The long and short of it: assessing duration of therapy for common infections in children

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Children's Wisconsin
Kids deserve the best.

Objectives

1. Recognize strategies to optimize antimicrobial use, focusing on using the shortest, effective duration
2. Summarize the evidence supporting shortened courses of antibiotic therapy for the treatment of some common bacterial infections in children
3. Identify factors which may modify the effectiveness of short course treatment

How to pick a duration of therapy

Diagnosis → Severity of illness → Time to clinical improvement

Risk, fear, anxiety

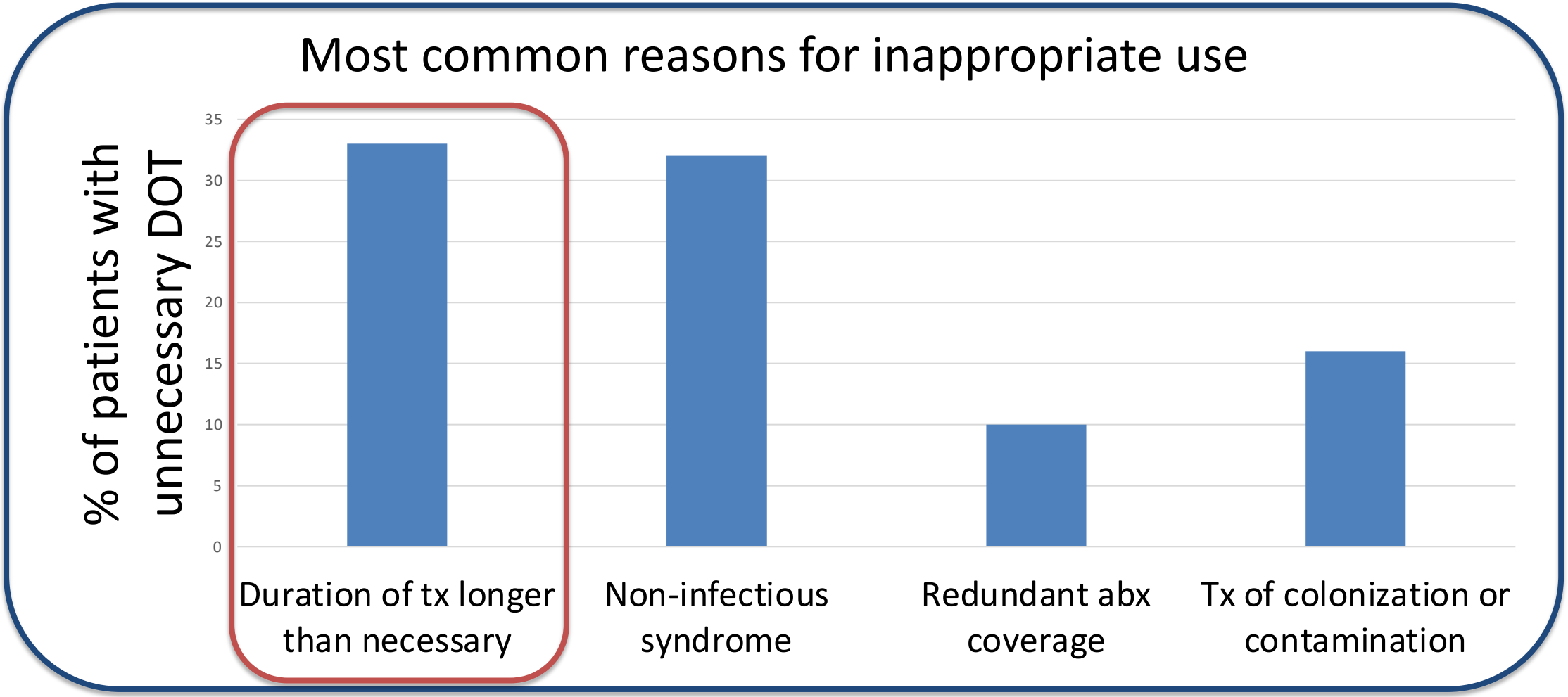
Kusha D. et al Can the Future of ID Escape the Inertial Dogma of Its Past? : The Exemplars of Shorter Is Better and Oral Is the New IV, *Open Forum Infectious Diseases*, 2022

Antibiotics commonly prescribed too long

- Systematic scoping review of literature Jan ‘00 - Aug ‘21
- Key drivers:
  - **Individual factors**: knowledge/skills, diagnostic uncertainty
  - **Professional interactions**: trainee vs senior, specialty consults, liability
  - Guideline factors: evidence, trust, conflicts w/ local guideline
  - Patient factors: patient/family expectations, co-morbidities
  - Resources: tracking dates, inaccurate stop orders
  - Organizational leadership and political/legal factors
- Conclusion: development of stewardship interventions to optimize antibiotic therapy duration are needed

Janssen RME, et al. *JAC* 2022; 77(8):2105-2119.

CDC reports up to 50% of antibiotic use is inappropriate



Hecker et al. *Arch Intern Med.* 2003;163(8):972-8.

What's the risk in one more day?

- Retrospective, single center cohort study
- Adults w/ severe sepsis/shock (n = 7,118)
- Treated with cefepime, meropenem, pip/tazo ≥ 3 days
- Objective: to correlate duration of exposure with development of new resistance

Teshome et al. Pharmacotherapy 2019;39(3):261-268.

Every day counts!
4% ↑ risk of new resistance each day of therapy

	Adjusted hazard ratio (95% CI)
Any	1.04 (1.04-1.05)
Cefepime	1.08 (1.07-1.09)
Meropenem	1.02 (1.01-1.03)
Piperacillin/tazobactam	1.08 (1.06-1.09)

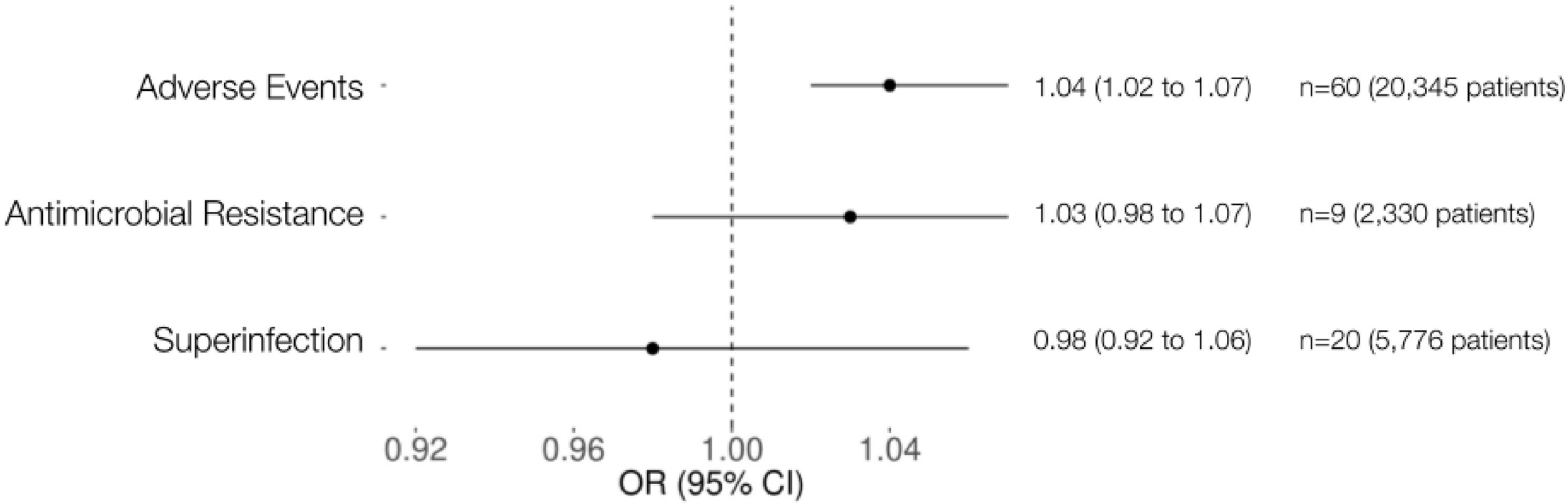
Teshome et al. *Pharmacotherapy* 2019;39(3):261-268.

What's the risk in one more day?

- Modified umbrella review of systematic reviews
  - Meta-analysis of individual randomized controlled trials
- Primary outcomes = proportion of patients experiencing:
  - Adverse drug events
  - Superinfections
  - Antimicrobial resistance (defined by study authors)
- Odds ratios pooled across studies to estimate overall daily odds ratio for harm for a given outcome

Curran et al. *Clin Microbiol Infect*. 2022 Apr;28(4):479-490.

4% ↑ risk of adverse event each day of therapy



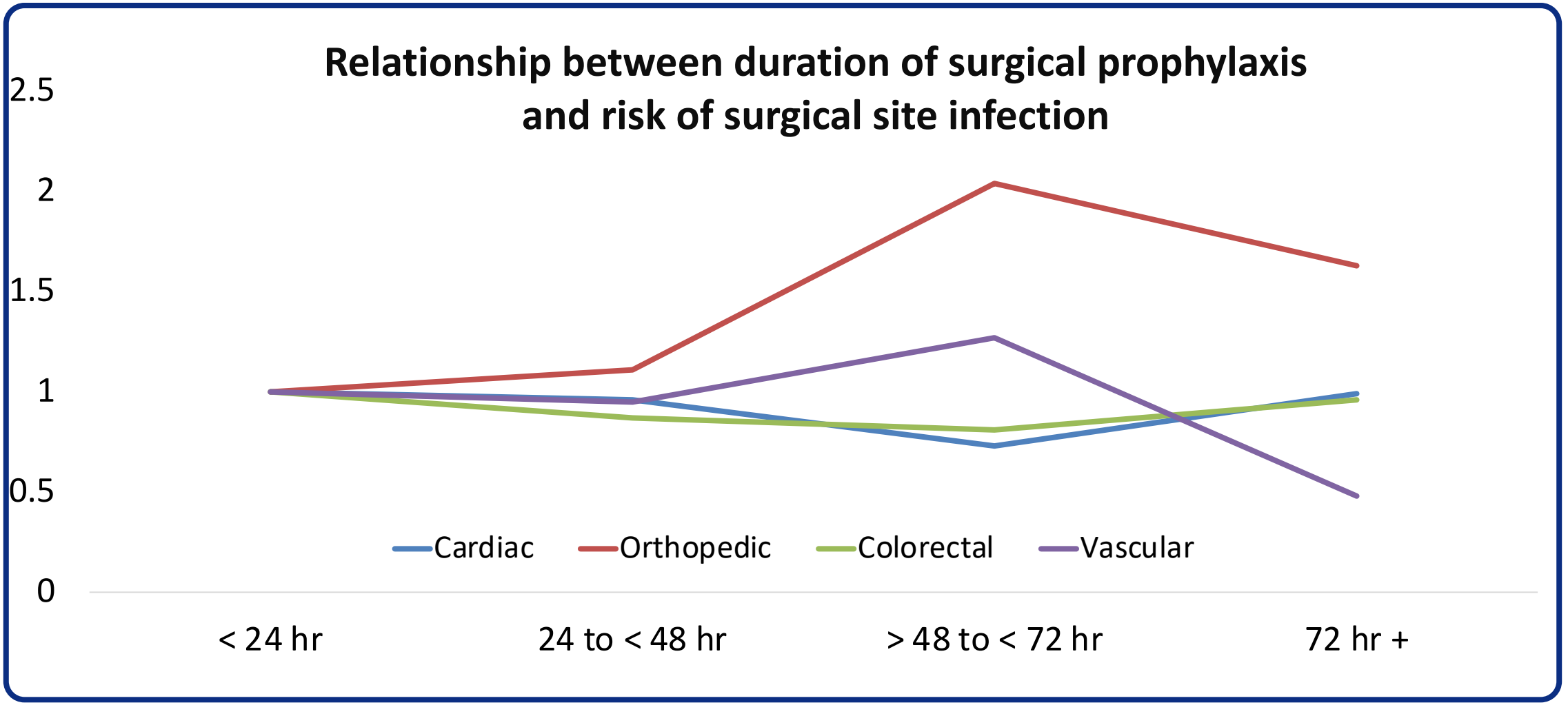
Curran et al. *Clin Microbiol Infect*. 2022 Apr;28(4):479-490.

What's the risk in one more day?

- Retrospective cohort study
- Adults (n=79,058) hospitalized post cardiac, orthopedic, colorectal, or vascular surgery
- Objective: characterize relationship b/w duration of surgical prophylaxis with surgical site infection (SSI) and drug-related effects

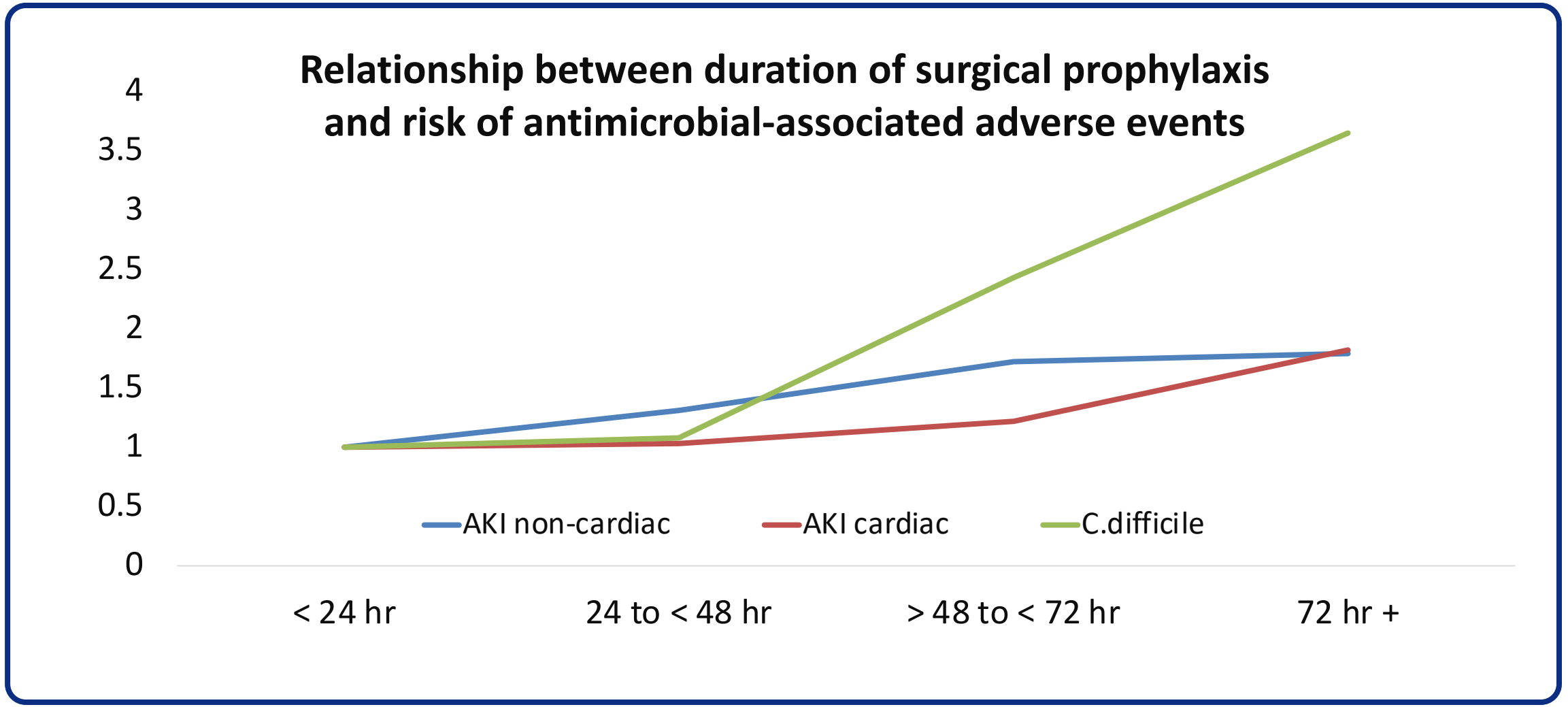
Branch-Elliman, et al. *JAMA Surg* 2019; 154(7):590-598.

No difference in rate of SSI



Branch-Elliman, et al. JAMA Surg 2019; 154(7):590-598.

↑ risk of AKI and *C.difficile* after 24-48h



Branch-Elliman, et al. JAMA Surg 2019; 154(7):590-598.

Shorter Is Better

Diagnosis	Short (d)	Long (d)	Result	#RCT
CAP	3-5	5-14	Equal	14
Atypical CAP	1	3	Equal	1
Possible PNA in ICU	3	14-21	Equal	1*
VAP	8	15	Equal	2
cUTI/Pyelonephritis	5 or 7	10 or 14	Equal	9**
Intra-abd Infection	4	10	Equal	2
GNB Bacteremia	7	14	Equal	3†
Cellulitis/Wound/Abscess	5-6	10	Equal	4‡
Osteomyelitis	42	84	Equal	2
Osteo Removed Implant	28	42	Equal	1
Debrided Diabetic Osteo	10-21	42-90	Equal	2φ
Septic Arthritis	14	28	Equal	1
AECB & Sinusitis	≤5	≥7	Equal	>25
Neutropenic Fever	AFx72h/3 d	+ANC>500/9 d	Equal	2
Post Op Prophylaxis	0-1	1-5	Equal	55Ψ
Erythema Migrans (Lyme)	7	14	Equal	1
P. vivax Malaria	7	14	Equal	1

Total: 17 Conditions **>120 RCTs**

*Infiltrate on CXR but low CPIS score (≤6), both ventilated and non ventilated, likely CAP, HAP, and VAP combined; **2 RCT included males, the smaller one found lower 10-18 d f/up cure in males with 7 days of therapy but no difference at longer follow-up, larger exclusive male study found no diff in cure; †GNB bacteremia also in UTI/cIAI RCTs; ‡3 RCTs equal, 1 (low dose oral flucox) ↑relapses 2° endpoint; φall patients debrided, in 1 study total bone resection (clean margins); ΨIncludes meta-analysis of 52 RCTs; refs at https://www.bradspellberg.com/shorter-is-better

#shorterisbetter

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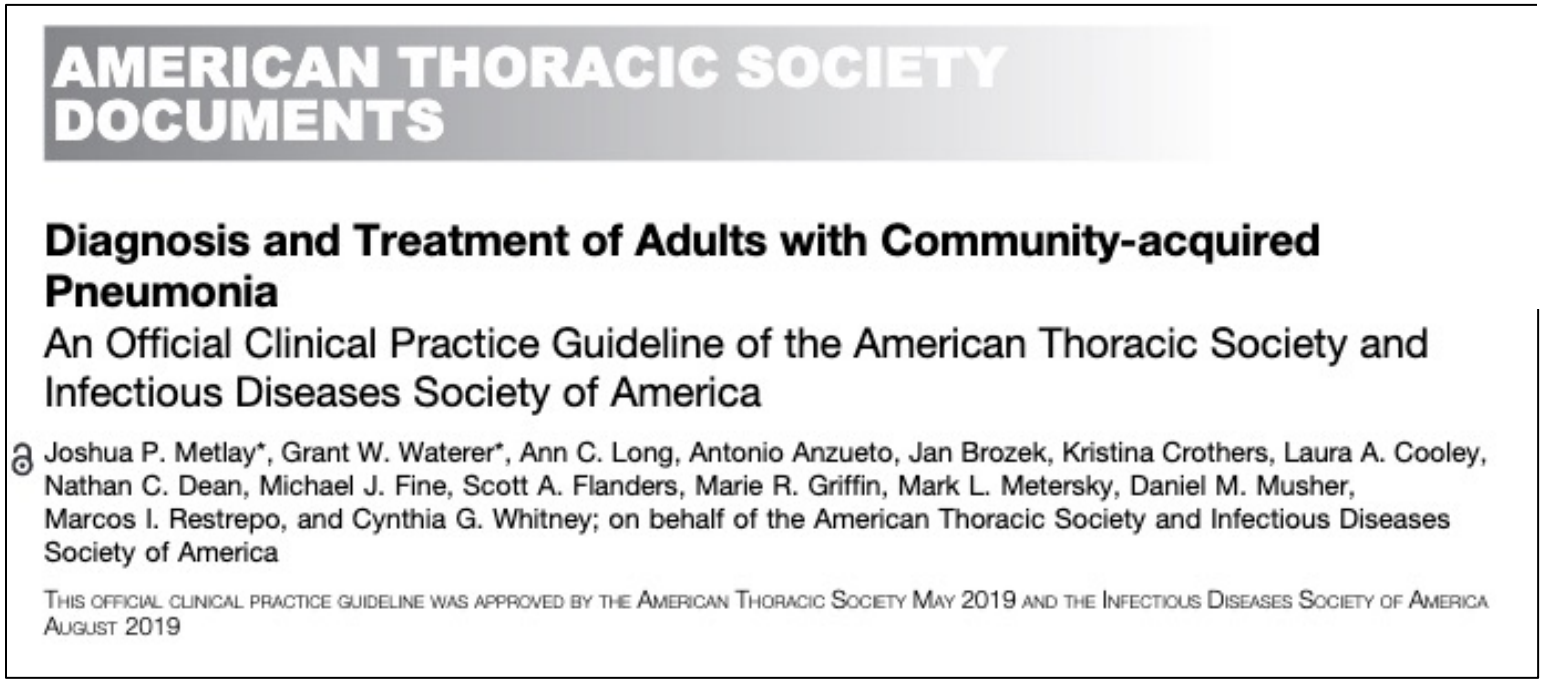
To be covered today….

- Community acquired pneumonia
- Urinary tract infections
- Skin/soft tissue infections
- Febrile neonate

IDSA CAP Guidelines, updated 2019



AMERICAN THORACIC SOCIETY DOCUMENTS

Diagnosis and Treatment of Adults with Community-acquired Pneumonia

An Official Clinical Practice Guideline of the American Thoracic Society and Infectious Diseases Society of America

Joshua P. Metlay*, Grant W. Waterer*, Ann C. Long, Antonio Anzueto, Jan Brozek, Kristina Crothers, Laura A. Cooley, Nathan C. Dean, Michael J. Fine, Scott A. Flanders, Marie R. Griffin, Mark L. Metersky, Daniel M. Musher, Marcos I. Restrepo, and Cynthia G. Whitney; on behalf of the American Thoracic Society and Infectious Diseases Society of America

THIS OFFICIAL CLINICAL PRACTICE GUIDELINE WAS APPROVED BY THE AMERICAN THORACIC SOCIETY MAY 2019 AND THE INFECTIOUS DISEASES SOCIETY OF AMERICA AUGUST 2019

Durations as short as 5 days effective among patients who are clinically stable and afebrile by 48-72 hours

Metlay JP, et al. Am J Respir Crit Care Med 2019;200(7):e45-67

SAFER trial in outpatient CAP – 5 days is enough

- Non-inferiority, blinded, RCT
- Children 6 months – 10 years old (281 randomized)
- Pneumonia = fever, symptoms, and radiographic findings
- Well enough for treatment in outpatient setting
- Intervention – 5 days high dose amoxicillin + 5 days placebo
- Control – 10 days high dose amoxicillin
- Short course non-inferior (ITT analysis)

Pernica JM, et al. JAMA Pediatr 2021;175(5):475-482.

But what about hospitalized kids?

Hospitalized children (> 6 months old) diagnosed with uncomplicated* CAP based on clinical and radiologic criteria (n=439)

*Excluded patients with more complex disease (e.g., large pleural effusion, pulmonary abscess, tracheostomy dependence, severe immunosuppression)

Dichotomized by treatment duration (retrospectively)

Inpatient + Outpatient Duration

Short course
(5-7 days)
N=168

Long course
(8-14 days)
N=271

Same RJ, et al. JPIDS 2021;10(3):267-273

5 days enough for uncomplicated CAP

	Short course	Long course	OR (95% CI)
Duration of therapy (days), median (IQR)	6 (5-7)	10 (9-10)	
Treatment failure*, %	3	6	0.48 (0.18-1.3)
Unplanned ED or outpatient visit related to CAP, %	2	3	0.54 (0.14-2.07)
Hospital admission for pneumonia, %	2	3	0.43 (0.11-1.74)
Deaths	0	0	

* Subanalysis excluding patients with positive respiratory viral test – no difference in treatment failure

Same RJ, et al. JPIDS 2021;10(3):267-273

First prospective inpatient CAP study supports shorter duration

- Multi-center, double blind, RCT
- Children 3mos - ≤5y/o (324 randomized); high risk population
- Pneumonia = >37.5, clinical symptoms, and radiographic consolidation
- Ready for oral antibx transition w/in 1-3 days
- Intervention – 1-3days IV + 3days amox-clav + 8days placebo
- Control – 1-3days IV + 11days amox-clav
- No clinical benefit to extended duration of therapy

McCallum et al. *PIDJ Journal, 41* (7), 549-555.

Optimal durations for UTI emerging…

American Academy of Pediatrics
DEDICATED TO THE HEALTH OF ALL CHILDREN™

FROM THE AMERICAN ACADEMY OF PEDIATRICS

CLINICAL PRACTICE GUIDELINE

Urinary Tract Infection: Clinical Practice Guideline for the Diagnosis and Management of the Initial UTI in Febrile Infants and Children 2 to 24 Months

- Febrile children 2- 24 months old
- Very little data to address duration
- Recommended duration of 7-14 days

Pediatrics 2011;128:595-610

On the horizon:

The SCOUT Study
Short **CO**urse Therapy for **U**rinary **T**ract Infections in Children

Investigating treatment of urinary tract infections with 10 versus 5 days of antibiotics

A National Institutes of Health Sponsored Research Study

Can urinary tract infections be treated effectively with shorter courses of antibiotics?

Background:

- UTI is one of the most frequently occurring serious bacterial infections in childhood.
- Standard UTI treatment has been a 10-day course of antibiotics.
- Overuse of antibiotics for UTI results in diarrhea, diaper rash, and increased bacterial resistance.
- This study will determine whether a 5-day course of antibiotics may be all that your child needs with fewer side effects.

Eligibility:

Your child **must**:

- Have a UTI
- Be between 2 months and 10 years of age
- Not have any medical problems
- Provide urine and stool samples

Find more information online at www.chp.edu/scout

Contact Information:
Alejandro Hoberman, MD, and Nader Shaikh, MD
412-692-UTIS (8847)
The UTI Center

Sponsored by the National Institute of Allergy and Infectious Diseases, National Institutes of Health

www.chp.edu/scout

Children's Hospital of Pittsburgh of UPMC

- Multi-center, Non-inferiority RCT
- 2 months – 10 years old w/ confirmed UTI
- Outpatient treatment (select antibiotics)
- Primary outcome:
  - Treatment failure @ 5 vs 10 days
  - Inclusion: afebrile & asymptomatic @ day 5

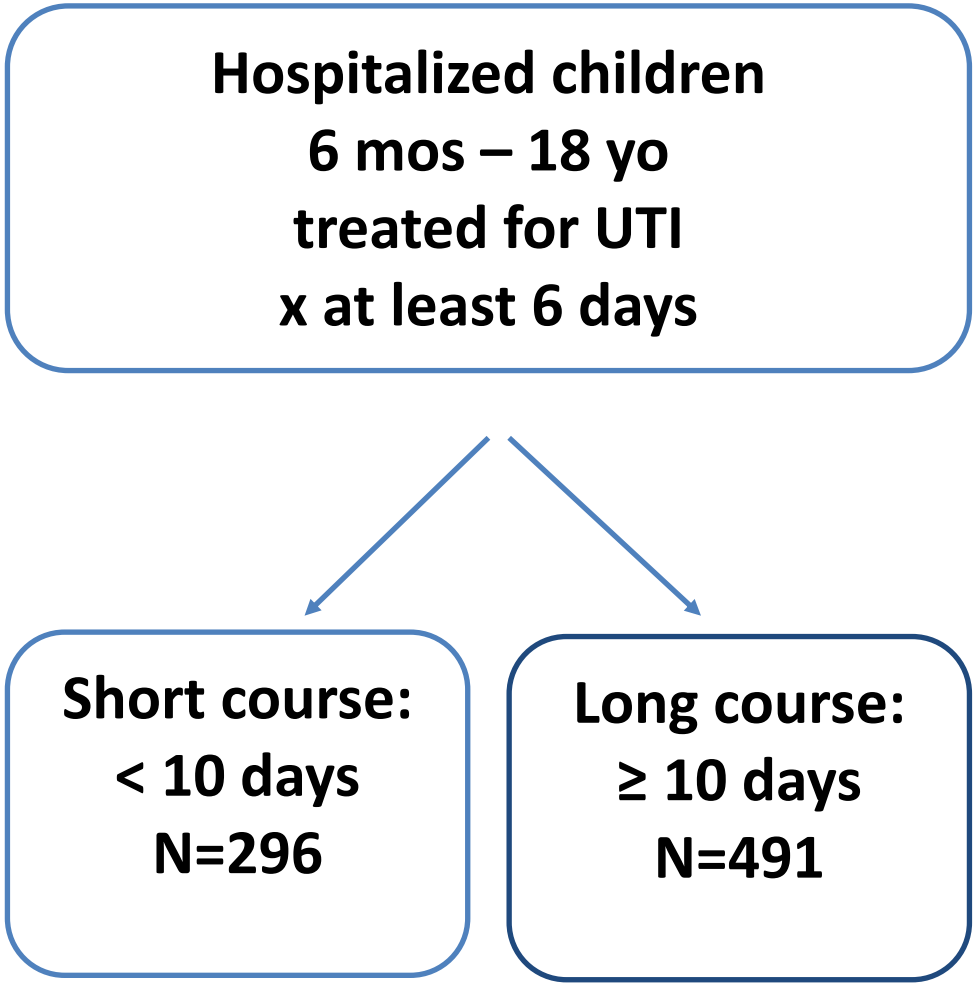
Zaoutis et al. 639. Open Forum Infect Dis. 2020 Dec 31;7(Suppl 1):S380

SCOUT Study - Preliminary results

- 693 children randomized
  - 345 short course, 348 standard course; median age 4yrs
- Treatment success rates:
  - 322/336 (96%) short course vs 326/328 (99%) standard course (ITT)
    - Short course found inferior
  - PP analysis: 305/314 (97%) short vs 306/308 (99%) standard
  - NNT 28 (ITT) and 43 (PP)
- Treatment failure unrelated to age, fever, antibiotic type, or study site

Zaoutis et al. 639. Open Forum Infect Dis. 2020 Dec 31;7(Suppl 1):S380

7 days as good as 10 days for pyelonephritis



Included:

Microbiological criteria PLUS

Fever PLUS

At least one clinical sign/symptom

Excluded:

-Drugs not expected to reach appropriate concentration in kidney parenchyma

-Renal abscess

MT Fox, et al. JAMA Netw Open. 2020;3(5):e203951

7 days as good as 10 days for pyelonephritis

Outcome	Short	Long	OR (95% CI)
Duration of therapy (days), median (IQR)	8 (7-8)	11 (11-12)	
Composite outcome of treatment failure, N (%)	33/296 (11)	46/491 (9)	1.2 (0.8-2)
Subsequent resistance among patients with recurrent UTI and cx data, N (%)	6/15 (40)	14/22 (64)	0.4 (0.1-1.4)

Treatment failure (not mutually exclusive)

- Readmitted for UTI symptoms
- Unanticipated ED/outpatient visit for UTI symptoms
- Prescribed additional antibiotics for lingering symptoms
- Mortality

MT Fox, et al. JAMA Netw Open. 2020;3(5):e203951

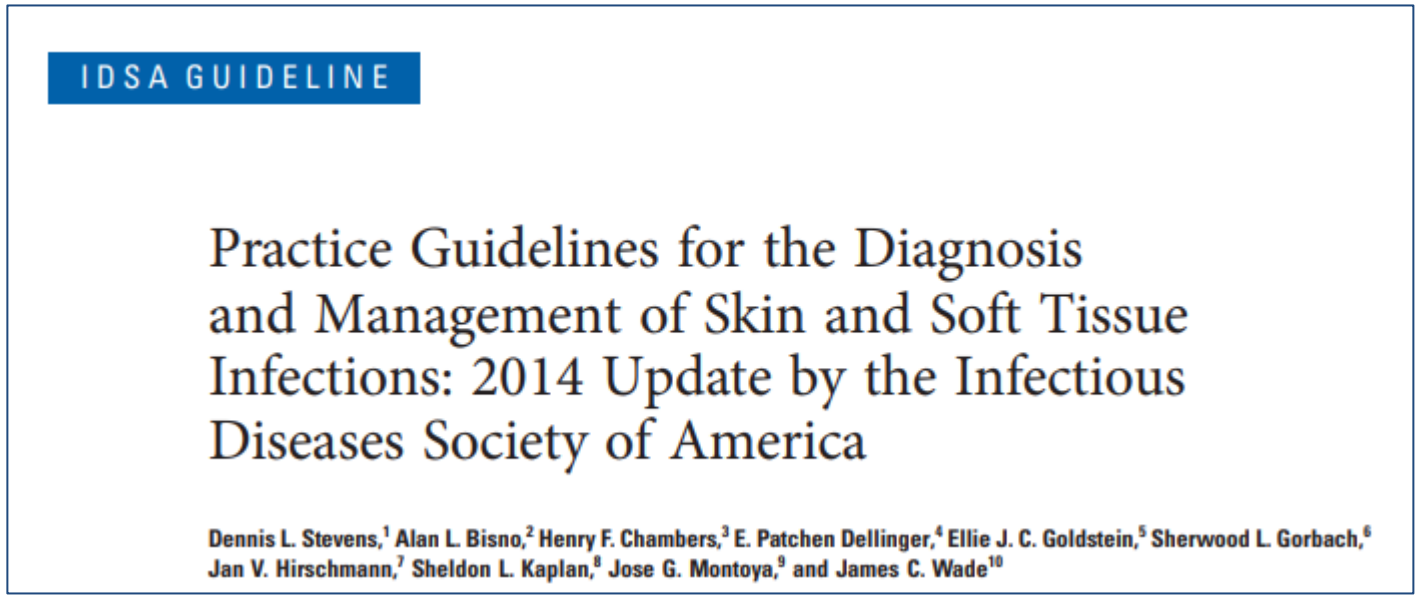
7 days as good as 10 days for pyelonephritis

Also no difference in outcomes comparing short vs long

- By age categories
  - 6 mos – 3 years
  - 4 years – 13 years
  - 14 years – 18 years
- Among patients with urologic abnormalities
- Or by antibiotic class used for culture-directed therapy

MT Fox, et al. JAMA Netw Open. 2020;3(5):e203951

What is the shortest effective duration for skin/soft tissue infection (SSTI)?


IDSA GUIDELINE

Practice Guidelines for the Diagnosis and Management of Skin and Soft Tissue Infections: 2014 Update by the Infectious Diseases Society of America

Dennis L. Stevens,[1] Alan L. Bisno,[2] Henry F. Chambers,[3] E. Patchen Dellinger,[4] Ellie J. C. Goldstein,[5] Sherwood L. Gorbach,[6] Jan V. Hirschmann,[7] Sheldon L. Kaplan,[8] Jose G. Montoya,[9] and James C. Wade[10]

"The recommended duration of antimicrobial therapy is 5 days, but treatment should be extended if the infection has not improved within this time period (strong, high)."

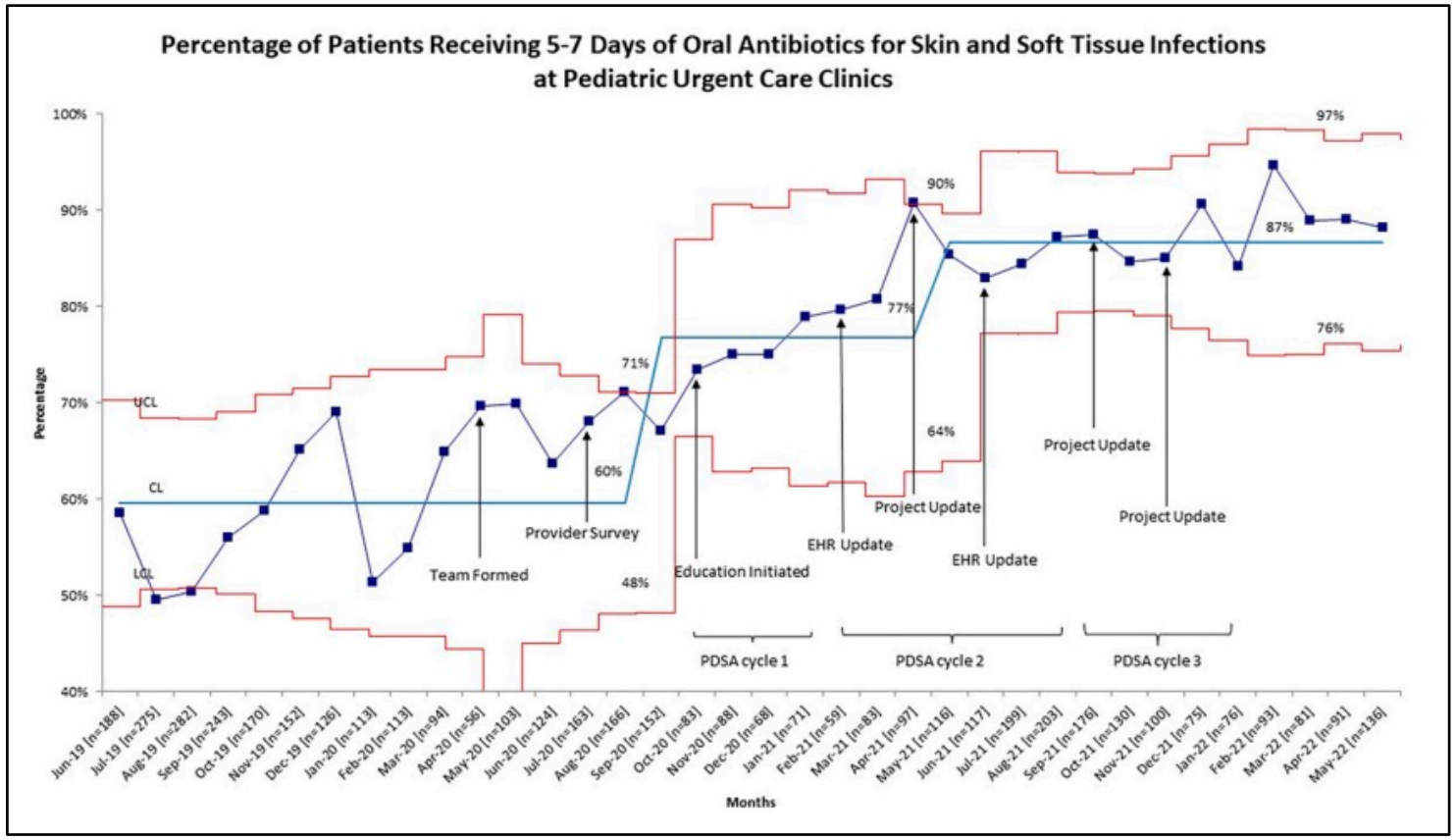
Stevens DL, et al. Clinical Infectious Diseases 2014;59(2):e10-52.

What about children?

- Aim: to increase proportion of children receiving 5-7 days of oral antibiotics for SSTI in urgent care clinics (UCC)
- Methods:
  - Education (15 minutes at monthly meetings)
    - SSTI treatment duration recommendations (IDSA guideline)
    - Address any barriers/concerns
  - Technology updates (pre-populated orders for shorter duration)
    - Cephalexin, clindamycin, SMX/TMP orders in the SSTI folder
  - Provided outcome and balancing measure updates monthly

Hamner M, et al. Pediatrics 2022;150(6):e2022057974.

Shorter durations effective, no worse outcomes



Proportion discharged with Rx for 5-7 days:

- Before: 60%
- After: > 85% (target)

No change in proportion returning to clinic for treatment failure

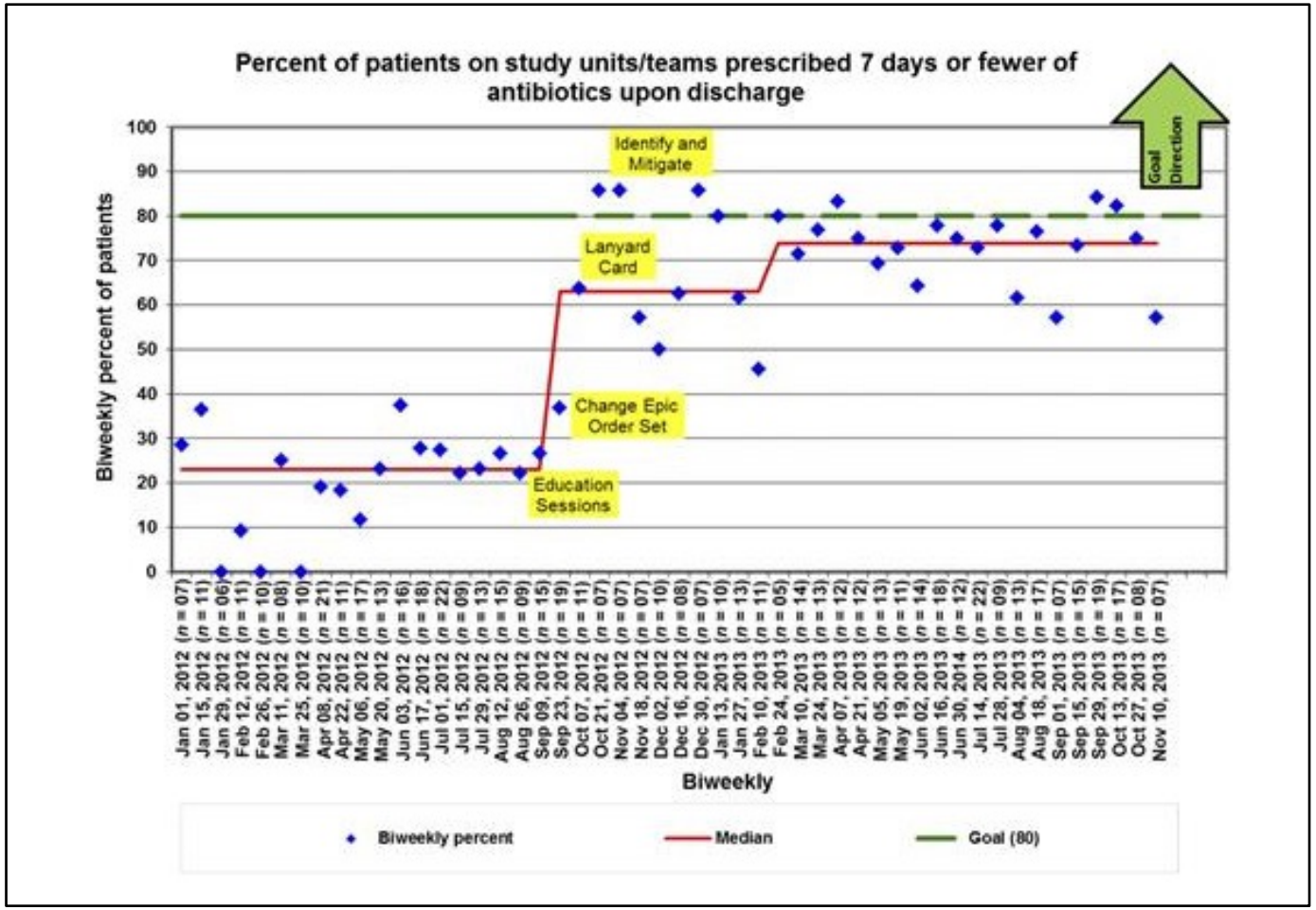
Hamner M, et al. Pediatrics 2022;150(6):e2022057974.

What about inpatient children with SSTI?

- Aim: to increase proportion of hospitalized children (> 3 mos old) discharged with an antibiotic prescription to complete ≤ 7 days of treatment
- Methods:
  - Physician education (15 minute during regular team meeting)
    - Background information
    - Clarified recommendations for duration of therapy
    - Provided lanyard card with treatment regimens and optimal duration
  - Modification of order set defaults

Schuler CL, et al. Pediatrics 2016;137(2):e20151223.

Shorter durations effective, no worse outcomes



Proportion discharged with ≤ 7 days:

- Before: 23%
- After: 74% (target 80%)

No change in treatment failure or recurrence rates

Schuler CL, et al. Pediatrics 2016;137(2):e20151223.

Can we “safely do less” for some febrile neonates presenting with fever?

- AAP febrile neonate guideline updated due to:
- Changing bacteriology
  - –*E.coli* now most common
  - –*L. monocytogenes* rare
- Cost of unnecessary care
- Advances in testing

Pantell RH, et al. Pediatrics 2021;148(2):e2021052228

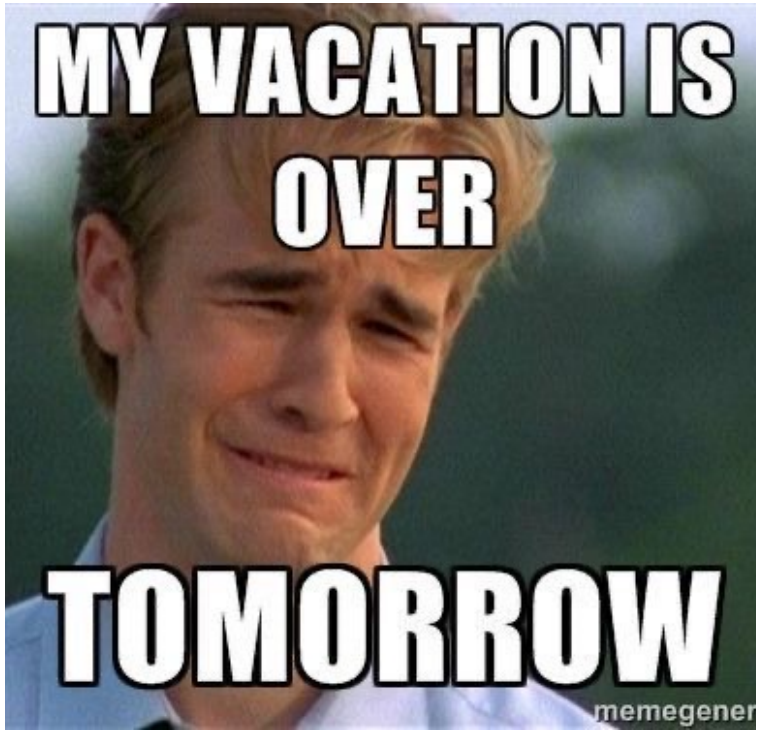
Yes! If we stratify risk by age/clinical status

- Well appearing 8-60 day old infants
- No evident source of infection
- Cultures negative, no source identified at 24-36 hours

- Discontinue antimicrobials
- Options for *no* antibiotics in babies >22 days old
  - normal inflammatory markers and urinalysis

Pantell RH, et al. Pediatrics 2021;148(2):e2021052228

Shorter is not always better



Shorter is not always better

- Patients at increased risk of complications
  - Immunocompromised
- Complicated infections
  - Endocarditis
  - Endovascular infection
  - Pneumonia w/ effusion/empyema
  - Necrotizing pneumonia
  - Abscesses

Take home messages

- When appropriate, shorter courses may be as effective as longer courses
- Shorter courses may decrease:
  - Adverse events
  - Emergence of resistance
  - Hospital length of stay
  - Overall costs