First Do No Harm: Unintended Consequences of Antibiotics and Prescribing Strategies to Prevent Them

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Disclosures

- No relevant conflicts of interest
- No discussion of off-label antibiotic uses

Medscape Physician Survey, 2019

https://www.medscape.com/slideshow/2019-lifestyle-happiness-6011057?src=soc_tw_share#1

Performance/Learning Objectives

- Describe the relationship between antibiotic use and antibiotic resistance, adverse events, and *C. difficile* infection
- Identify current evidence regarding the optimal diagnosis and treatment of common infections
- Implement strategies to improve the management of common infections in clinical practice

Antibiotics save lives, but…

Mortality due to cellulitis in pre- and post-antibiotic eras

Spellberg B. CID 2009; 49:383-91

Antibiotics have unintended consequences

- Selection of resistant organisms
- *C. difficile* infection
- Adverse drug events
- Drug interactions
- Disruption of microbiome
- Patient burden
- Health care costs

Fluoroquinolone (FQ) resistance among outpatient *E. coli*, 2003-2012

Pedela R. *Infect Control Hops Epidemiol* 2017; 38:461

C.difficile is closely associated with antibiotic exposure

Dantes R. *Open Forum Infect Dis* 2015 Sep; 2(3)
Stevens V. *Clin Infect Dis* 2011;53: 42-8

Most commonly implicated drugs in ED visits for adverse drug events, 2013-2014

Shehab N.
JAMA 2016;
316:2115

Antibiotic Stewardship

http://www.shea-online.org/index.php/practice-resources/priority-topics/antimicrobial-stewardship

Why focus on outpatient setting?

1. Sanchez *EID* 2014; 20:2041
2. Fleming-Dutra K. *JAMA* 2016; 315:1864

JAMA 2016; 315:1864

NATIONAL ACTION PLAN FOR COMBATING ANTIBIOTIC-RESISTANT BACTERIA

Goal: Reduction of unnecessary antibiotic use by 50% in outpatient settings by 2020

3 principles to optimize outpatient antibiotic prescribing

1) Ensure an appropriate indication for antibiotics exists (Right indication)
2) When indicated, choose the antibiotic regimen with the narrowest spectrum of activity possible (Right antibiotic)
3) Prescribe the shortest effective duration of therapy (Right duration)

Case 1

23yo healthy woman presents with 7 days of cough, sinus pain, and congestion. The sinus pain improved at first but began worsening yesterday and she has felt more ill.

Exam: Temp 37.8, HR 85, BP 108/68. Non-toxic appearing but uncomfortable, moderate right maxillary sinus tenderness, clear nasal discharge.

States antibiotics have worked for sinus infections in past and requests a prescription.

What is the most appropriate management?

A. Tell her it's a viral infection and will pass
B. Prescribe a 5-day antibiotic course
C. Prescribe a 10-day antibiotic course
D. Recommend nasal saline rinses and symptomatic relief

Ensure an appropriate indication for therapy

Acute sinusitis

Chow A. *Clin Infect Dis* 2012; 54:e72-e112

Prescribing patterns for acute sinusitis in clinical practice

Chauhan L. *Infect Control Hosp Epidemiol* 2018; 39:991

RESEARCH LETTER

LESS IS MORE

Antibiotic Therapy Duration in US Adults With Sinusitis

King LM. *JAMA Int Med* 2018; 178:992-994

Acute bronchitis

1) Jenkins T. Am J Med 2013; 126:327

Patient expectations and antibiotics

1) Ashworth M. *Br J Gen Pract* 2016; 66:e40
2) Martinez KA. JAMA Int Med 2018 (Oct 1)
3) Sirota M. *Health Psychology* 2017; 36:402
4) Linder JA. JAMA Int Med 2014; 174:2029

Communication strategies to improve patient satisfaction when antibiotics not indicated

https://www.medscape.com/viewarticle/730224?src=par_cdc_stm_mscpedt&faf=1

Case 2

56yo obese woman presents with 2 days of progressive bilateral lower extremity redness, swelling, and pain. She has been fatigued but denies fever, chills, feeling ill, SOB, or CP. She had an unprovoked LLE DVT 3 months prior for which she is on rivaroxaban.

Exam: Temp 37.2, HR 91, BP 145/92. Symmetric bilateral erythema and edema from the ankles to mid-calves with mild tenderness to palpation. Scaling skin with patchy hyperpigmentation over shins.

What is the most appropriate next step?

A. Order a LLE ultrasound
B. Recommend leg elevation and compression stockings
C. Prescribe clindamycin
D. Prescribe cephalexin

JAMA Dermatol 2014:
150:1056

Outcomes

	Dermatology consultation N = 20	PCP management N = 9	P
Ultimately diagnosed with cellulitis	2/20 (10%)	9/9 (100%)	<.001
Diagnosed as cellulitis by Dermatologist	2/20 (10%)	3/9 (33%)	0.29
Antibiotic treatment for cellulitis	2/20 (10%)	9/9 (100%)	<.001

Beware of pseudocellulitis

Know common causes:

- **Stasis dermatitis**
- Contact dermatitis
- Insect bite reaction
- Gout
- Hematoma
- Deep venous thrombosis

Raff AB. *JAMA* 2016; 316:325

Case 3

73yo woman with diabetes presents for a routine follow-up visit. She notes her urine has been cloudy over last several days. No fevers, chills, dysuria or other urinary symptoms, or vaginal discharge.

Exam: Normal vitals. Alert, appropriate, well-appearing. No abdominal tenderness.

Urine dipstick with 2+ LE and nitrites, otherwise negative. Urine culture grows >100,000 cfu/mL of *E. coli*, susceptibilities pending. You call the patient who is feeling well without change in urine cloudiness.

What is the most appropriate next step regarding the positive urine culture?

A. Prescribe nitrofurantoin
B. Prescribe fosfomycin
C. Repeat urinalysis and culture in 2 weeks
D. Counsel to return if symptoms of infection develop

Asymptomatic bacteriuria

1) Nicolle LE. *Clin Infect Dis* 2005; 40:643
2) Zalmanovici Trestioreanu A. *Cochrane Database Syst Rev* 2015
3) Ghandi T. *ICHE* 2009; 30:193-95

Case 4

45yo woman presents with RLE erythema, swelling, and pain that began suddenly 12 hours ago. Unable to bear weight due to the pain. Long history of poorly controlled diabetes mellitus (A1C 10.2).

On exam has findings consistent with RLE cellulitis. No wound, purulence, or evidence of abscess. She has tinea pedis and onychomycosis.

What is the most appropriate therapy?

A. Trimethoprim-sulfamethoxazole (TMP-SMX)
B. Cephalexin
C. Clindamycin
D. Cephalexin plus TMP-SMX

Narrowest spectrum of antibiotic activity

JAMA 2017;
317:2088

Outcomes and adverse events

- Clinical cure in 83.5% (TMP-SMX) vs. 85.5% (placebo)
- No significant difference in any secondary outcome:
  - Need for hospitalization
  - Recurrent or new site of skin infection
  - Missed days of normal activity or school/work
  - Days of pain medication
- Treatment-related adverse event:
  - 42% (TMP-SMX) vs. 36% (placebo)

Case 5

67yo woman with well-controlled diabetes mellitus presented with dysuria, frequency, and hematuria. No fevers, chills, nausea, vomiting, flank pain. A urine dipstick supported a diagnosis of cystitis and she was prescribed a short antibiotic course.

Her symptoms resolved quickly but 3 days into treatment she had a syncopal event and was found to have a blood glucose of 37. She denied recent changes to her oral hypoglycemic agents or diet.

Which of the following antibiotics had she most likely been prescribed?

A. Nitrofurantoin
B. Fosfomycin
C. Levofloxacin
D. Pivmecillinam

Fluoroquinolones FDA warnings and labeling changes

https://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm346750.htm

Use of fluoroquinolones in primary care

https://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm346750.htm

Penicillin (PCN) allergies

1) Trubiano JA. *JAMA* 2017; 318:82
2) https://www.cdc.gov/antibiotic-use/community/for-hcp/Penicillin-Allergy.html

Shenoy ES. JAMA 2019; 321:188

Shortest effective duration of therapy

Case 6

31yo otherwise healthy woman presents with 3 days of dysuria, fever up to 102.8°F, flank pain, and nausea. You diagnose acute pyelonephritis and prescribe 5 days of levofloxacin.

The urine culture grows *E. coli* resistant to levofloxacin and TMP-SMX. You call the patient and she is clinically stable but still symptomatic. You change her antibiotic to cefdinir.

What is the most appropriate duration of therapy?

A. 5 days

B. 7 days

C. 10 days

D. 21 days

Beta-lactams for acute pyelonephritis IDSA guideline

Gupta K. *Clin Infect Dis* 2011; 52:e1-3

Recommended duration of therapy for acute pyelonephritis, by antibiotic

Gupta K. *Clin Infect Dis* 2011; 52:e1-3

Impact of shortening treatment duration on overall antibiotic exposure

Incremental shifts in treatment durations achieve substantial reductions in overall antibiotic exposure

Bacterial infections for which 5 – 7 days of antibiotic therapy is advocated

- Acute bacterial sinusitis
- Cellulitis or drained skin abscess
- Complicated cystitis or catheter-associated UTI
- Pyelonephritis treated with a fluoroquinolone
- Acute otitis media in adults and children >2 yrs
- Community-acquired pneumonia
- Nosocomial pneumonia
- Intra-abdominal infection

The exceptions: common infections where <10 days NOT recommended

- Acute pyelonephritis treated with oral beta-lactams or TMP-SMX
- Acute otitis media in young children
- Group A streptococcal pharyngitis
- *C. difficile* infection
- *H. pylori* infection
- *S. aureus* bacteremia

Key points

- Incremental shifts in duration of therapy result in relatively large changes in overall antibiotic exposure
- We should reset our default duration to 5 days
- If you are writing a prescription for longer than 7 days, ask yourself why?
- Know the exceptions where longer durations are appropriate

Our role

Before we prescribe, take an **antibiotic time-out**:

- Ensure an appropriate **indication** for antibiotics exists
- Choose the narrowest **spectrum** antibiotic regimen possible
- Prescribe the shortest effective **duration** of therapy

Questions/comments?

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