Disclosures

I have the following financial relationships with the manufacturer(s) and/or provider(s) of commercial services discussed in this activity:

Contracted research with:
◦ Pfizer (pediatric nirmatrelvir-ritonavir, maternal RSV vaccine)
◦ Merck (monoclonal antibody for RSV prevention)

I <u>do not</u> intend to discuss an unapproved/investigative use of a commercial product/device in my presentation.

Learning Objectives

1. Review the importance of duration on outcomes in antibiotic prescribing

2. Identify scenarios in which evidence suggests antibiotic prescribing can be shortened from current typical practice

3. (Briefly) Discuss strategies for safely implementing shorter antibiotic courses

How to Overuse Antibiotics

Unnecessary antibiotics

Prescribing when not indicated

Viral URI, bronchitis, etc.
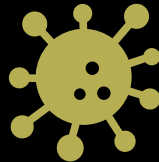
Excessive Spectrum

Treatment not targeted

Excessive Duration

Longer courses than necessary

Why Worry About Durations?

1. Longer duration → increased risk of adverse outcomes:
   - Antibiotic resistance
   - C-diff infection
   - Adverse effects

2. Should be an easier target
   - Easy to measure
   - Easy to move

3. Crosses multiple care settings, populations, and diagnoses

Cumulative Antibiotic Exposures Over Time and the Risk of *Clostridium difficile* Infection

Vanessa Stevens,[1,3,4] **Ghinwa Dumyati,**[2] **Lynn S. Fine,**[2] **Susan G. Fisher,**[3] **and Edwin van Wijngaarden**[3]

[1]Center for Health Outcomes, Pharmacoinformatics, and Epidemiology, Department of Pharmacy Practice, School of Pharmacy and Pharmaceutical Sciences, State University of New York at Buffalo, Buffalo, New York; [2]Department of Medicine, [3]Department of Community and Preventive Medicine, and [4]Department of Pharmacy, University of Rochester, Rochester, New York

Numerous studies have evaluated *which* antibiotics cause the most C-diff

Population: one year of all patients at an academic hospital in Rochester, NY (>10,000 patients, 241 cases of C-diff

Antibiotic exposure in days and risk of C-diff (adjusted hazard ratio, compared to <4 days):

- 4-7 days: 1.4
- 8-18 days: 3.0
- >18 days: 7.8

Conclusion: Longer durations of antibiotics are more likely to cause C-diff

Clinical Infectious Diseases, 2011

Excess Antibiotic Treatment Duration and Adverse Events in Patients Hospitalized With Pneumonia

A Multihospital Cohort Study

Valerie M. Vaughn, MD, MSc; Scott A. Flanders, MD; Ashley Snyder, MS; Anna Conlon, PhD; Mary A.M. Rogers, PhD, MS; Anurag N. Malani, MD; Elizabeth McLaughlin, MS, RN; Sarah Bloemers, MPH; Arjun Srinivasan, MD; Jerod Nagel, PharmD, BCPS; Scott Kaatz, DO; Danielle Osterholzer, MD; Rama Thyagarajan, MD; Lama Hsaiky, PharmD, BCPS; Vineet Chopra, MD, MSc; and Tejal N. Gandhi, MD

6481 patients hospitalized with CAP or HCAP in 43 Michigan hospitals

67.8% of patients had excess duration
◦ CAP: should be 5 days (unless time to clinical stability was >48 hours)
◦ HCAP (or *Staph aureus* or *Pseudomonas*): should be 7 days

Results:
◦ Each excess day associated with 3% increased risk of antibiotic-associated adverse events
◦ Excess duration was not associated with any difference in mortality, readmission, or ED visit

Why Do We Need to "Fix" Durations?

Durations mostly set by tradition

- Low tolerance for failure (reasonable!)

Individualization is hard

- Much easier to just set a duration

Trials comparing durations are relatively new

- Guidelines may not have incorporated new durations

Duration practice often very engrained

A 180 on Durations and Resistance

Traditional teaching: "Finish the full course or you'll end up with antibiotic resistance!"

Organisms *rarely* develop resistance *during* an antibiotic course. Exceptions:
◦ Tuberculosis and other mycobacterial infections
◦ Unusual patient scenarios (such as cystic fibrosis)
◦ Rifampin
◦ Serious infections with certain Gram-negative species (such as *E. cloacae*)

The <u>real</u> concern:
◦ Exposure of the patient's *entire microbiome* to prolonged, repeated, and/or broad-spectrum antibiotics

Duration of Antibiotic Therapy: Shorter Is Better

The evidentiary basis of traditional durations of antibiotic therapy is that a week is 7 days (2), which is why tried-and-true antibiotic regimens are 7 to 14 days long. The definition of a week was decreed by Roman Emperor Constantine the Great nearly 2000 years ago (2). This seems an unsatisfactory evidentiary basis for modern medical practice.

Common durations:

- Touchdown (7 days)

- Touchdown and a field goal (10 days)

- Two touchdowns (14 days)

"Hey, how long do we usually treat _____?"

Antibiotic Durations: Identifying Opportunities

What we need to see

◦ Clearly defined patient population

◦ A typical antibiotic duration practice

◦ Evidence that the typical practice is longer than it needs to be

  ◦ Trustworthy guidelines
  ◦ Evidence that came out since guidelines

Case: Importance of Individualization

A 19 y/o F who was a trauma victim developed ventilator-associated pneumonia due to MSSA. The ICU team gave nafcillin x 7 days (great!).

She had fever and respiratory worsening a few days after finishing. Ultrasound found a pleural empyema, and a chest tube evacuated a large amount of pus, which grew MSSA. She was treated for…7 days.

Case: Importance of Individualization

She worsened again after completing antibiotics.

We treated for 21 days, ensuring that the chest tube could be removed without reaccumulation of pleural fluid, and the infection resolved.

Standard durations are not appropriate for every case!

Patient Population

Changing durations should be very clear about who is <u>not</u> included

Common groups that need to be excluded:
- Immunocompromised patients
- Young infants
- Patients who didn't respond as expected – suggests complicated infection
- Patients who don't have source control – such as:
  - Abscess that hasn't been drained (pleural empyema, intra-abdominal abscess, renal abscess, etc.)
  - Patients with a central line infection with the line still in place
  - Prosthetic joint infection with the hardware still in place

Duration of Outpatient Antibiotic Therapy for Common Outpatient Infections, 2017

Laura M. King,[1] Adam L. Hersh,[2] Lauri A. Hicks,[1] and Katherine E. Fleming-Dutra[1]

[1]Division of Healthcare Quality Promotion, Centers for Disease Control and Prevention, Atlanta, Georgia, USA, and [2]Division of Pediatric Infectious Diseases, University of Utah, Salt Lake City, Utah, USA

- Commercial antibiotic prescription database
- Compared typical durations to guideline recommendations for:
  - Pharyngitis (IDSA)
  - Sinusitis (IDSA)
  - Acute otitis media (AAP)
  - Community-acquired pneumonia (IDSA)
  - Cellulitis and abscess (IDSA)
  - Acute cystitis (IDSA)

King, et al., *Clinical Infectious Diseases*, 2021

Condition and Population	Guideline-recommended Duration of Oral Antibiotic Therapy[a]	Median Course Duration in Days (IQR)
Pharyngitis		
Adult	10 days [2]	10 (10–10)
Pediatric	10 days [2]	10 (10–10)
Sinusitis		
Adult	5–7 days[c] [3]	10 (10–10)
Pediatric	10–14 days [3]	10 (10–10)
Acute otitis media		
Pediatric, all	10 days[d] [4]	10 (10–10)
Pediatric, <2 years	10 days[d] [4]	10 (10–10)
Pediatric, ≥2 years	10 days, shorter courses (5–7 days) may be appropriate for select older children[d] [4]	10 (10–10)
Community-acquired pneumonia		
Adult	≥5 days; 5 days appropriate for most patients[e] [5]	10 (7–10)
Pediatric	No recommendation[f] [6]	10 (10–10)
Cellulitis		
Adult	5 days[g] [7]	10 (7–10)
Pediatric	5 days[g] [7]	10 (10–10)
Abscess		
Adult	5–10 days [7]	10 (7–10)
Pediatric	5–10 days [7]	10 (10–10)
Acute cystitis		
Females 12–64 years	Varies by agent; 1–7 days [8]	7 (5–7)

King, et al., *Clinical Infectious Diseases*, 2021

Opportunities

Website by Brad Spellberg, MD: "Shorter is Better." https://www.bradspellberg.com/shorter-is-better

UTI: Cystitis

Acute cystitis		
Females 12–64 years	Varies by agent; 1–7 days [8]	7 (5–7)

Cystitis means <u>all</u> of the following:
◦ Nonpregnant adult female
◦ No signs of pyelonephritis (fever, flank pain, CVA tenderness)
◦ Signs of UTI (dysuria, frequency, urinary urgency, suprapubic pain)
◦ Positive urinalysis (>10 WBC/hpf, positive leuk esterase, and/or positive nitrite)
◦ Positive urine culture

Duration depends on antibiotic choice:
◦ Nitrofurantoin x 5 days
◦ TMP-SMX x 3 days
◦ Fosfomycin x1 dose
◦ Gentamicin x1 dose
◦ Ciprofloxacin or levofloxacin x3 days
◦ Cephalexin x 5-7 days

Pyelonephritis/Febrile UTI (Adults)

Positive urinalysis and urine culture with:
- Fever (or chills, rigors, altered mental status) AND/OR
- Flank pain or costovertebral angle tenderness

Suggests bacterial infection has ascended into the renal pelvis/kidney
- Longer duration

Ciprofloxacin for 7 days versus 14 days in women with acute pyelonephritis: a randomised, open-label and double-blind, placebo-controlled, non-inferiority trial

Torsten Sandberg, Gunilla Skoog, Anna Bornefalk Hermansson, Gunnar Kahlmeter, Nils Kuylenstierna, Anders Lannergård, Gisela Otto, Bo Settergren, Gunilla Stridh Ekman

248 nonpregnant adult women with acute pyelonephritis

Intervention: ciprofloxacin 500 mg BID x 7 vs 14 days

Results:
- Clinical cure: 97% in 7-day group vs 96% in in 14-day group
- Minimal differences in adverse events
  - 5 cases of candidiasis in 14-day group vs 0 in 7-day group

Conclusion:
- 7 days is fine for pyelonephritis in adults (there was a similar trial in men with similar results)
  - Assuming appropriate initial clinical response
- Some experts recommend 5-7 days for FQs, 7-10 days for TMP-SMX and beta-lactams

Sandberg, *Lancet*, 2012

Pediatric Febrile UTI

In infants and young children, most UTIs diagnosed by fever
◦ "Complicated," i.e., presumed pyelonephritis
◦ "Cystitis" rare in young children

2010 AAP Guidelines (ages 2-24 months): "7-14 days"
◦ "…attempted to identify a single, preferred, evidence-based duration…but data comparing 7, 10, and 14 days directly were not found."
◦ 10-14 days used very commonly, vs 5-10 in adults

Short-Course Therapy for Urinary Tract Infections in Children
The SCOUT Randomized Clinical Trial

Theoklis Zaoutis, MD; Nader Shaikh, MD; Brian T. Fisher, DO; Susan E. Coffin, MD; Sonika Bhatnagar, MD;
Kevin J. Downes, MD; Jeffrey S. Gerber, MD; Timothy R. Shope, MD; Judith M. Martin, MD; Gysella B. Muniz, MD;
Michael Green, MD; Jennifer P. Nagg, RN; Sage R. Myers, MD; Rakesh D. Mistry, MD; Shawn O'Connor, BS;
Walter Faig, PhD; Stephen Black, MS; Elizabeth Rowley, PhD; Kellie Liston, BA; Alejandro Hoberman, MD

Placebo-controlled RCT comparing 5 vs 10 days

- 2 months to 10 years of age
- Antibiotic chosen by real-world prescriber (mostly cefdinir, cephalexin, TMP-SMX)
- Required UTI symptoms (sometimes vague), positive UA, and positive urine culture
- Enrolled on Day 2-5 of initial antibiotics, if they had improved
  - Randomized to complete 10 days or stop at 5 days (and take placebo)

Results:

- 693 children randomized 1:1
- Treatment failures (UTI by Day 14):
  - 5-day group: 14/345 (4.2%)
  - 10-day group: 2/348 (0.6%)
- 5 days was *not* noninferior

Conclusion: 10 days better, but number needed to treat = 28. Short course may be acceptable in lower-risk patients.

Zaoutis et al., *JAMA Pediatrics*, 2023

Short Oral Antibiotic Therapy for Pediatric Febrile Urinary Tract Infections: A Randomized Trial

Giovanni Montini, MD,[a,b] Antimo Tessitore, MD,[c] Karen Console, MD,[c] Luca Ronfani, MD,[d] Egidio Barbi, MD,[c,e] Marco Pennesi, MD,[e] on behalf of the STOP Trial Group

Similar design

Ages 3 months to 5 years

5 vs 10 days of antibiotics

All took amox-clav
◦ Per Italian national antibiogram

Patients had to respond to treatment prior to randomization

Results:
- 142 patients randomized 1:1
- UTI recurrence (within 30 days):
  ◦ Short: 2/72 (2.8%)
  ◦ Standard: 10/72 (14.3%)

Conclusion: Short-course *superior*

Why the difference? (endpoint timing?)

TABLE 3 Primary End Point

	Short (n = 72)	Standard (n = 70)	Difference %	95% CI	99.5% CI
Intention-to-treat					
Recurrence of UTI, n (%)	2 (2.8%)	10 (14.3%)	−11.51%	−20.54 to −2.47	−24.45 to 1.43
Recurrence of febrile UTI, n (%)	1 (1.4%)	4 (5.7%)	−4.33%	−10.40 to 1.75	−13.02 to 4.37
Per protocol					
Recurrence of UTI, n (%)	2 (2.8%)	10 (14.3%)	−11.51%	−20.54 to −2.47	−24.45 to 1.43
Recurrence of febrile UTI, n (%)	1 (1.4%)	4 (5.7%)	−4.33%	−10.40 to 1.75	−13.02 to 4.37

Montini et al., *Pediatrics*, 2023

Pediatric Febrile UTI

In infants and young children, most UTIs diagnosed by fever
- ◦ "Complicated," i.e., presumed pyelonephritis

2010 AAP Guidelines (ages 2-24 months): "7-14 days"
- ◦ 10-14 days used very commonly, vs 5-10 in adults

Clinical trials: 5 days better? 10 days better?

Our practice:
- ◦ 5-7 days for febrile UTI if relatively normal urinary tract; extension if abnormal imaging, failure to respond within ~3 days
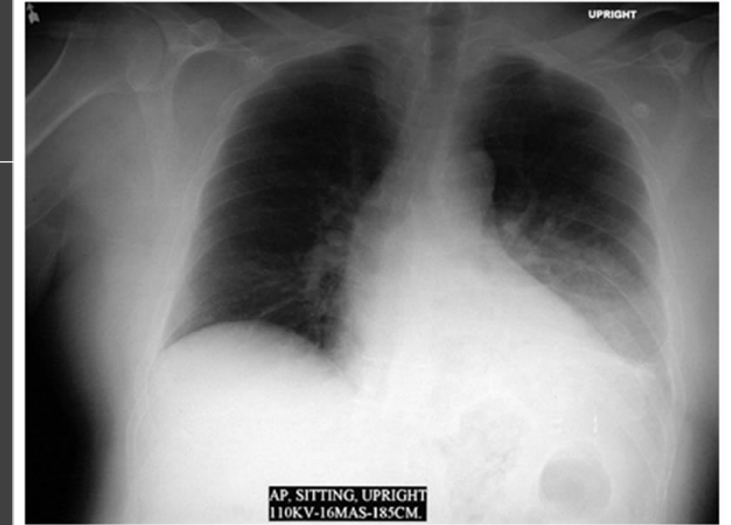
Pneumonia (CAP)

Traditional durations: 10 days

Equivalent outcomes found for:
◦ Amoxicillin 3 vs 8 days
◦ Cefuroxime 7 vs 10 days
◦ Levofloxacin 5 vs 10 days
◦ Ceftriaxone 5 vs 10 days

Recommendation (IDSA/ATS Guidelines):
◦ 5 days, as long as the patient is improving
◦ If patient not stable (normal vital signs and mental status) by 5 days → concern for complications

Pneumococcal pneumonia: Chest radiograph

UPRIGHT

AP, SITTING, UPRIGHT
110KV-16MAS-185CM.

64-year-old male with insulin-dependent diabetes mellitus. He was admitted with bacteremic pneumococcal pneumonia. Note the left lower lobe opacity.

Courtesy of Thomas J Marrie, MD.

UpToDate®

Pediatric CAP

IDSA Guidelines (2011): 10 days

SCOUT-CAP Trial (Williams, et al., *JAMA Pediatrics*, 2022):
◦ Randomized 380 children (6-71 months) to 5 vs 10 days (nonsevere)
◦ Amox, amox-clav, or cefdinir

Results:
◦ Absolutely no difference in outcomes
◦ Numerically more adverse events in 10-day course, not significant

Conclusion:
◦ 5 days is sufficient for ambulatory pediatric CAP
◦ Still a question for pediatric CAP with hospital admission

Cellulitis

Erysipelas of the lower leg. The rash is intensely red, sharply demarcated, swollen, and indurated.

Reproduced with permission from: Berg D, Worzala K. Atlas of Adult Physical Diagnosis. Philadelphia: Lippincott Williams & Wilkins, 2006. Copyright © 2006 Lippincott Williams & Wilkins.

UpToDate®

Commonly used durations: 7-10 days

Multiple studies have compared 5 or 6 vs 10 days
◦ No difference

Recommendation: cephalexin x 5 days

Sinusitis

tomy

Frontal sinus

Ethmoid sinuses (anterior)

Maxillary sinus

Nasal septum

ocation of the frontal, ethmoid, maxillary, and

UpToDate
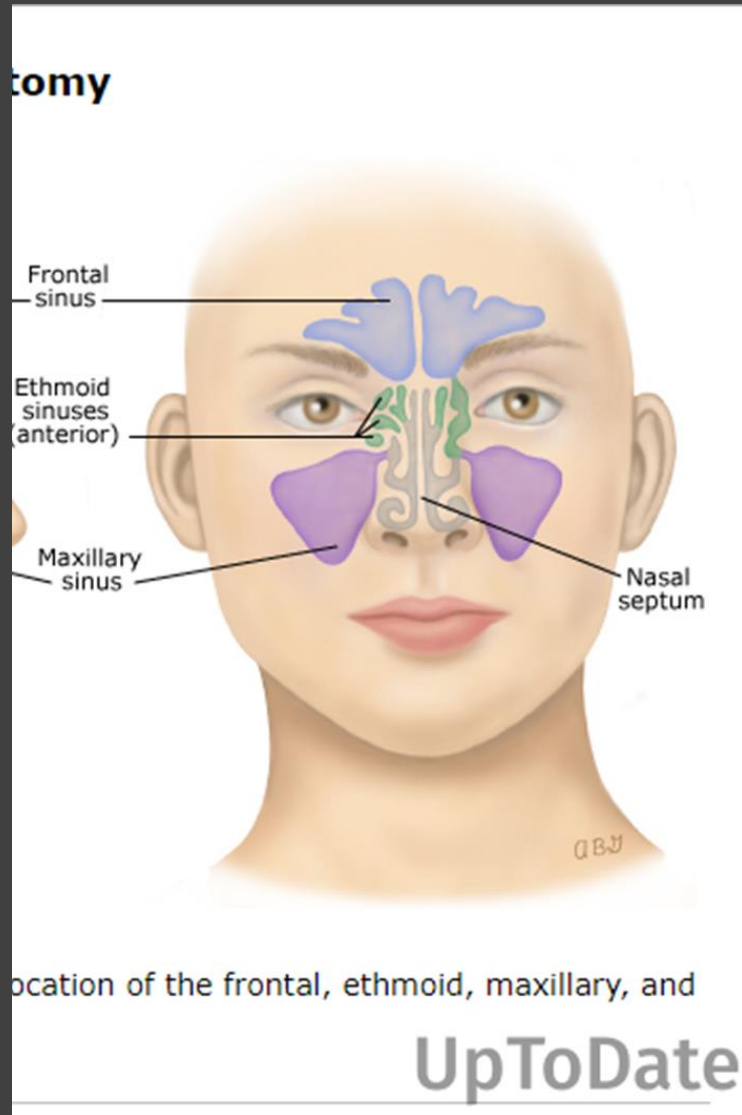
IDSA Guidelines:
- Adult: 5-7 days
- Pediatric: 10-14 days

Adults: meta-analysis of 12 trials with >4000 patients (Falagas et al., *Brit Jour Clin Pharm*, 2009)
- 3-7 days just as good as 6-10 days

Pediatrics
- AAP Red Book 2021: "Five days of therapy is often sufficient."

Trends in the Antibiotic Treatment of Acute Sinusitis: 2003–2020

Timothy J. Savage, MD, MPH, MSc,[a] Matthew P. Kronman, MD, MSCE,[b] Sushama Kattinakere Sreedhara, MBBS, MSPH,[a] Massimiliano Russo, PhD,[a] Su Been Lee, BA,[a] Theresa Oduol, BS,[a] Krista F. Huybrechts MS, PhD[a]

10-day courses by far the most common (80%)

14-day courses slowly declining, 5-7-day courses slowly rising
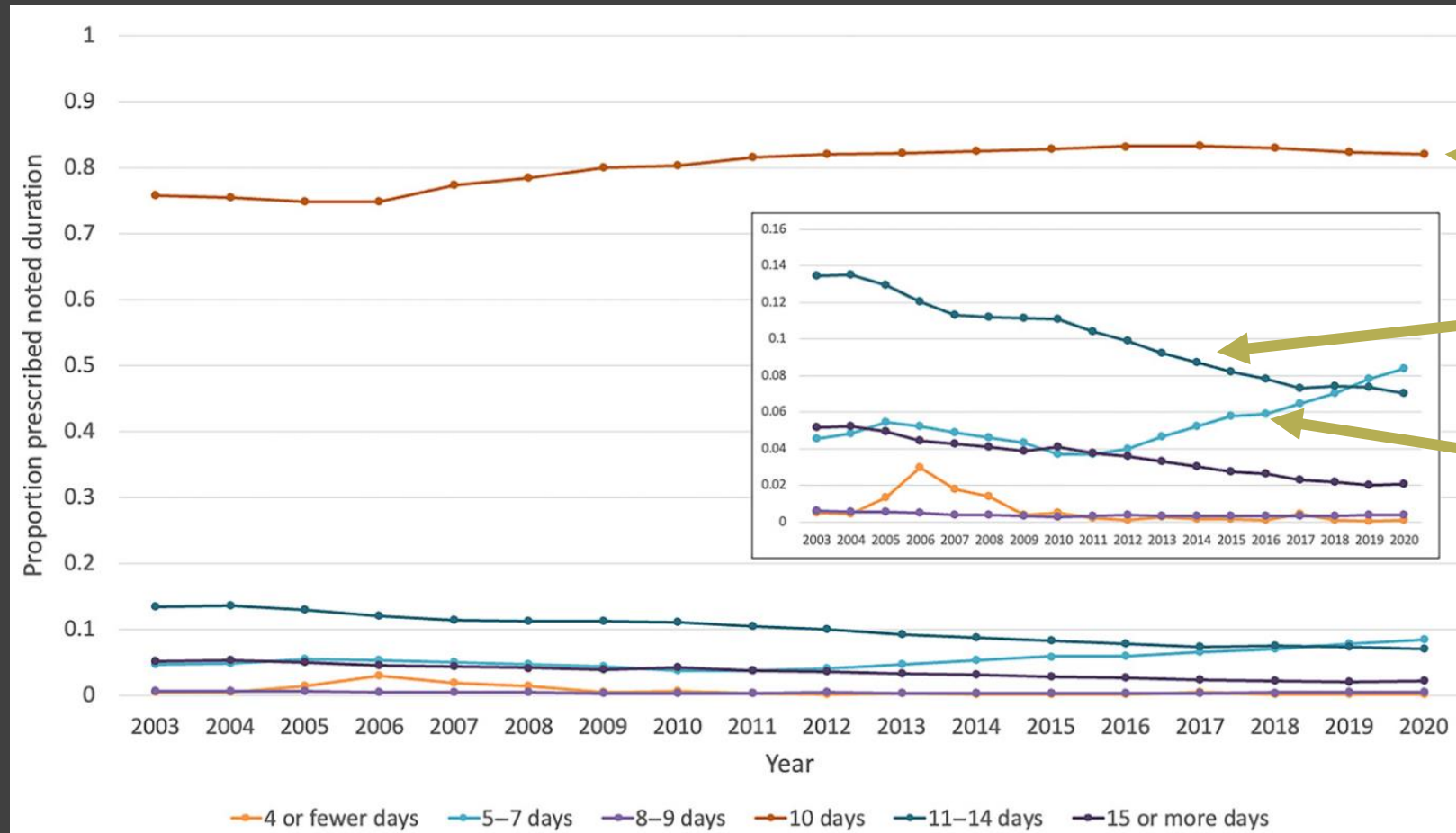
Streptococcal Pharyngitis

Streptococcal pharyngitis treated x 10 days since ~discovery of penicillin. IDSA guidelines say 10 days.

Duration was not really studied…

Goals of treating strep throat:
◦ Preventing acute rheumatic fever/rheumatic heart disease
◦ Alleviating acute symptoms

Treatment *at all* can be controversial
◦ Vast majority resolve spontaneously
◦ Most high-income countries have very low rates of rheumatic fever

Gunilla Skoog Ståhlgren,[1] Mia Tyrstrup,[2,3] Charlotta Edlund,[1] Christian G Giske,[4,5] Sigvard Mölstad,[3] Christer Norman,[6] Karin Rystedt,[7,8] Pär-Daniel Sundvall,[8,9] Katarina Hedin[3,10]

Patients 6 years and older with streptococcal pharyngitis randomized to 5 vs 10 days
◦ Penicillin <u>QID</u> x 5 days vs TID x 10 days

Results:
◦ Patients in the 5-day group actually had faster improvement, but no difference in cure at 9 days.
◦ 1-month follow-up:
  ◦ Negative throat culture: 80.4% of 5-day vs 90.7% of 10-day
  ◦ Relapse within one month: no difference (4.5% vs 3.9%)

Conclusions:
◦ 5 days just as good as 10 days for symptomatic improvement
◦ 10 days better for microbiologic eradication (rarely important)
◦ Limitation: US rarely uses PO penicillin, and we would never use four-times-daily dosing

How Do We Make This Change?

1. Education

2. Quality Improvement
   ◦ EHR modifications
     ◦ Order sets or panels, duration quick buttons
   ◦ Individualized provider feedback
   ◦ Publication and easy access to prescribing guidelines

Increasing Guideline-Concordant Durations of Antibiotic Therapy for Acute Otitis Media

Holly M. Frost, MD, FAAP[1,2,3], Yingbo Lou, MS[4], Amy Keith, MPH[2], Andrew Byars, BS[5], and Timothy C. Jenkins, MD[6,7]

AAP Guideline-recommended duration:
- <2 years: 10 days
- 2-5 years: 7 days
- >5 years: 5-7 days

Yet most providers default to 10 days for all

Setting: Denver Health (28 FQHC clinics, 3 urgent cares, 1 pediatric ED)

Two interventions:
- Epic change to encourage appropriate duration (applied to all prescribers)
- Monthly individualized feedback to some prescribers (all those in primary care pediatrics)
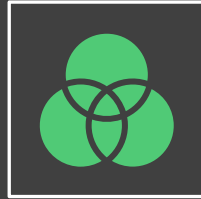 - Told them their percentage of prescriptions that were guideline-compliant over time
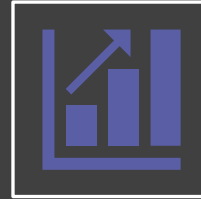
QI Requirements

Evidence-based best-practice duration

Common practice that is not aligned with best practice

Data

Implementation method

Conclusions

Antibiotic durations for most conditions are set by tradition

◦ Durations herd by the number of days in a week or the number of fingers on your hands

Clinical practice may conflict with guidelines

Guidelines may lag behind new evidence

Hard for clinicians to change

Durations very amenable to education and QI

Appropriate Use of Short-Course Antibiotics in Common Infections: Best Practice Advice From the American College of Physicians

Rachael A. Lee, MD, MSPH; Robert M. Centor, MD; Linda L. Humphrey, MD, MPH; Janet A. Jokela, MD, MPH; Rebecca Andrews, MS, MD; and Amir Qaseem, MD, PhD, MHA; for the Scientific Medical Policy Committee of the American College of Physicians*

Emphasis: Identifying patients/scenarios in which short-course is appropriate

Addressed 5 conditions:

1. COPD Exacerbations: "Limit duration to 5 days"

2. CAP: Minimum of 5 days, should have clinical stability by then

3. Uncomplicated cystitis: nitrofurantoin x5 days, TMP-SMX x3 days, or Fosfomycin x1

4. Pyelonephritis: FQ x 5-7 days or TMP-SMX x 14 days (more studies needed for shorter courses of TMP-SMX)

5. Cellulitis (without purulence): 5-6 days

Duration Suggestions

Condition/Population	Recommended Duration	Comments and Strength
Cystitis	1 dose: gentamicin or Fosfomycin 3 days: fluoroquinolone or TMP-SMX 5-7 days: nitrofurantoin or cephalexin	Fairly well-established evidence
Pyelonephritis	7 days 7-10 days for beta-lactams, TMP-SMX	May consider longer course if urologic abnormalities, slow response, etc.
CAP	Adults: 5 days (assuming expected response) Pediatrics: 5 days (outpatient); 5-7 days (inpatient)	Inpatient duration in peds needs more study
Sinusitis	Adults: 5-7 days Pediatrics: 5-10 days (5-7?)	Adults: clear, strong recs Pediatrics: less data about <10 days
Streptococcal pharyngitis	IDSA: 10 days WHO: 5 days if low risk for RHD	Might still be controversial. Definitive study used PO penicillin at TID or QID dosing.
Acute otitis media	<2 years: 10 days 2-5 years: 7 days ≥5 years: 5-7 days	Fairly strong evidence, AAP guideline recommendations
Cellulitis	IDSA, ACP: 5-6 days	Strong evidence

Resources

"Shorter is Better" website by Brad Spellberg, MD:
https://www.bradspellberg.com/shorter-is-better

CDC Antibiotic Stewardship Resource Bundles: Antibiotic Stewardship Resource Bundles | Antibiotic Prescribing and Use | CDC

NC CLASP Websites:
◦ https://spice.unc.edu/ncclasp/nursinghomes/
◦ https://spice.unc.edu/ncclasp/acutecare/
◦ https://spice.unc.edu/ncclasp/outpatient/

UNC Carolina Antimicrobial Stewardship Program Durations Best Practices

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Questions?