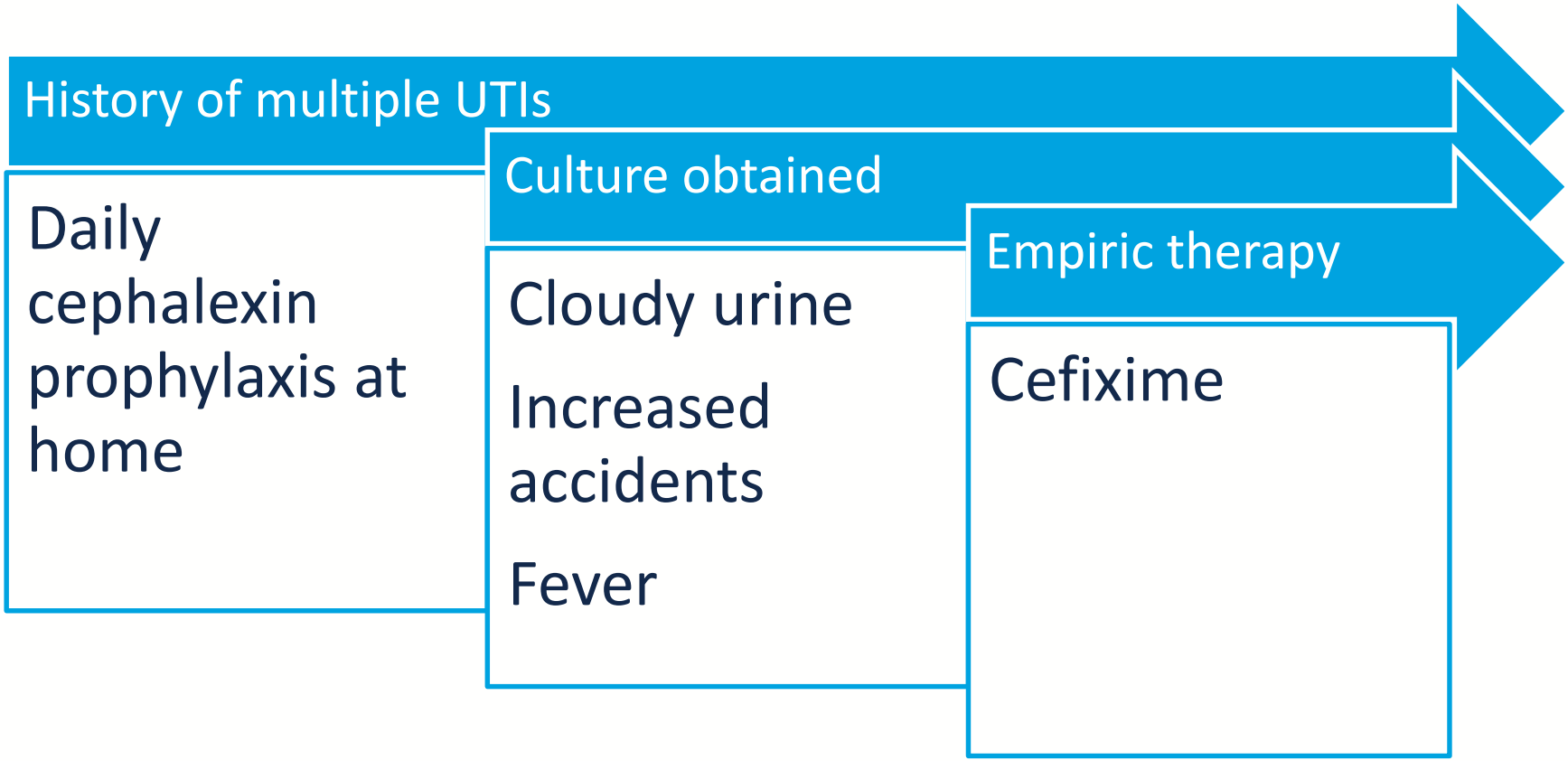
Evidence-based = challenging

[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



ESCHERICHIA COLI Extended-spectrum beta-lactamase producer

	MDIL	MINT
Amikacin	<=2	S
Tobramycin	<=1	S
Trimethoprim/Sulfa	>=320	R
Piperacillin/Tazobactam	<=4	S
Meropenem	<=0.25	S
Gentamicin	<=1	S
Ciprofloxacin	<=0.25	S
Ceftriaxone	>=64	R
Ceftazidime		R
Cefoxitin	<=4	S
Cefepime		R
Cefazolin	>=64	R
Ampicillin/Sulbactam	>=32	R
Ampicillin	>=32	R
Levofloxacin	0.5	S

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

Shaikh N et al. *J Pediatr*. 2016;171:116-121. Wragg R et al. *J Pediatr Surg*. 2017;52:286-288.
Nieminen O et al. *Acta Paediatrica*. 2016;106:327-333.

Antimicrobial choice

Empiric

- Use local antibiogram data
  - Urinary isolates from your population ideal
- Consider risk factors
  - Previous patient cultures

Directed

- Use susceptibility panel
  - Most narrow option
  - Least likely to cause collateral damage
- Patient-specific factors
  - Allergies

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 carbapenems
- Often resistant to other classes as well

Hsu AJ, Tamma PD. *Clin Infect Dis*. 2014;58:1439-48.

Extended Spectrum Beta-Lactamases

Treatment Options

ESCHERICHIA COLI Extended-spectrum beta-lactamase producer

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Amikacin	<=2	S
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Ciprofloxacin	<=0.25	S
Ceftriaxone	>=64	R
Ceftazidime		R
Cefoxitin	<=4	S
Cefepime		R
Cefazolin	>=64	R
Ampicillin/Sulbactam	>=32	R
Ampicillin	>=32	R
Levofloxacin	0.5	S

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

Hsu AJ et al. *Clin Infect Dis*. 2014;58:1439-48. Reffert JL et al. *Pharmacotherapy*. 2014:34:845-857.
Principi N et al. Chemotherapy. 1990;36:41-45.

Oral: Fluoroquinolones

- Well-absorbed (80-100%)

Ciprofloxacin → Levofloxacin → Moxifloxacin: NOT for UTIs

- 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

Meropenem	Ertapenem	Doripenem	Imipenem/ cilastatin

- 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

Hsu AJ et al. *Clin Infect Dis*. 2014;58:1439-48.

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

Hsu AJ et al. *Clin Infect Dis*. 2014;58:1439-48.

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

Kerneis S et al. *Infectious Diseases*. 2015;47:789-95. Guet-Rivellet H et al. *Antimicrob Agent Chemother.* 2014;58:4899-4901.

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

Broad Spectrum Antimicrobial for Topical Application: Clorpactin WCS-90. Guardian Laboratories. Hauppauge, New York. August 2000.
Clorpactin WCS-90. Lexi-Comp Online. Lexi-Comp, Inc. Hudson, OH. Accessed August 31, 2017

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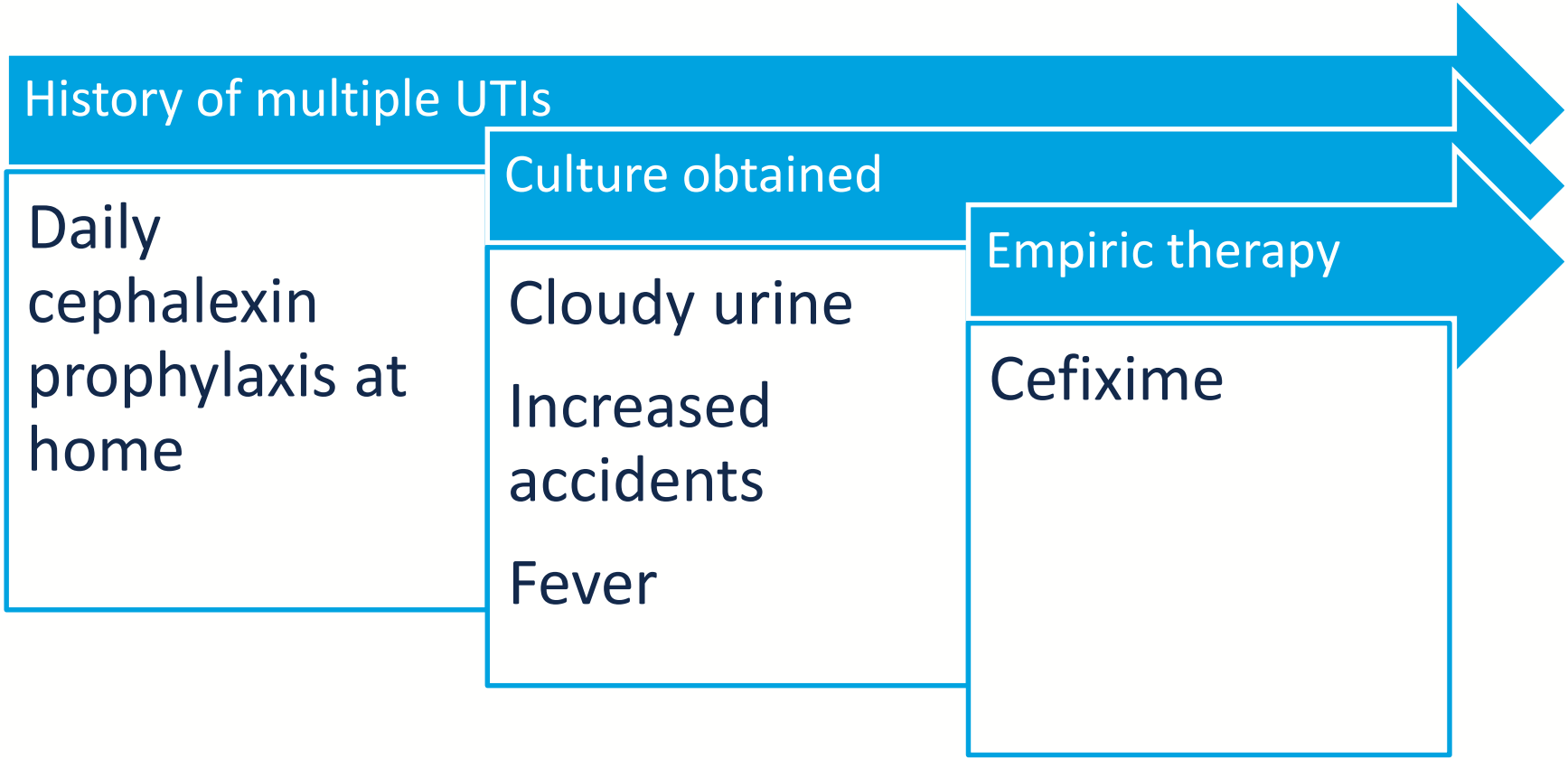

- Ciprofloxacin 15 mg/kg PO Q12H
- Fosfomycin a reasonable option
- If bacteremic or upper tract involved → IV piperacillin/tazobactam

10 year-old with a KPC-UTI and Bacteremia

Susceptibility

	Klebsiella pneumoniae - Carbapenem Resistant		
	BACTERIAL SUSCEPTIBILITY MIC PANEL		CARBAPENEM RESISTANCE GENE DETECTION - PCR-RT
Ampicillin	>=32 ug/mL	Resistant	
Ampicillin/Sulbactam	>=32 ug/mL	Resistant	
Cefazolin	>=64 ug/mL	Resistant	
Cefepime	>=64 ug/mL	Resistant	
Ceftriaxone	>=64 ug/mL	Resistant	
Ciprofloxacin	>=4 ug/mL	Resistant	
Gentamicin	4 ug/mL	Susceptible	
IMP			Not Detected
KPC			Detected
Levofloxacin MIC	>=8 ug/mL	Resistant	
Meropenem	>=16 ug/mL	Resistant	
NDM			Not Detected
OXA48			Not Detected
Piperacillin/Tazobactam	>=128 ug/mL	Resistant	
Tobramycin	>=16 ug/mL	Resistant	
Trimethoprim/Sulfa	>=320 ug/mL	Resistant	
VIM			Not Detected

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

De Pascale G et al. *Critical Care*. 2017;21:173. Hsu AJ et al. *Clin Infect Dis*. 2014;58:1439-48

Newer Therapies

Ceftazidime/ avibactam

- Approved in adults 2015
- Ceftazidime is well-studied in children
- Avibactam isn't
  - Most BLI aren't
- Active against ESBLs and many carbapenemases
  - No Ambler class B

Meropenem/ vaborbactam

- Approved in adults last week
  - Complicated UTI
- Not yet available
- Will be reserved for patients/isolate in true need

Zasowski EJ et al. *Pharmacotherapy*. 2015;35:755-770.
https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm573955.htm

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Susceptibility

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	BACTERIAL SUSCEPTIBILITY MIC PANEL		
Ampicillin	<=2 ug/mL	Susceptible	
Vancomycin	1 ug/mL	Susceptible	

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

Paterson DL. *Clin Infect Dis*. 2004;38:s341-5.

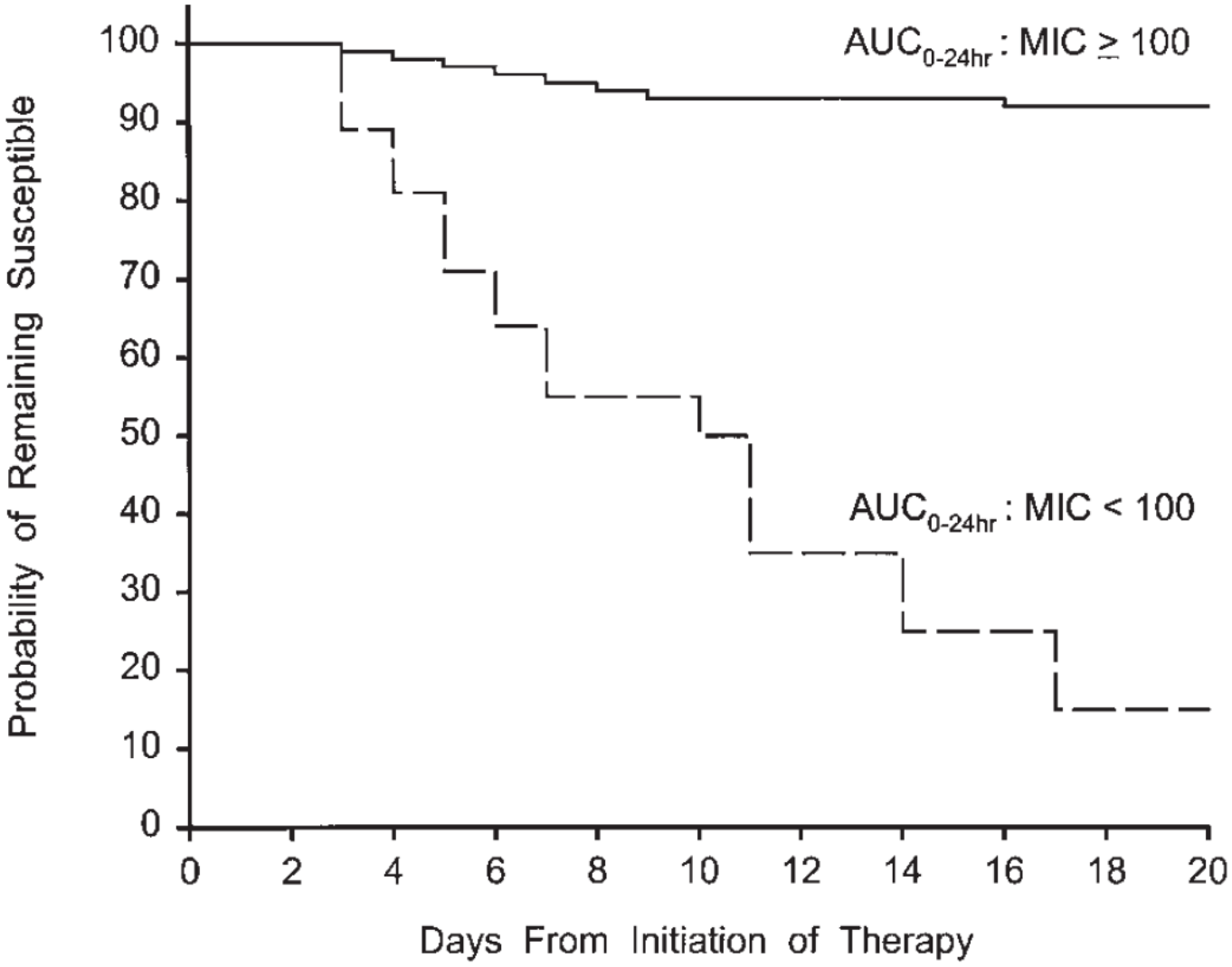
Fluoroquinolones

- 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**

Kaur K et al. *J Community Support Onc*. 2016;14(2):54-65.
Jackson MA et al. *Pediatrics*. 2016;138(5):e1-e13.

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



Rodvolt, KA et al. Pharmacotherapy 2001; 21:233S–252**S**

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

Brandstrom P et al. *Pediatr Nephrol*. 2015;30:425-432.

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

Brandstrom P et al. *Pediatr Nephrol*. 2015;30:425-432.
Hari P et al. *Pediatr Nephrol*. 2015;30:479-486.

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

RIVUR trial investigators. *N Engl J Med*. 2014;370(25):2367-76.

The Problem with Data

Studied populations vary drastically

Adherence to therapy should be considered

Bacteria are constantly evolving

The "holy grail" study is unlikely to be completed

- 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

Prophylaxis in Hydronephrosis

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

Easterbrook B et al. *Can Urol Assoc J*. 2017;11:s3-11.

Surgical Prophylaxis

Optimal peri-operative prophylaxis

Prevents infection & therefore antibiotic use

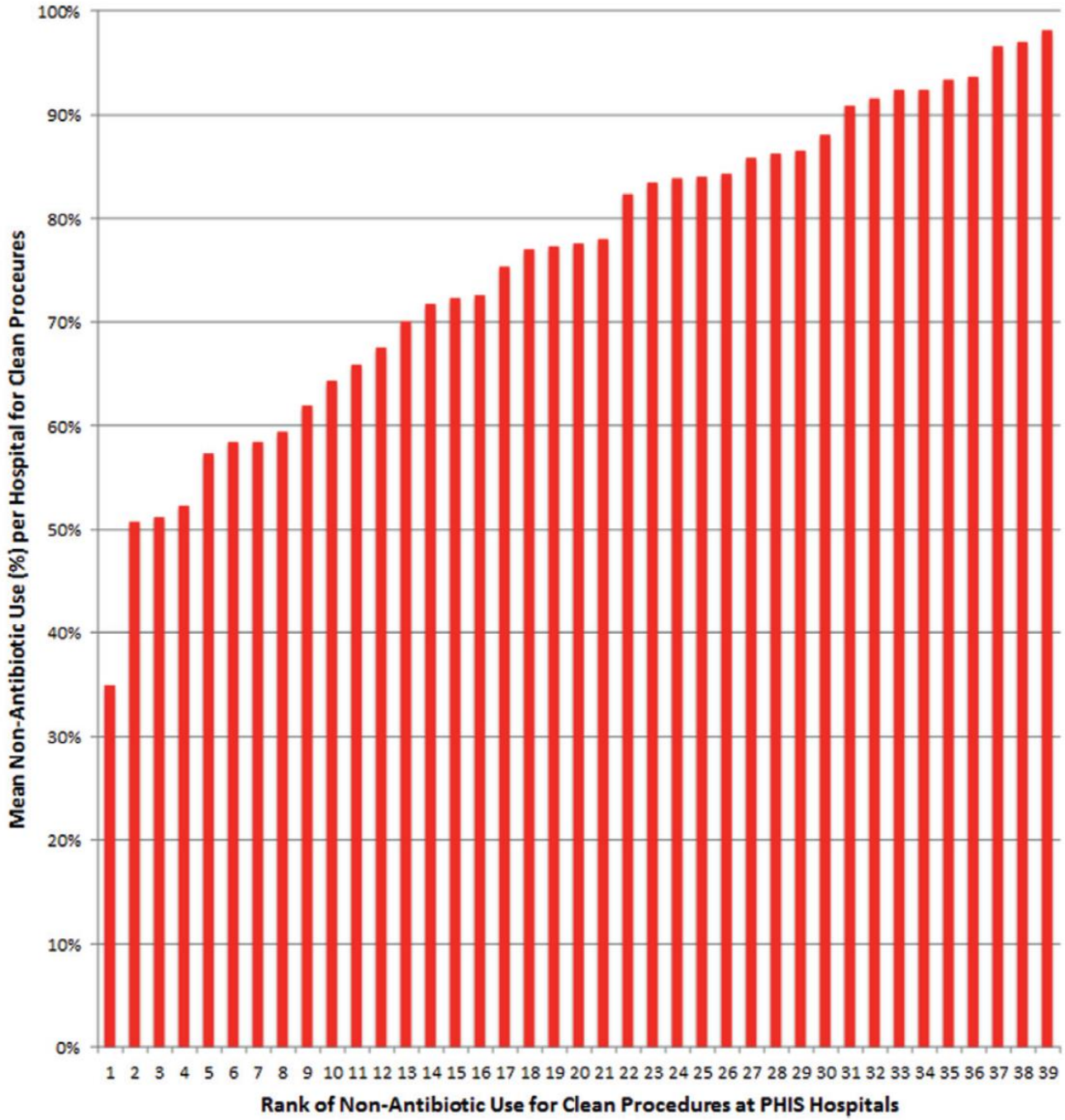
Avoids antibiotic exposure when unnecessary

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

Chan KH et al. *J Urol*. 2017;197:944-950.

Sandora TJ et al. *JAMA Pediatr.* 2016;170:570.



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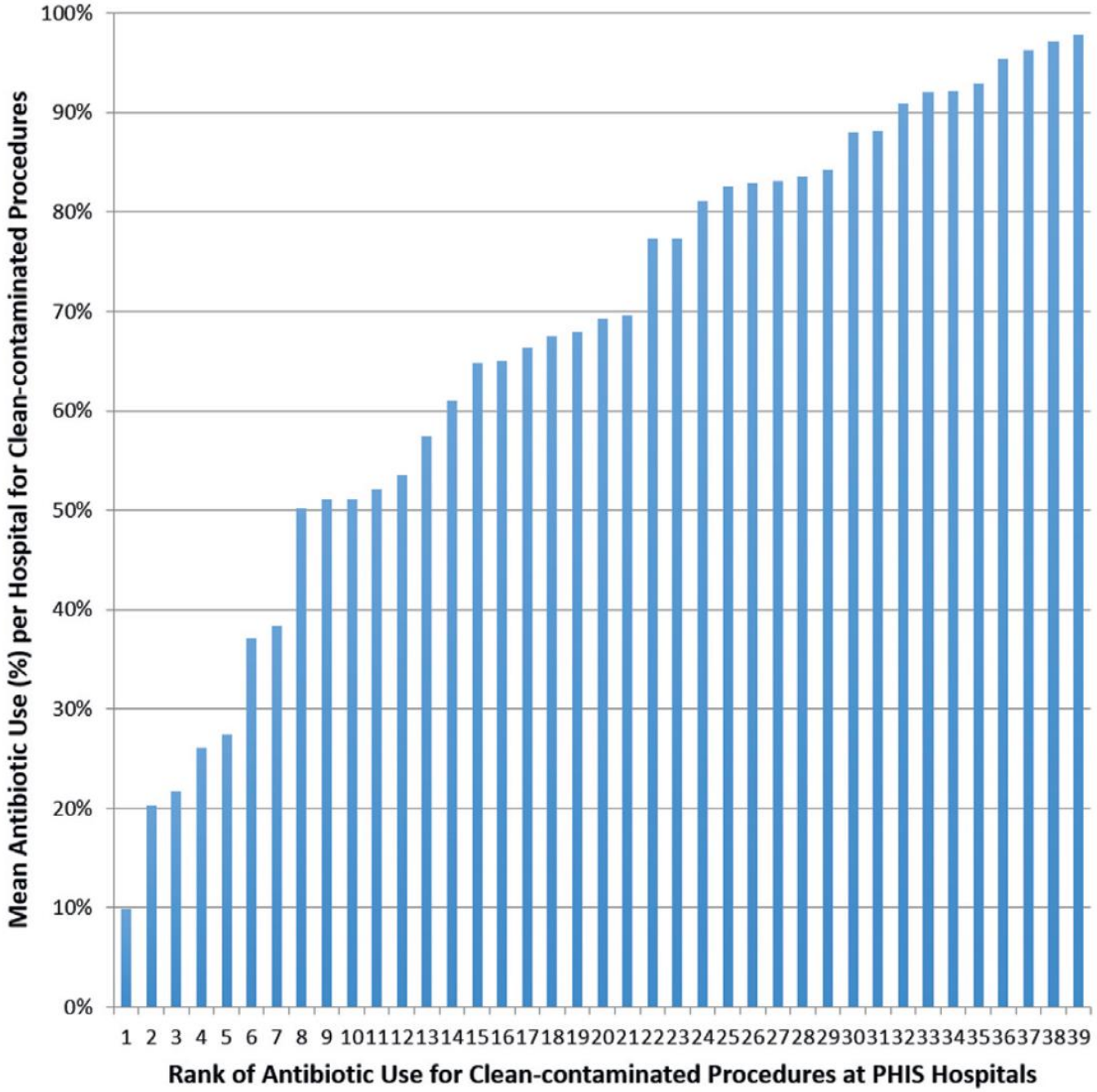


Chan KH et al. *J Urol*. 2017;197 :944-950.

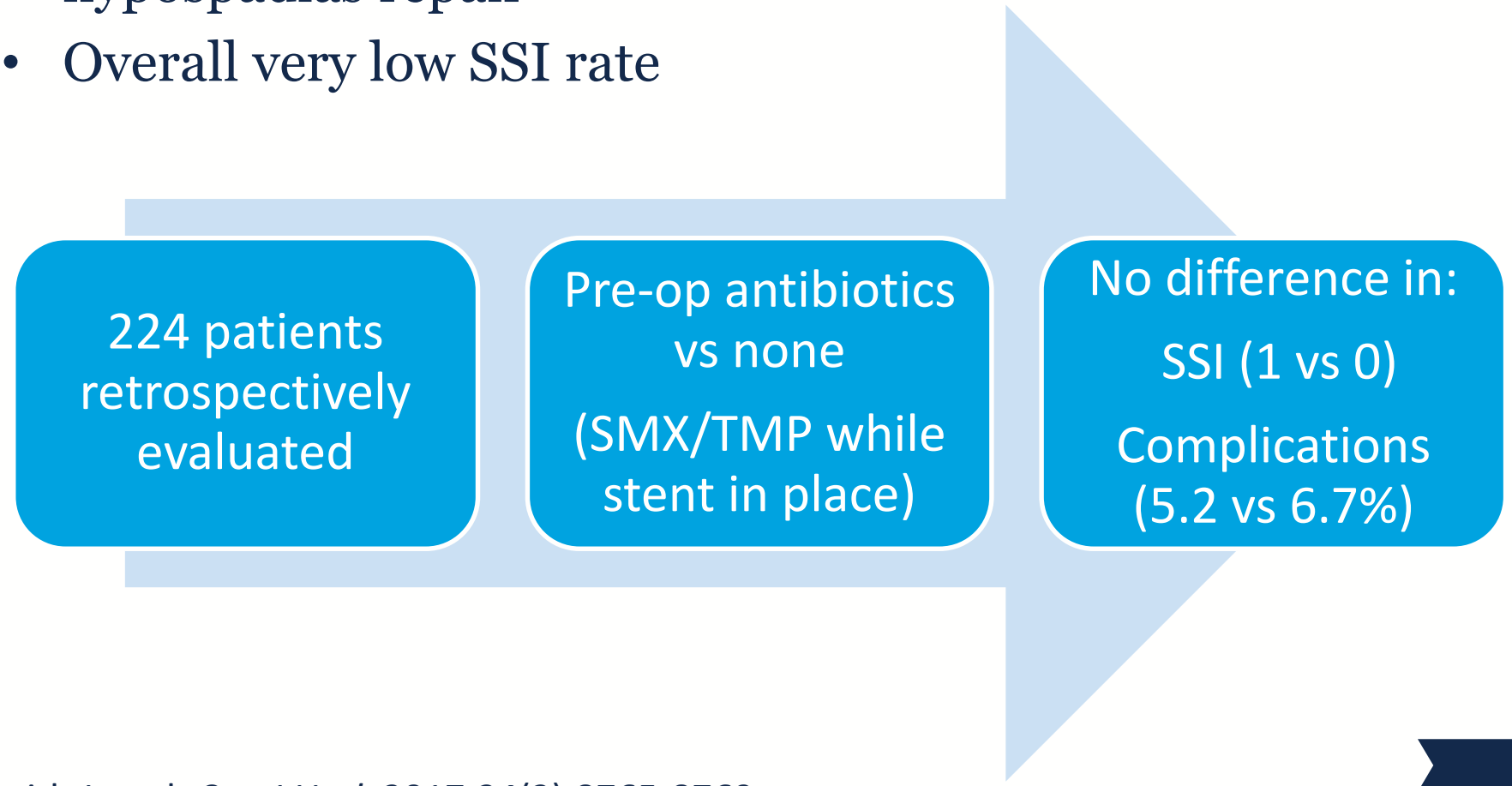
Prophylaxis in Outpatient Circumcision

- 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)

Chan KH et al. *J Pediatr Urol*. 2017;13:205.e1-205.e6.

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



Smith J et al. *Can J Urol*. 2017;24(2):8765-8769.

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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More Good Articles

- Hsu J, Tamma PD. Treatment of multidrug-resistant gram-negative infections in children. *Clin Infect Dis*. 2014;58(10):1439-48.
- Greenfield SP et al. Vesicoureteral reflux and antibiotic prophylaxis: why cohorts and methodologies matter. *J Urol*. 2016;196:1238-43.