Brigham and Women's Hospital
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Responsible Use of Antibiotics

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Disclosures

- None

Antibiotic Update: 2024

Overview of the "problem"

Case-based review – commonly encountered problems in clinical practice

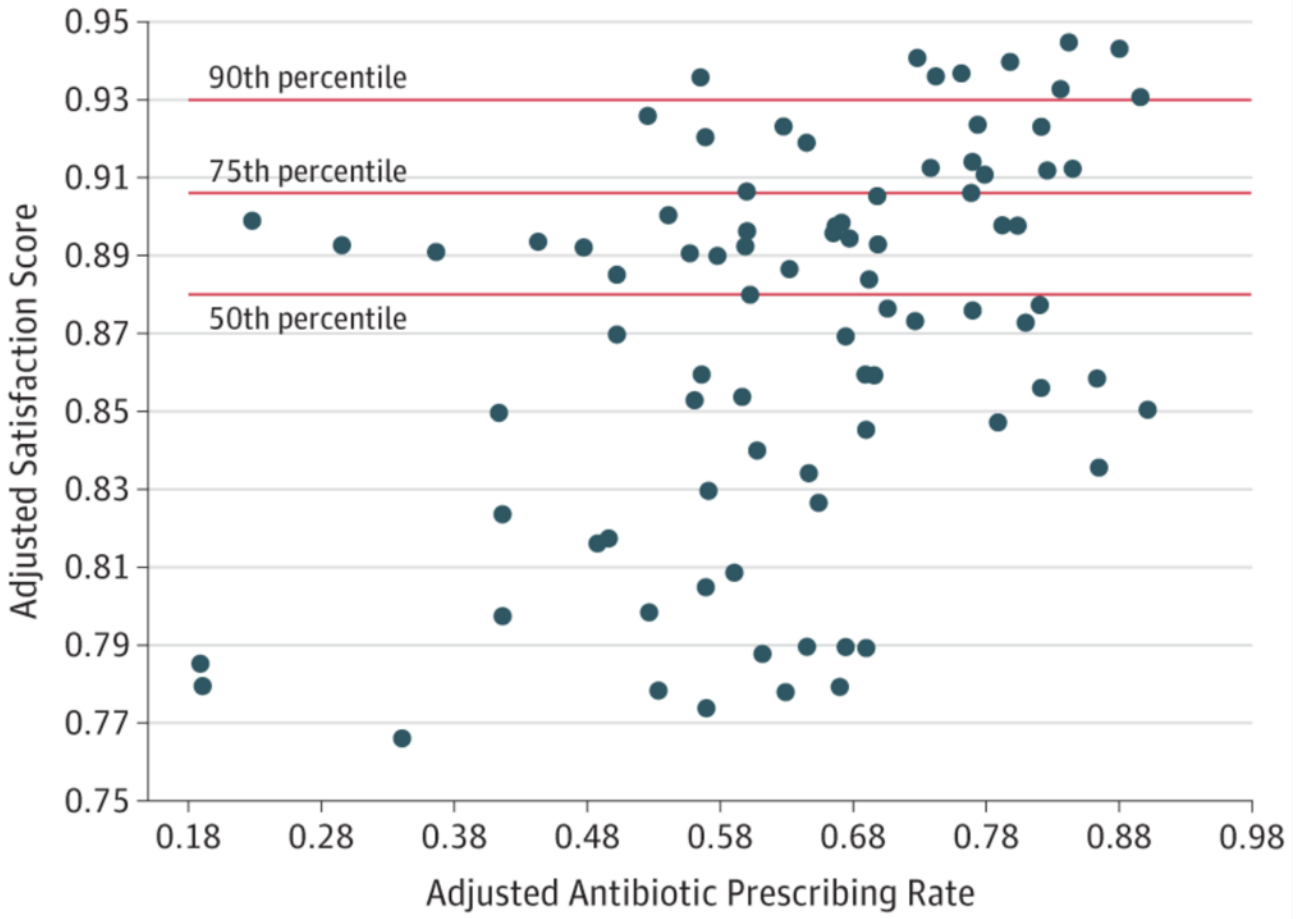
Learning Objectives

- At completion of this presentation, learners will:
  - Understand the pressures faced by clinicians to prescribe antibiotics
  - Select appropriate treatments for commonly encountered infections
  - Understand certain antibiotic adverse effects and how to avoid them
  - Have a few laughs

"The answer isn't more troops – what you need is an antibiotic."

“Don’t forget to take a handful of our complimentary antibiotics on the way out.”

Antibiotics for URIs and Patient Satisfaction



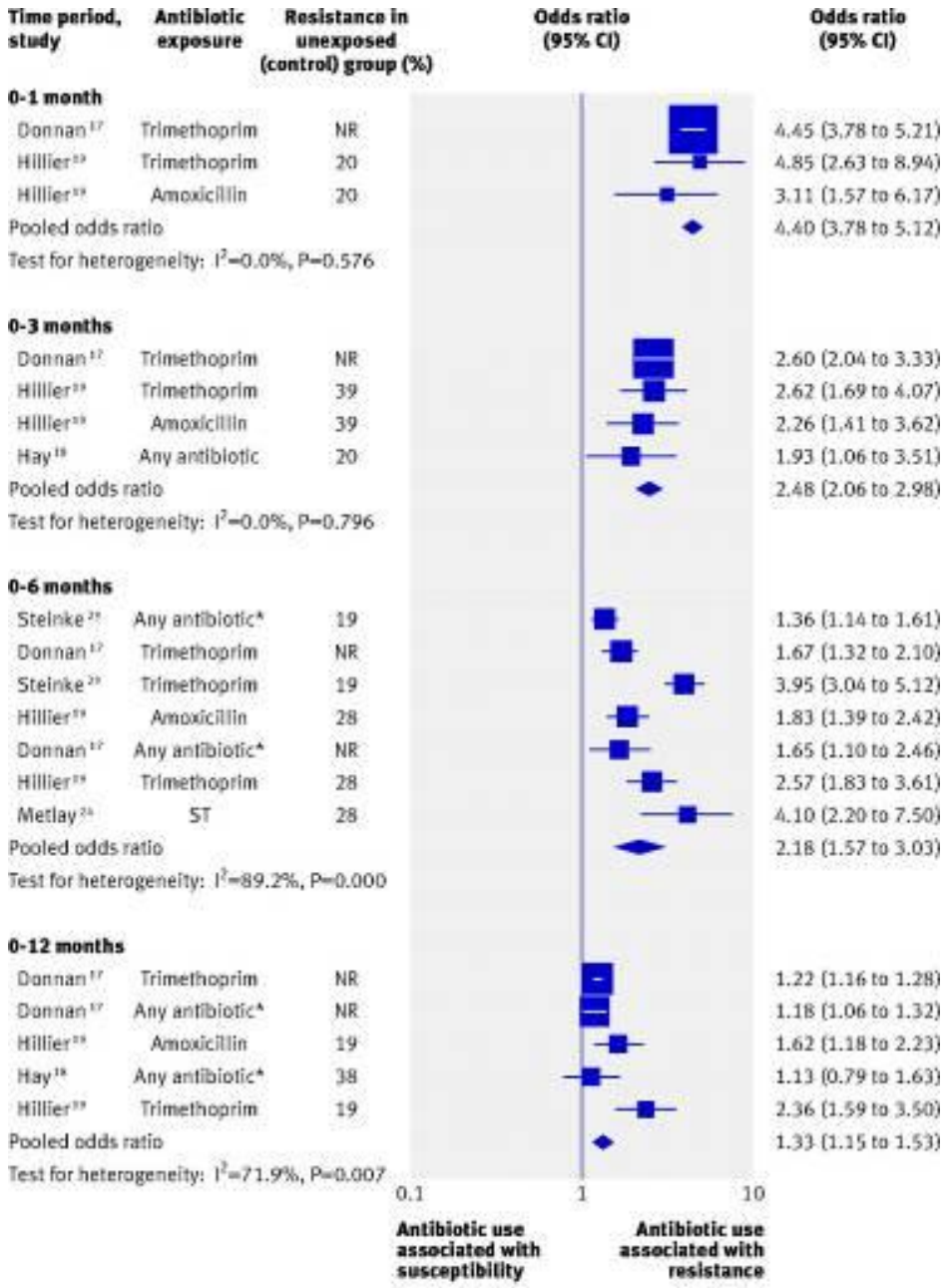
"Few physicians achieved even the 50th percentile of satisfaction while maintaining low rates of antibiotic prescribing. **To reach the top quartile, a physician had to prescribe antibiotics at least half the time; almost all physicians above the 90th percentile had a rate of antibiotic prescribing greater than 75%."**

Martinez KA, et al. JAMA Int Med 2018.

NYC Subway advertisement for an on-line pharmacy, 2017.

Systematic review:

Antibiotic use in outpatients increases risk of resistance



Costelloe, C. et al. BMJ 2010;340:c2096

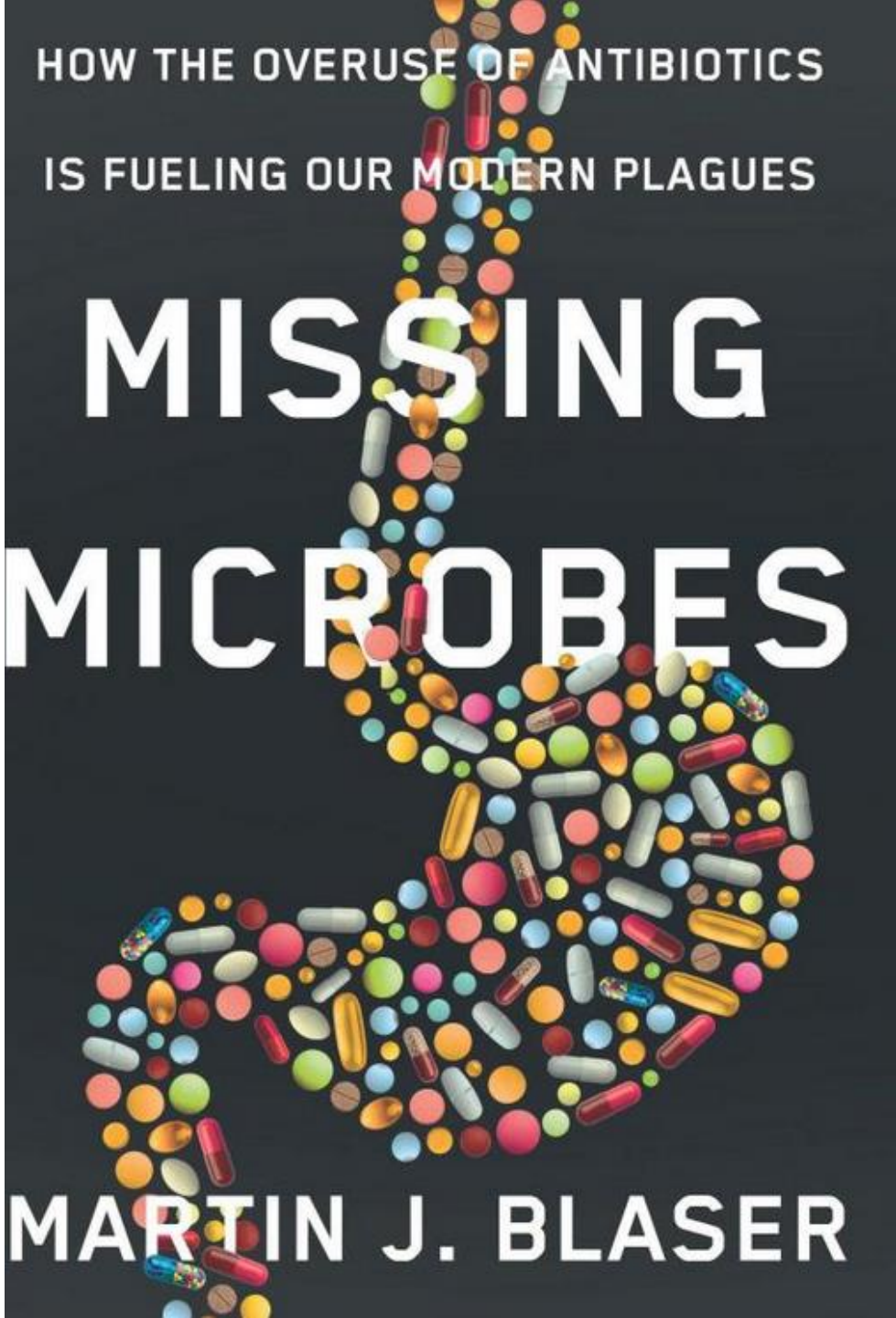
Result 02 Klebsiella species not K. pneumoniae or K. oxytoca
>100 x E6 cfu/L
This organism is phenotypically carbapenemase POSITIVE.
Genotypic confirmation to follow.

Result	K.sp.
Amikacin	R
Amoxicillin/Clavulana	R
Ampicillin	R
Ceftriaxone	R
Cephalexin	R
Ciprofloxacin	R
Ertapenem	R
Gentamicin	R
Meropenem	R
Nitrofurantoin	R
Piperacillin/Taz	R
Tobramycin	R
Trimethoprim/sulfa	R

Beware "Pirate" bacteria!

Selected Conditions Linked to Alteration of the Human Microbiome

- Obesity
- Type II diabetes
- Asthma
- Food allergies
- Esophageal reflux
- Gluten sensitivity



Case Presentations

28 y.o. man with “spider bite”

- Noted painful nodules approximately 1 week ago
- Started himself on oral cephalexin that happens to be left over in his medicine cabinet
- Worried it might be a spider bite – did not actually see a spider
- Two days later, he is no better: T = 100.8; two nodules noted (buttock, inner thigh), largest 5 x 8 cm with surrounding erythema and purulent drainage

Question

- In addition to incision and drainage and other local care, how would you manage?

A. Oral trimethoprim-sulfamethoxazole
B. Oral clindamycin
C. Oral linezolid
D. No antibiotics

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Non-prescription antibiotic use is common

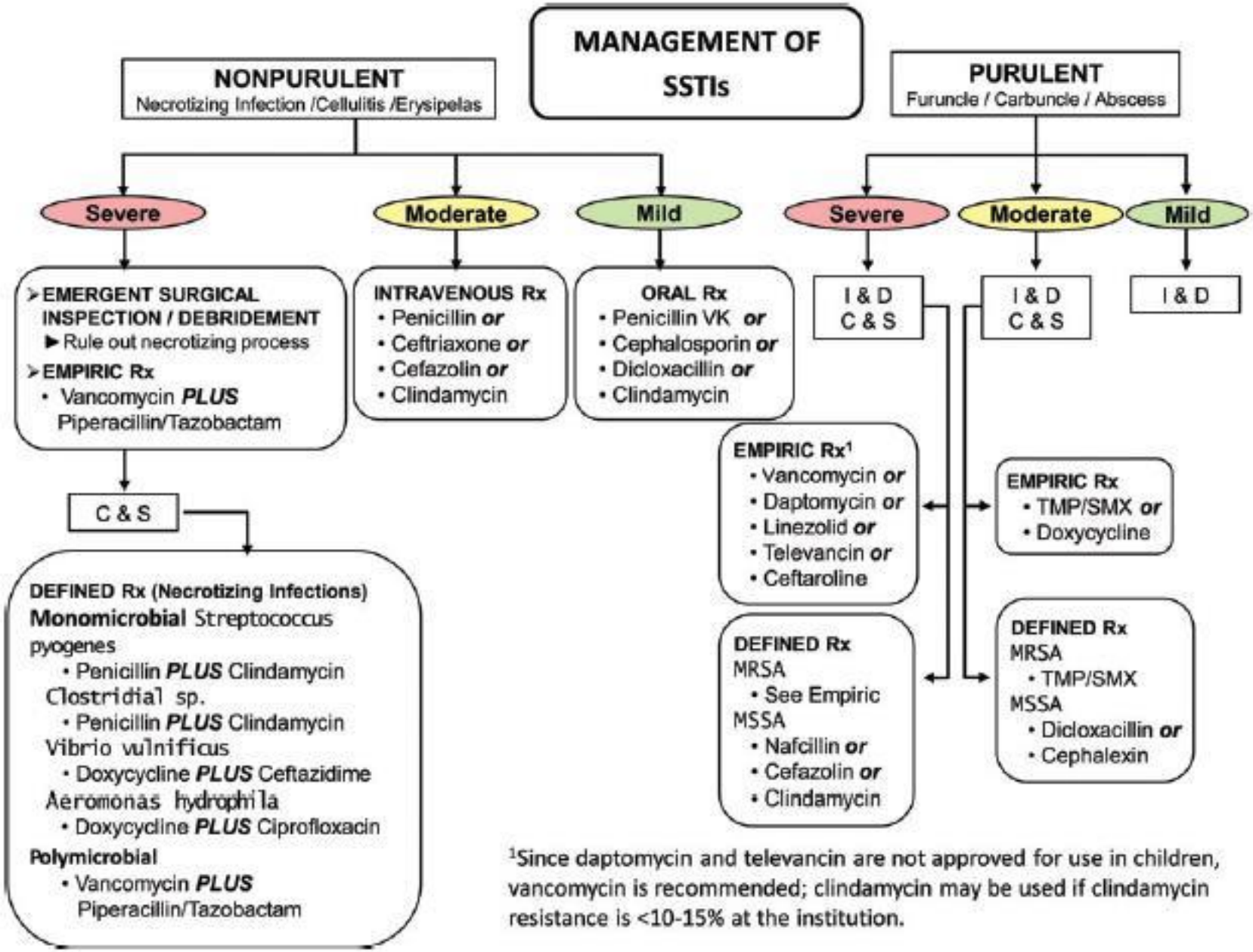
- Comprehensive survey of published literature including 31 high-quality studies
- Actual non-prescription antibiotic use: 1% to 66%
- Storage of antibiotics for future use: 14% to 48%
- Intention to use antibiotics in the future if “needed”: 25%
- Risk factors: Easy access through international on-line sources, difficulty with healthcare system

Grigoryan L et al., *Annals Int Med* 2019.

Skin and soft-tissue infections

- Most community-acquired cases caused by *Staph aureus*, beta-hemolytic streptococci
  - Staph: abscesses
  - Strep: cellulitis, lymphangitis, erysipelas
- Special cases:
  - DM with ulcer: GNR, anaerobes – but also staph, strep
  - Bites: *P. multocida*, *Capnocytophaga* spp, mixed flora
  - Water: *Aeromonas*, *Vibrio* spp. (esp. with liver disease), *M. marinum*
  - Thorns: *Sporothrix schenkii*

Stevens DL, et al; *Clinical Infectious Diseases* 2005;41:1373-1406.



[1]Since daptomycin and televancin are not approved for use in children, vancomycin is recommended; clindamycin may be used if clindamycin resistance is <10-15% at the institution.

Stevens *et al*. Clin Infect Dis 2014; 59 (2): e10

Community-acquired MRSA

- *Early 2000s*: Increased reports of community outbreaks of skin and soft tissue infections (SSTI) due to MRSA
- *2010s*: Most common cause of microbiologically-confirmed soft tissue infection in the USA
- *2020s:* Rates of MRSA slowly declining – why?

Naimi T, et al, JAMA. 2003;290:2976-2984; Moran G, et al, NEJM 2006:355:666-74. JAMA 2012;308:50-59.

Risk Factors for MRSA

- Prior use of antibiotics
- Reported “spider bite”
- History of MRSA
- Close contact with someone who has similar condition
- *But*: among patients with none of these factors, 48% still had MRSA

Moran G, et al, NEJM 2006:355:666-74.

Is it a spider bite?

IF YOU THINK YOU HAVE A SPIDER BITE, IT MIGHT ACTUALLY BE AN INFECTION THAT NEEDS MEDICAL ATTENTION.

When in doubt, check it out.

www.cdc.gov/mrsa

Soft tissue infections: Randomized trials support treatment

Trimethoprim-sulfamethoxazole (TMP/SMX) vs placebo

- Greater likelihood of abscess cure with TMP/SMX
- Lower recurrence, need for hospitalization, need for surgery, spread within household with TMP/SMX
- No serious adverse events linked to treatment

TMP/SMX vs clindamycin vs placebo

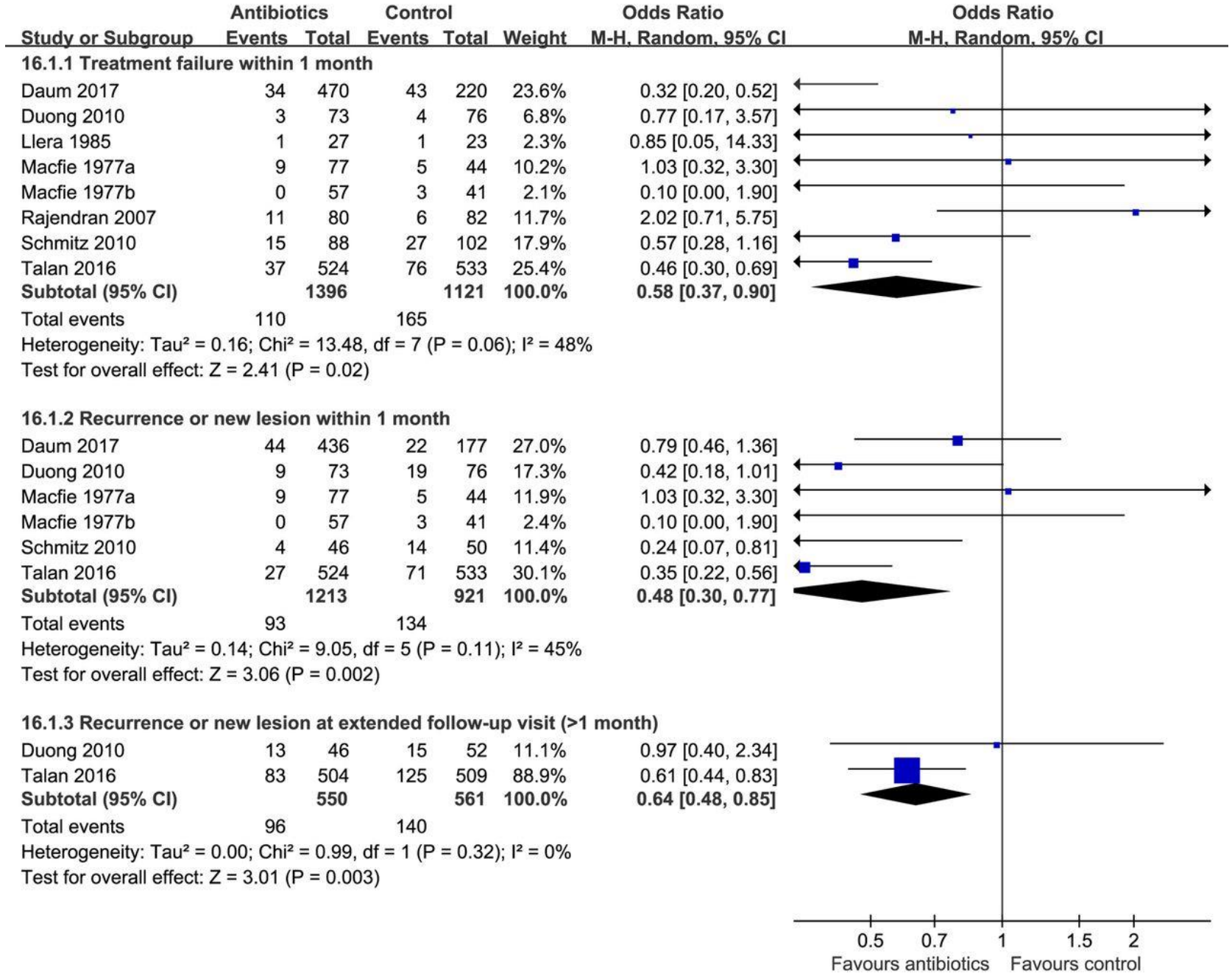
- Both clinda and TMP/SMX better than placebo for abscess cure
- Fewer recurrences with clindamycin but less well tolerated, but no C diff
- Patients with clindamycin-resistant isolates fared less well with clinda
- No difference when cultures did not grow *Staph aureus*

Talan et al. New Engl J Med 2016;374:823; Daum et al. New Engl J Med 2017;376:2545

Summary: Approach to skin abscess

- Obtain cultures for confirmation – can even do on dry nodules – to assess susceptibilities
- Low threshold for incision and drainage
- Empiric oral treatment: TMP-SMX, or doxycycline/minocycline, or clindamycin (caveat re: rising resistance – 40%), or linezolid
- Other options include vancomcyin, linezolid, daptomycin, telavancin, oritavancin, dalbavancin
- Antibiotics strongly recommended for large abscesses (5 cm), systemic illness, immunocompromised hosts, diabetes, face/hands/genitalia – maybe for all?
- Duration: 7-14 days

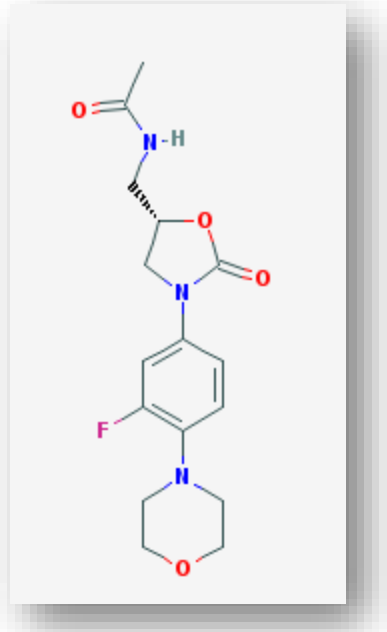
NEJM 2008; 359:1063-1067; Liu Clin Infect Diseases 2011; N Engl J Med 2014; 370:1039-1047; Lake JG Clin Infect Dis 2020;71: 661-663.



Wang W, et al. BMJ Open 2018.

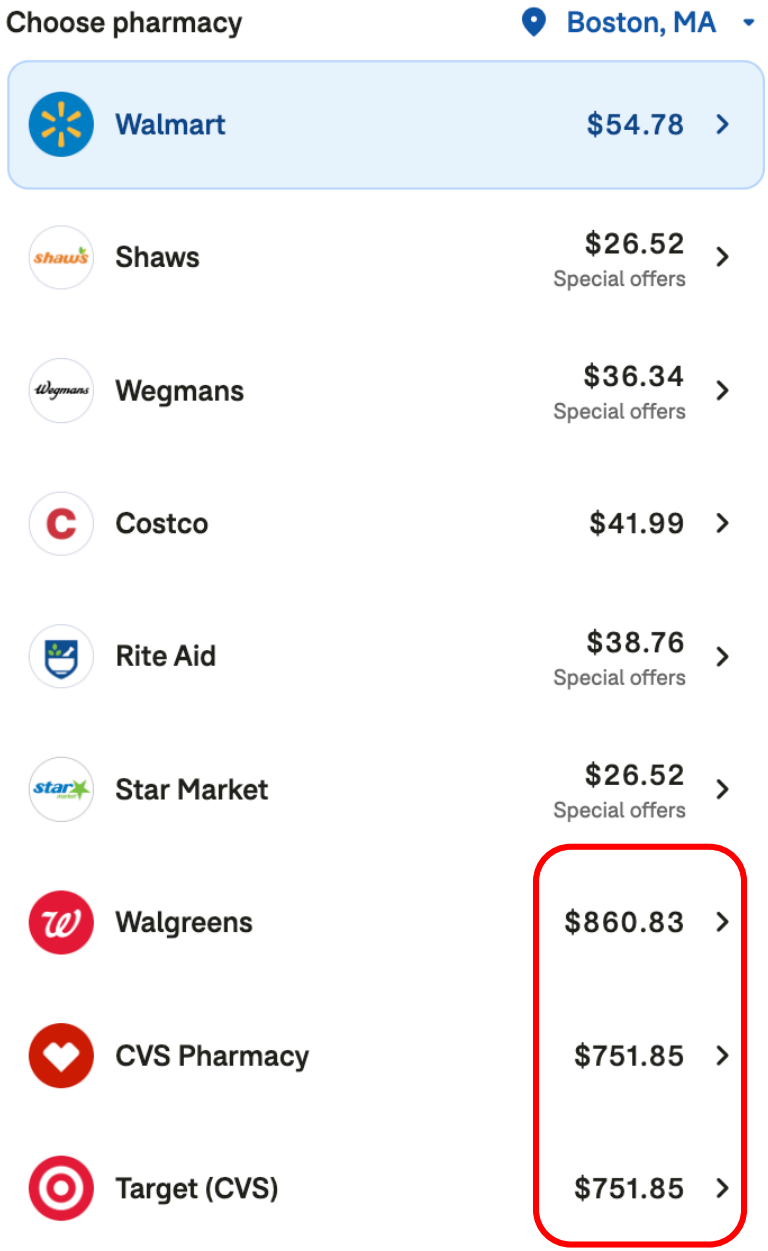
Linezolid – An important option for outpatient care

- Active against staph (including MRSA) and strep
- Excellent oral absorption and tissue penetration
- Dose: 600 mg twice daily
- Adverse effects – main risk factor is duration of therapy
  - Asthenia (the “blahs”)
  - Cytopenia
  - Neuropathy – peripheral and optic (may be irreversible)
- Drug interactions: Potential for serotonin syndrome when coadministered with SSRIs (not an absolute contraindication)
- Price down substantially due to generics – usually!



Price range for 10 Days of linezolid – Buyer beware!

Goodrx.com, Mar 2024.



Recurrent MRSA is a very challenging problem!

Very Recurrent MRSA: Strategies for Prevention

- Topical antibiotics: Mupirocin nasal ointment anterior nares BID
- Systemic antibiotics: Bactrim 1 DS BID, +/- rifampin 300 mg PO BID – all for 7-10 days
  - Not endorsed in guidelines, but anecdotally useful in some cases
- Household contacts (including pets) cultured/treated

- Local measures
  - COVER WOUNDS
  - Bathe for 10 minutes; 1 tsp bleach/gallon of water
  - Using a bath sponge, lather armpits, groin, anus, and under the breasts with chlorhexadine topical antiseptic (Hibiclens scrub) after draining bath water
  - Shower Hibiclens off
- Frequent laundering of towels, sheets, clothing

Daum RS, et al. N Engl J Med 2007;357:380; Liu Clin Infect Dis 2011.

“Never, ever, think outside the box.”

Animal bites: Special considerations

- *Pasturella multocida*
  - Early onset (1-3 days) cellulitis following cat (75%) or dog (50%) bites
  - *Not* susceptible to cephalexin, dicloxacillin, clindamycin
- *Capnocytophaga* species – can cause overwhelming sepsis in those with asplenia, alcoholism, liver disease
- Bartonella (“cat scratch”) – lymphadenopathy, fever 7-14 days after cat bite or scratch*
- Anaerobes
- Empiric therapy
  - **Preferred: amoxicillin-clavulanate**
  - Alternatives: doxycycline or TMP/SMX or moxifloxacin or cefpodoxime plus metronidazole or clindamycin

*treatment of choice: azithromycin

24 y.o. female with dysuria, frequency

- No systemic symptoms
- Two prior UTIs that she can remember – received TMP-SMX once, developed total body rash
- PE negative for fever or flank pain

Question

- What treatment should you recommend?

A. Amoxicillin-clavulanate
B. Nitrofurantoin
C. Fosfomycin
D. Ciprofloxacin

Question

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Therapy for lower UTI in healthy women

- Optimal therapy for UTI will not eradicate non-pathogenic vaginal flora (in particular, lactobacillus)
- Over one-third of bacterial strains causing UTI resistant to ampicillin/amoxicillin; 10-22% to TMP-SMX
- 2011: Guidelines on “preferred” regimens – soon to be updated

Clinical Infectious Diseases 2011; 52:e103-e120

Preferred initial regimens for UTI

- Nitrofurantoin 100 mg BID x 5 days
- TMP/SMX DS 1 PO BID x 3 days
- Fosfomycin 3 gm as a single dose
- 2nd Line: Amox-clav, cefdinir, cefaclor, cefpodoxime
- Not recommended
  - Fluoroquinolones – highly effective, but may lead to “collateral damage”
  - Amoxicillin and ampicillin

Clinical Infectious Diseases 2011; 52:e103-e120

Effect of 5-Day Nitrofurantoin vs Single-Dose Fosfomycin on Clinical Resolution of Uncomplicated Lower Urinary Tract Infection in Women

- Randomized clinical trial of nitrofurantoin 100 mg TID X 5 days vs fosfomycin 3 gm X 1
- Primary endpoint: clinical response at day 28
- N=513, median age 44
- Clinical response to nitrofurantoin (70%) significantly better than fosfomycin (58%); microbiologic response also favored nitrofurantoin
- Results raise questions about usefulness of fosfomycin for uncomplicated UTI

Huttner A, et al. JAMA 2018.

Fosfomycin

- Phosphonic acid, inhibits bacterial cell wall synthesis
  - FDA approval *E. coli* and *E. faecalis* uncomplicated cystitis
- Susceptibility in urinary isolates:
  - ~90.6% of *Enterococci*, 90-94% of *Enterobacteriaceae* (~95% *E. coli*, 90-95% *Klebsiella),* 89.7% PsA susceptible
  - Correlates with treatment-response are limited
- Response rates 3g dose: 58%-83%
- Complicated cystitis: repeat dose every 24-72 hours x 2-4 doses
- Barriers/limitations to use:
  - Unusual formulation
  - Limited data on non-*E. coli* and enterococcal isolates
  - Cost

Hirsch. *Int J Antimicrob Agents* 2015; 46 :642
Liu. J Microbiol Immunol Infect 2011; 44:364

47 y.o. man with 7 days of cough

- Previously-healthy non-smoker, well until 1 week prior when he developed sore throat, rhinorrhea
- Now with 3 days of progressive cough, in AM productive of thick sputum, “yellow-green”;
- Requests “Z-pack”, which he says always works great for him
- Exam: normal

Question

- How would you manage?

A. Azithromycin
B. Doxycycline
C. Levofloxacin
D. A “delayed” prescription for one of the above
E. No antibiotics

Question

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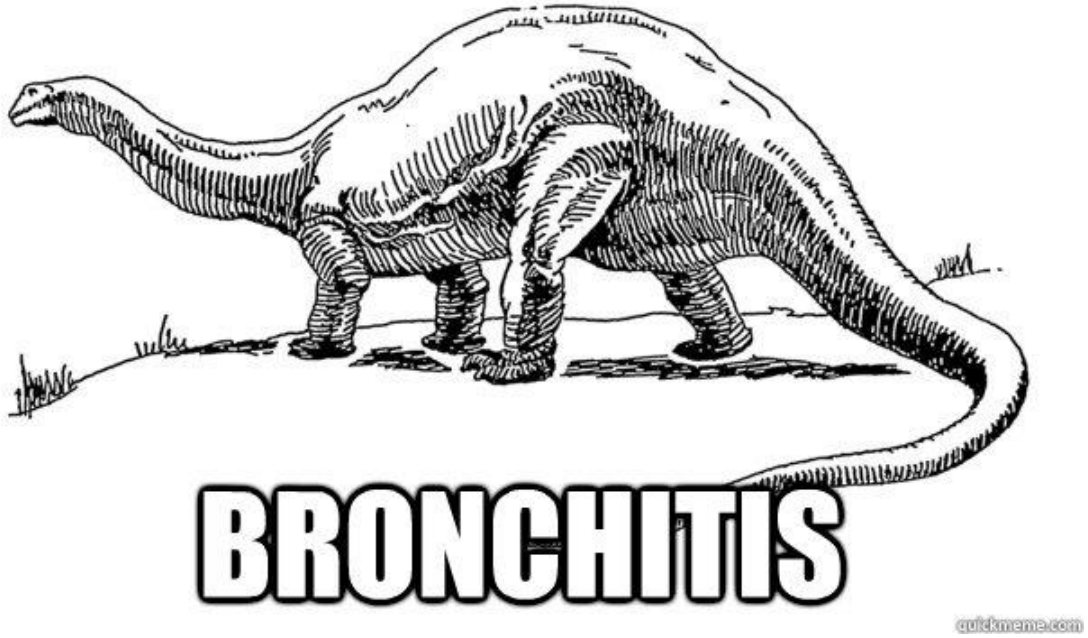
Choose your language carefully!

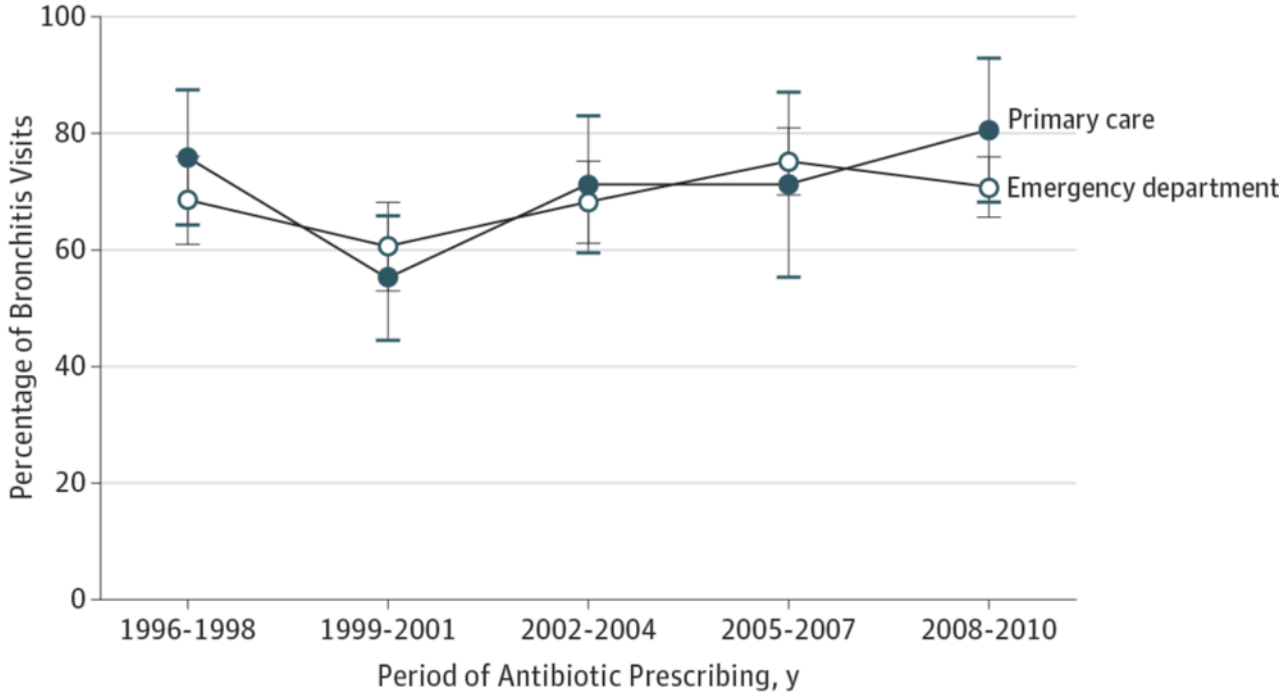


Survey of 459 patients regarding **treatment dissatisfaction** if no antibiotic given for “cough with grey phlegm for 1 week”, and illness called:

- “Bronchitis” 26%
- “Viral illness” 17%
- “Cold” 13%

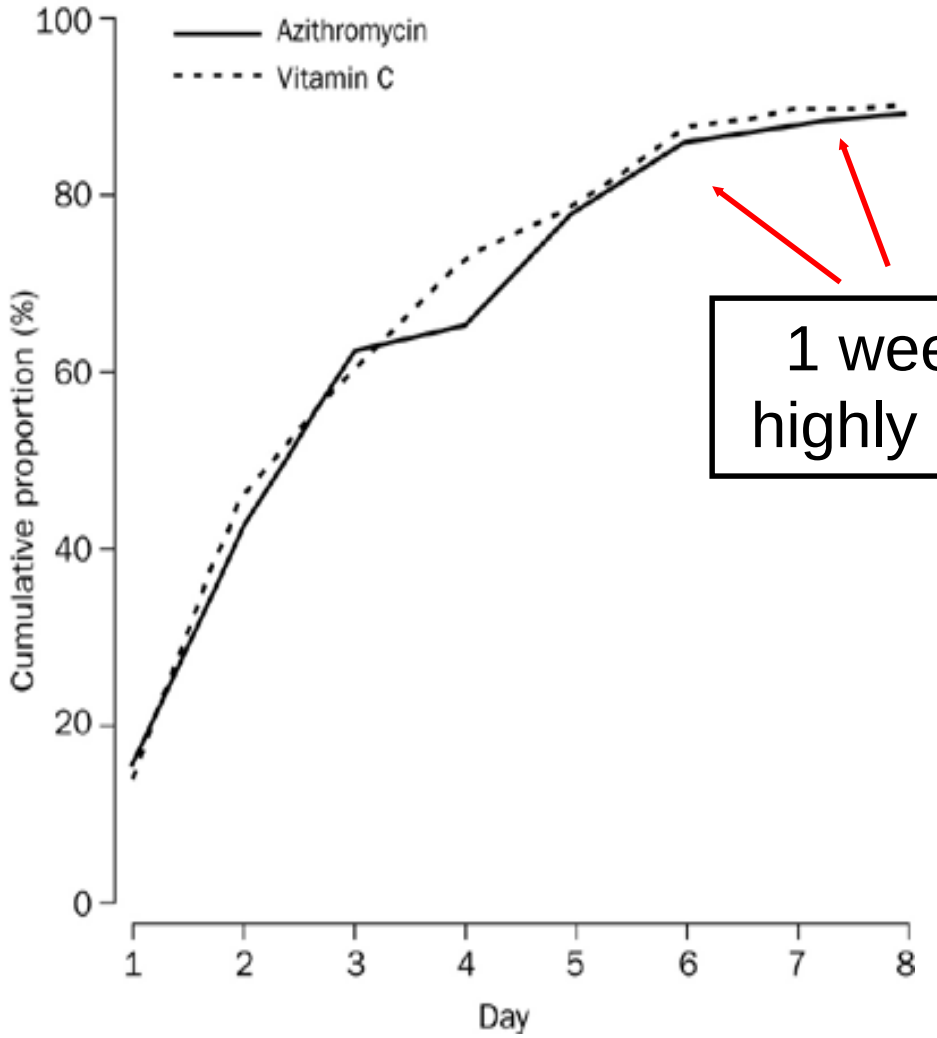
J Am Board Fam Pract. 2005 Nov-Dec;18(6):459-63.

Antibiotic prescribing for bronchitis is common



No. of sampled visits					
Primary care	168	167	185	217	234
Emergency department	293	401	499	462	527

JAMA. 2014;311(19):2020-2022.



1 week: 20% still highly symptomatic!

Proportion of pts who had returned to their usual daily activities.

Evans T, Lancet 2002;359:1648.

Taking an Antibiotic or Not?

ACUTE RESPIRATORY TRACT INFECTIONS (ARI)

Diagnostic Decision Support Tool

STEPS 1 and 2: Complete the Diagnostic Decision Support Tool according to your patient's ARI to estimate his/her probability of bacterial infection.
STEP 3: Share your estimate of probability with your patient.
STEP 4: Communicate the therapeutics options regarding the use of antibiotics (taking or not taking) and the benefits and risks associated with each option.
STEP 5 : Clarify the values and preferences of your patient regarding each option.
STEP 6: Evaluate the decisional comfort of your patient regarding his/her decision.

ACUTE RHINOSINUSITIS

To differentiate patients with an ACUTE RHINOSINUSITIS due to a bacteria from those whose ACUTE RHINOSINUSITIS is due to a virus

STEP 1

Tick all the key symptoms and signs identified in your patient with symptoms of rhinosinusitis

INITIAL QUESTION
Duration of symptoms
☐ < 10 days ☐ ≥ 10 days

ADDITIONAL QUESTIONS
☐ Double sickening (worsening after improving)
☐ Colored nasal discharge
☐ Facial/sinus pain
☐ Maxillary tooth pain
☐ No response to decongestants

ADDITIONAL SIGNS
☐ Purulent discharge in nasal cavity (middle meatus) and/or throat
☐ Sinus pain on **one side**
☐ Abnormal transillumination (**one side**)

ALERTS

- Persistent high fever
- Severely ill
- Orbital swelling or erythema
- Diplopia, proptosis or other neurologic signs

STEP 2

Encircle the clinical probability (%) of a bacterial acute rhinosinusitis according to signs and symptoms of patients assuming a prevalence of 15%

Additional symptoms/signs	<10 days	>10 days*
4+	30%	95%
3	15%	75%
2	5%	50%
1	2%	25%
0	1%	5%

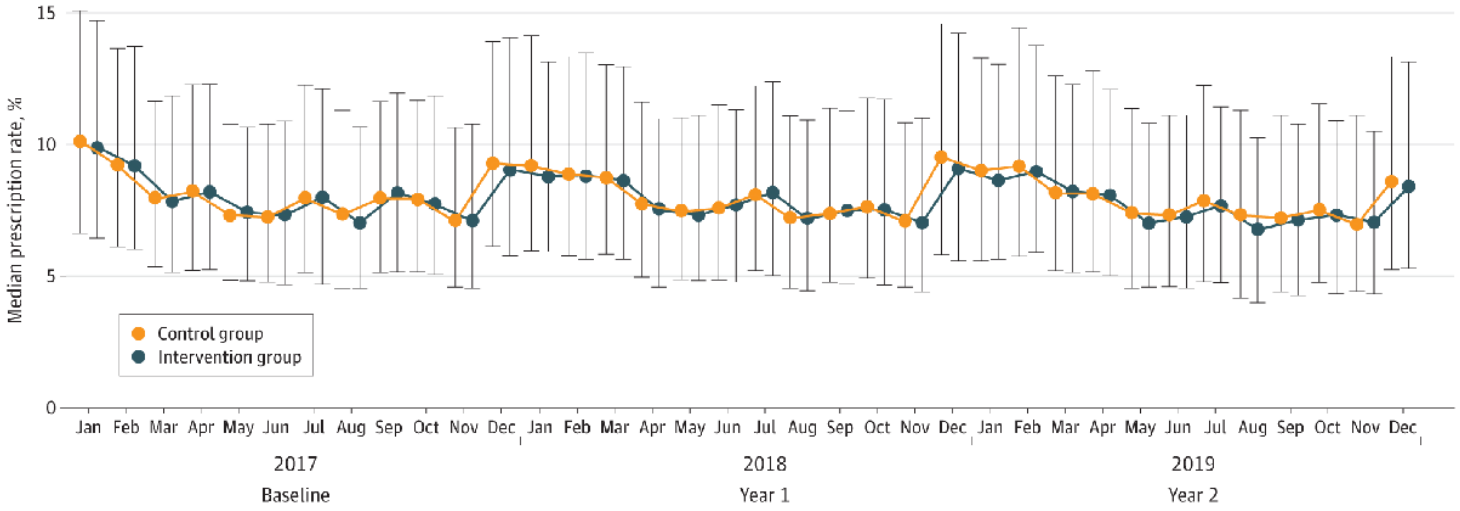
*Adults 7-10 days; children 10-14days

STEP 3 to 6 on the Shared Decision Making Support Tools

Legare F, et al CMAJ 2012 (online appendix).

What about provider feedback?

- Does *automated* quarterly antibiotic prescribing feedback with peer benchmarking reduce antibiotic among primary care physicians?
- Randomized trial of 3426 PCPs over 2-year period, with special focus on top 75% prescribers of antibiotics
- Results – no significant effect
  - Feedback group: 8.2 Rx/100 visits
  - Control: 8.4 Rx/100 visits

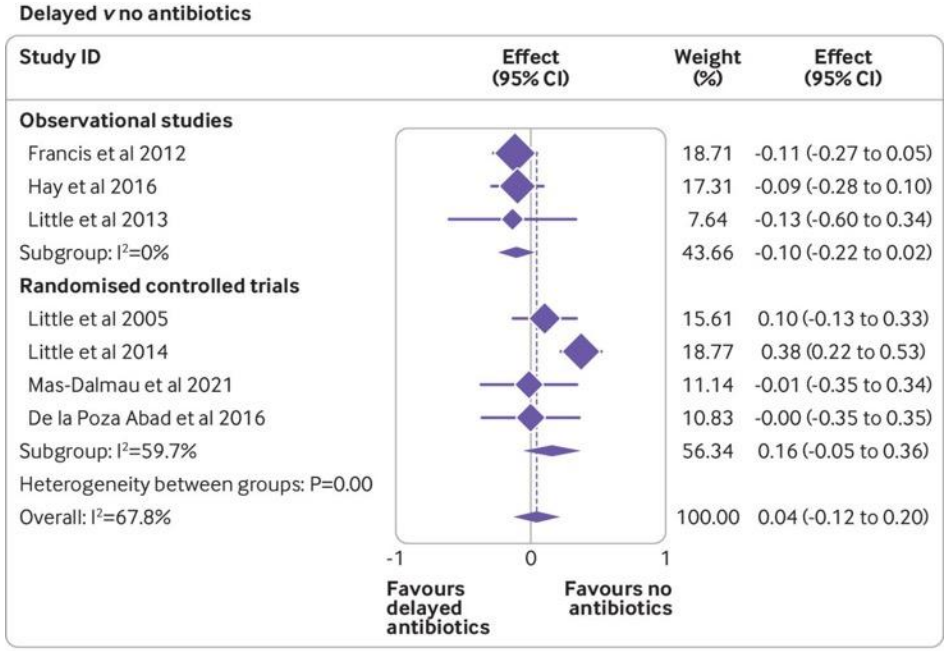


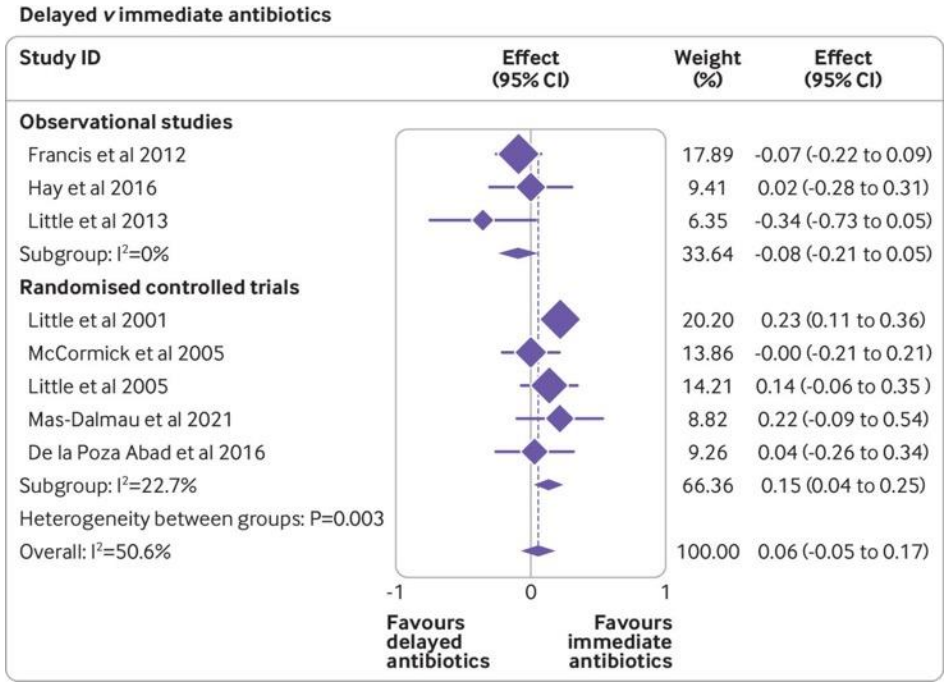
Aghlmandi S, et al. JAMA Intern Med 2023;183(3):213-220.

Delayed Antibiotic Prescribing

- Strategy: Prescribe an antibiotic but advise not to start unless their condition deteriorates or fails to improve after a set period
- Systematic review of clinical trials and cohorts
  - No adverse clinical outcomes (figure)
  - Compared with immediate antibiotics – reduces antibiotic exposure
  - Compared with no antibiotics – reduces subsequent visits, increases patient satisfaction

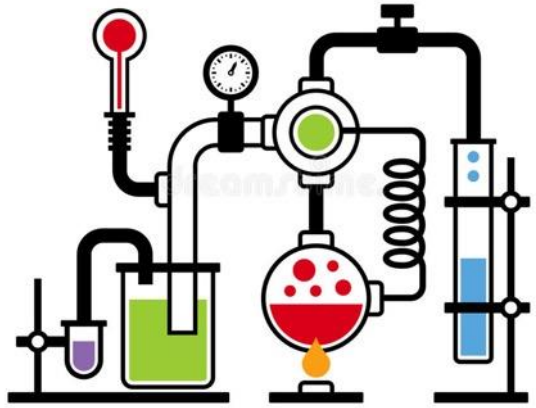
Stuart B, et al. BMJ 2021;373:bmj.n808





Can the lab help?

- C-reactive protein – non-specific marker of inflammation, rises more with bacterial infections
- Procalcitonin
  - Bacterial infection increases levels, while interferon gamma blocks production
  - Effect is rapid (within hours), and half-life is short
- Rapid viral diagnostic tests – increasingly available
- Studies support the use of these tests in reducing antibiotic exposure – but point-of-care availability and rapid turnaround are critical for implementation



Cals JW et al. Ann Fam Med 2010; Rhee C et al OFID 2016; Keske S, et al Eur J Clin Microbiol Infect Dis. 2018.

58 y.o. woman with fever, cough, pleuritic pain

- Also experiences a shaking chill
- PMHx: Diabetes, obesity, HTN, CHF
- PE: T 101.8, decreased breath sounds on right; CXR: dense RLL infiltrate
- Patient requests “Z-pack”, which she says always works great for her

Question

- How would you manage?

A. Amoxicillin-clavulanate
B. Azithromycin
C. Ciprofloxacin
D. Levofloxacin

Question

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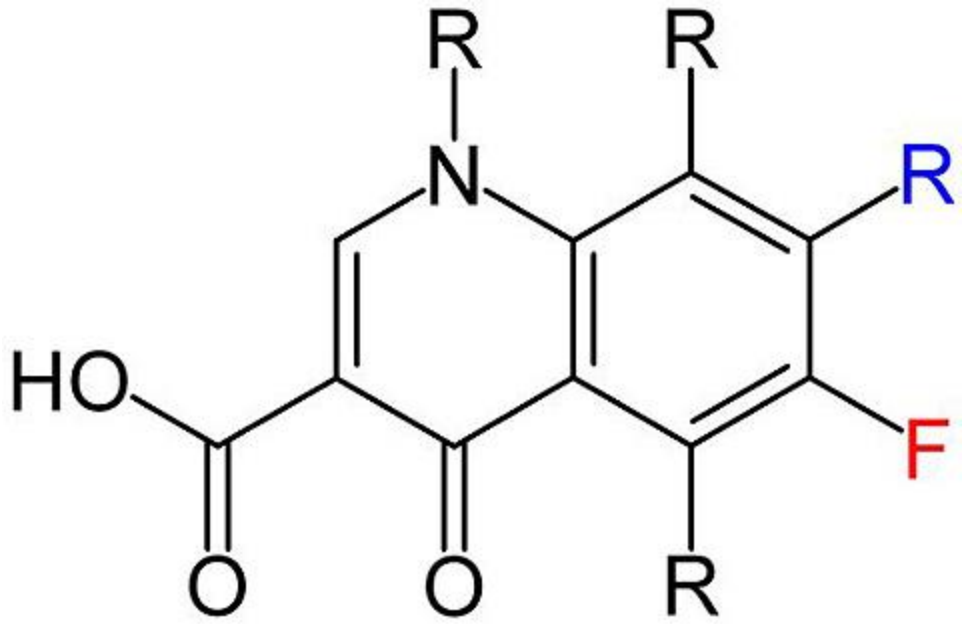
Ambulatory treatment of pneumonia – Patients with comorbidities

- Combination therapy:
  - amoxicillin-clavulanate or cephalosporin *AND*
  - azithromycin or doxycycline

OR

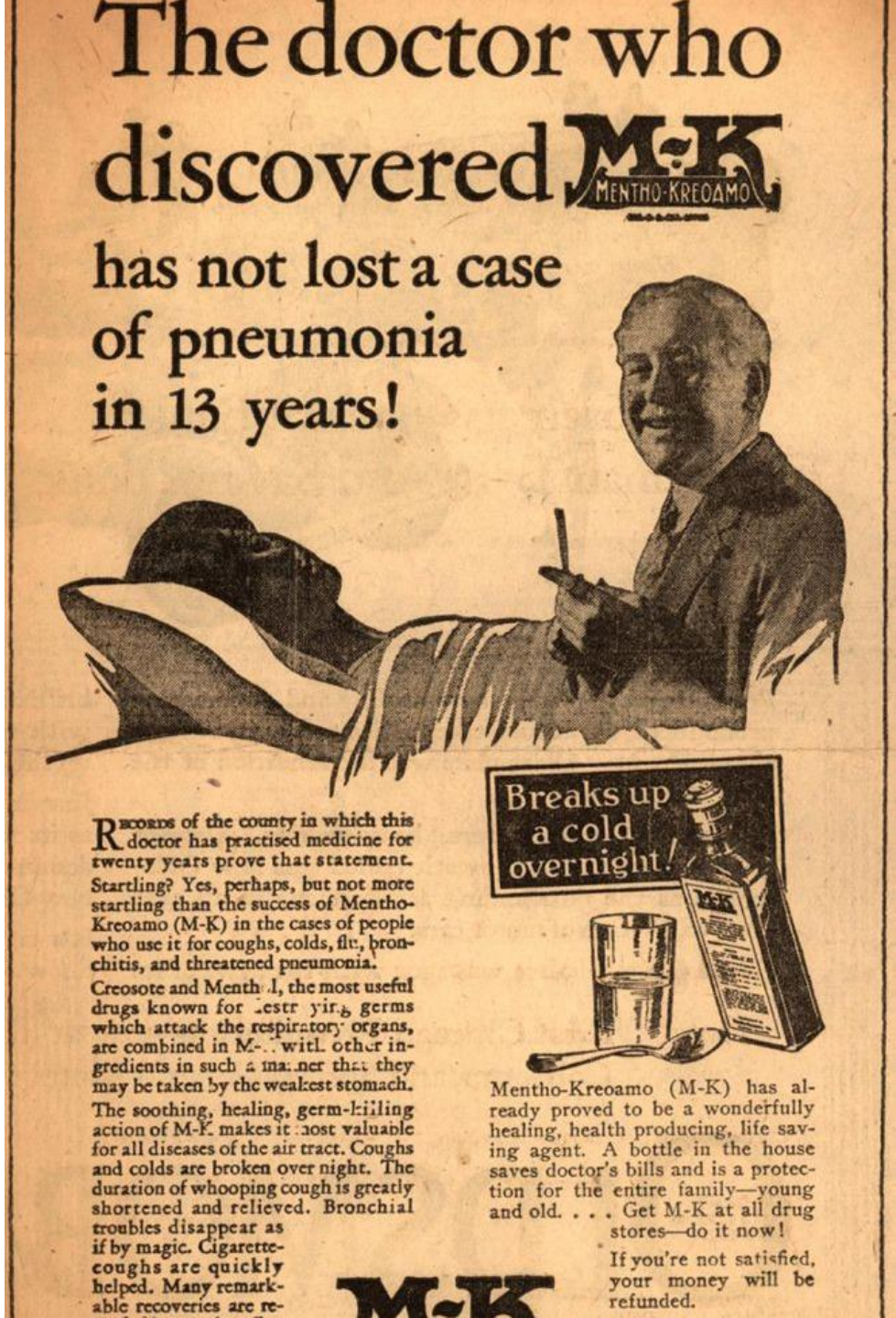
- Monotherapy with a respiratory fluoroquinolone (levofloxacin or moxifloxacin)



Metlay JP, et al. AJRCCM 2019.

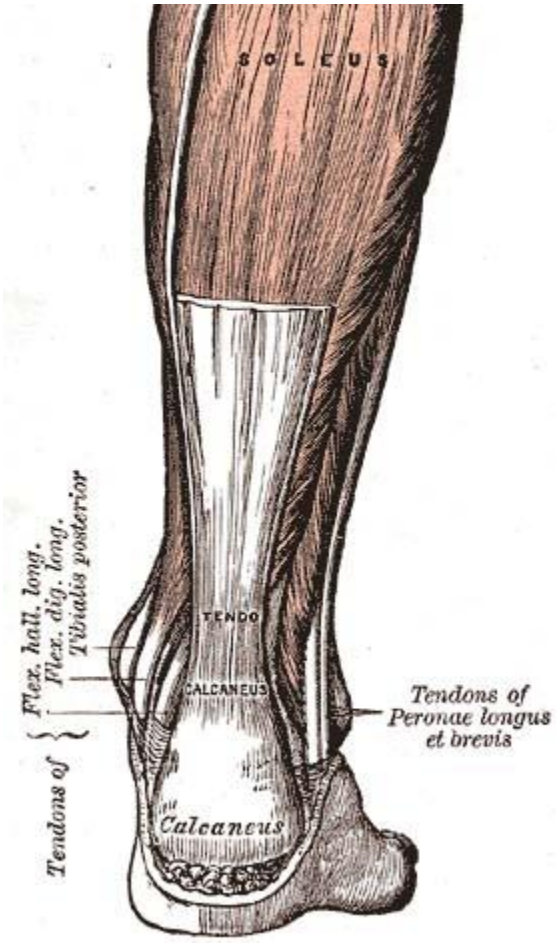
“Respiratory” Fluoroquinolones

- Levofloxacin and moxifloxacin – not ciprofloxacin (poor *Strep pneumo* activity and lung penetration)
- Antibacterial spectrum ideally suited to treatment of community-acquired pneumonia
  - *S. pneumoniae*
  - *H. influenzae*
  - Pathogens of “atypical” pneumonia: *Mycoplasma pneumoniae, Legionella pneumophila, Chlamydia pneumoniae*



Quinolones: Notable adverse effects

- Tendinitis/tendonopathy, tendon rupture
- QT prolongation
- *C difficile*
- Neuropsychiatric reactions, neuropathy
- Allergic reactions, including urticaria, anaphylaxis
- Photosensitivity
- Drug interaction: Mg, Fe, Ca, Al: decrease FQ absorption
- “Fluoroquinolone toxicity syndrome”



PERSONAL HEALTH | SEPTEMBER 10, 2012, 12:01 AM | 511 Comments

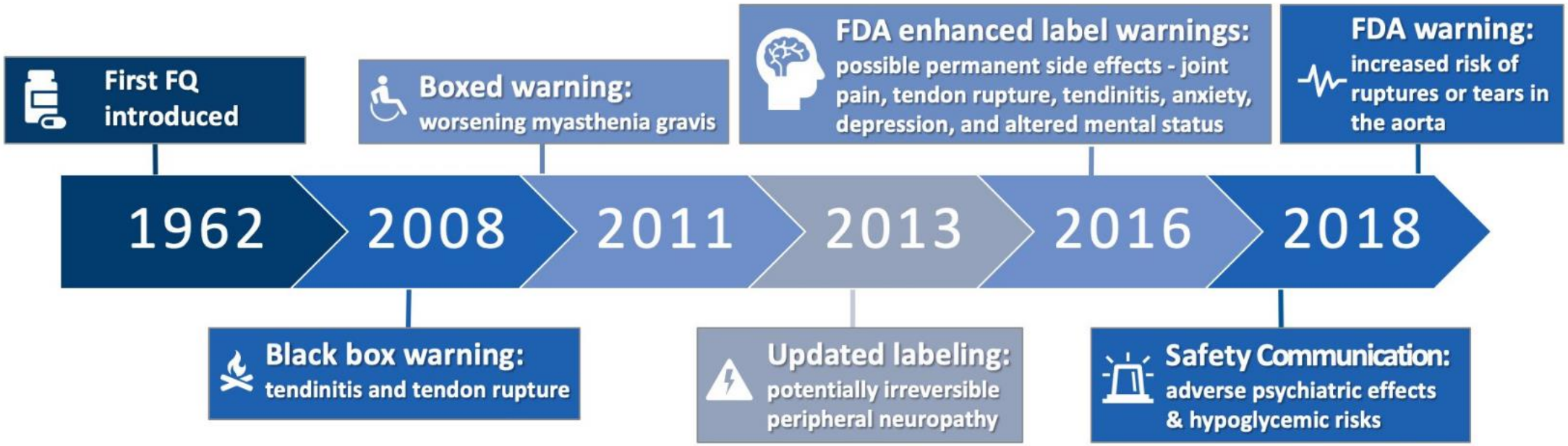
Popular Antibiotics May Carry Serious Side Effects

By JANE E. BRODY

Yvetta Fedorova

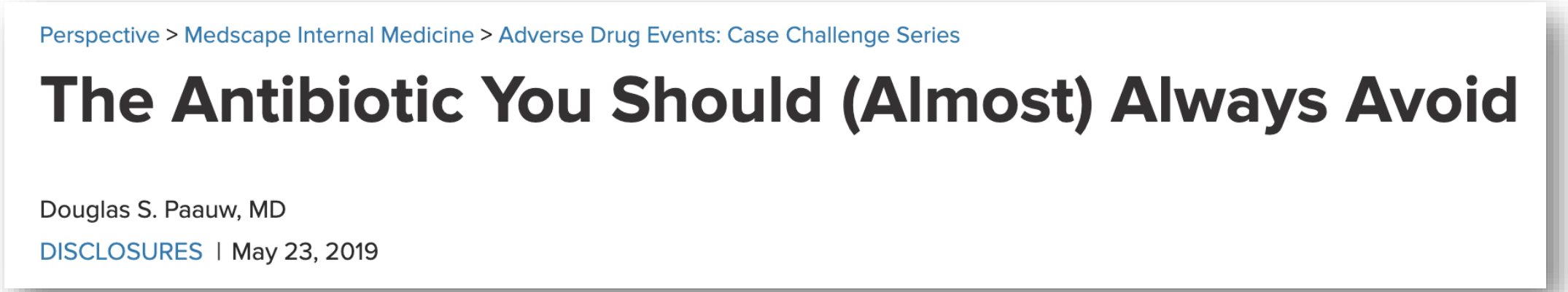
New York Times, Sept 10, 2012

Safety concerns with fluoroquinolones



MedWatch FDA Safety Report, Updated Dec 20 2018.
Graphic courtesy Travis Jones, PharmD.

Have we overreacted to the potential toxicity of quinolones?



Perspective > Medscape Internal Medicine > Adverse Drug Events: Case Challenge Series

The Antibiotic You Should (Almost) Always Avoid

Douglas S. Paauw, MD

DISCLOSURES | May 23, 2019

Medscape.com, May 23, 2019.

Which fluoroquinolone?

	GNR	GPC	Anaerobes	Metabolism	Comments
Ciprofloxacin	***	*	*	Renal	Preferred for GU infections; poor *Strep pneumo* coverage
Levofloxacin	**	**	*	Renal	Preferred for respiratory tract infections
Moxifloxacin	*	***	**	Hepatic	No activity vs. *Pseudomonas*

GNR = gram negative rods; GPC = gram positive cocci; relative activity denoted by number of *

Efficacy of Doxycycline for Mild-to-Moderate Community-Acquired Pneumonia in Adults: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

Get access >

- Systematic review of prospective clinical trials
- 6 deemed evaluable, including 834 patients, with comparators macrolides or fluoroquinolones
- Doxycycline comparable to both approaches
- Should it be added to treatment guidelines?

Doxycycline

Choi S, et al. Clin Infect Dis 2023;76:683-91.

74 y.o. male with right-sided chest pain

- Onset 3 days prior to visit
- PE: erythematous vesicles, macules, and papules present in a single mid-thoracic dermatome on the right, c/w zoster
- No other medical problems, on no medications

Question

- How would you manage?

A. Acyclovir
B. Valacyclovir or famciclovir
C. One of the above, plus corticosteroids
D. No antiviral therapy – too late for benefit

Question

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D. No antiviral therapy – too late for benefit

Therapy for herpes zoster

- Prompt antiviral therapy (< 72 h onset of rash) proven to diminish rate of new lesions, speed healing, reduce duration of pain
- Approved agents (all generic):
  - Acyclovir 800 mg 5X/day
  - Famciclovir 500 mg TID
  - Valacyclovir 1 gm TID
- Duration of Rx: 7 - 10 days

Herpes zoster: Common questions

- Which therapy?
- Should corticosteroids be given?
- Should therapy be given > 72 hours after onset of rash?
- Who's contagious?
- When should the get the zoster vaccine?

Beutner KR, et al. Antimicrob Agents Chemother 1995 Jul;39(7):1546-53. Whitley RJ, Ann Intern Med 1996 Sep 1;125(5):376-83. Wood MJ et al. N Engl J Med 1994 Mar 31;330(13):896-900. Viner K, J Infect Dis. 2012 May 1;205(9):1336-41.

A Brief Comment About Length of Antibiotic Therapy

"I understood why I needed to complete the full course, of course. What I didn't understand was why a full course took precisely seven days. Why not six, eight or nine and a half? Did the number seven correspond to some biological fact about the human digestive tract or the life cycle of bacteria?"

Professor Daniel Gilbert, "Magic by Numbers," New York Times, Oct 16, 2010

http://www.nytimes.com/2010/10/17/opinion/17gilbert.html?_r=2&scp=1&sq=numbers+antibiotic&st=nyt

The Reality: Only ID Doctors Know the Optimal Length of Antibiotic Therapy

… but now I'll share the secret formula

Mystery Solved!
How to Determine the Duration of Antibiotic Therapy

1. Choose a multiple of 5 (fingers of hand) or 7 (days of week).
2. Is the problem relatively mild or improving rapidly? Then choose 5 or 7.
3. Is it REALLY mild, so that it would get better on its own if you did nothing? Then break the rule, and go with 3.
4. Is it a serious problem? 10-14 days minimum.
5. Patient not doing better after initial course? Extend treatment, again using multiples of 5 or 7.
6. Bone or heart valve? Four weeks (28 days) or 6 weeks (42 days) – but never 5 weeks, because the 5's and 7s would cancel each other.
7. Avoid these lengths of therapy: 4, 9, 11, 13, 3.14159265 …

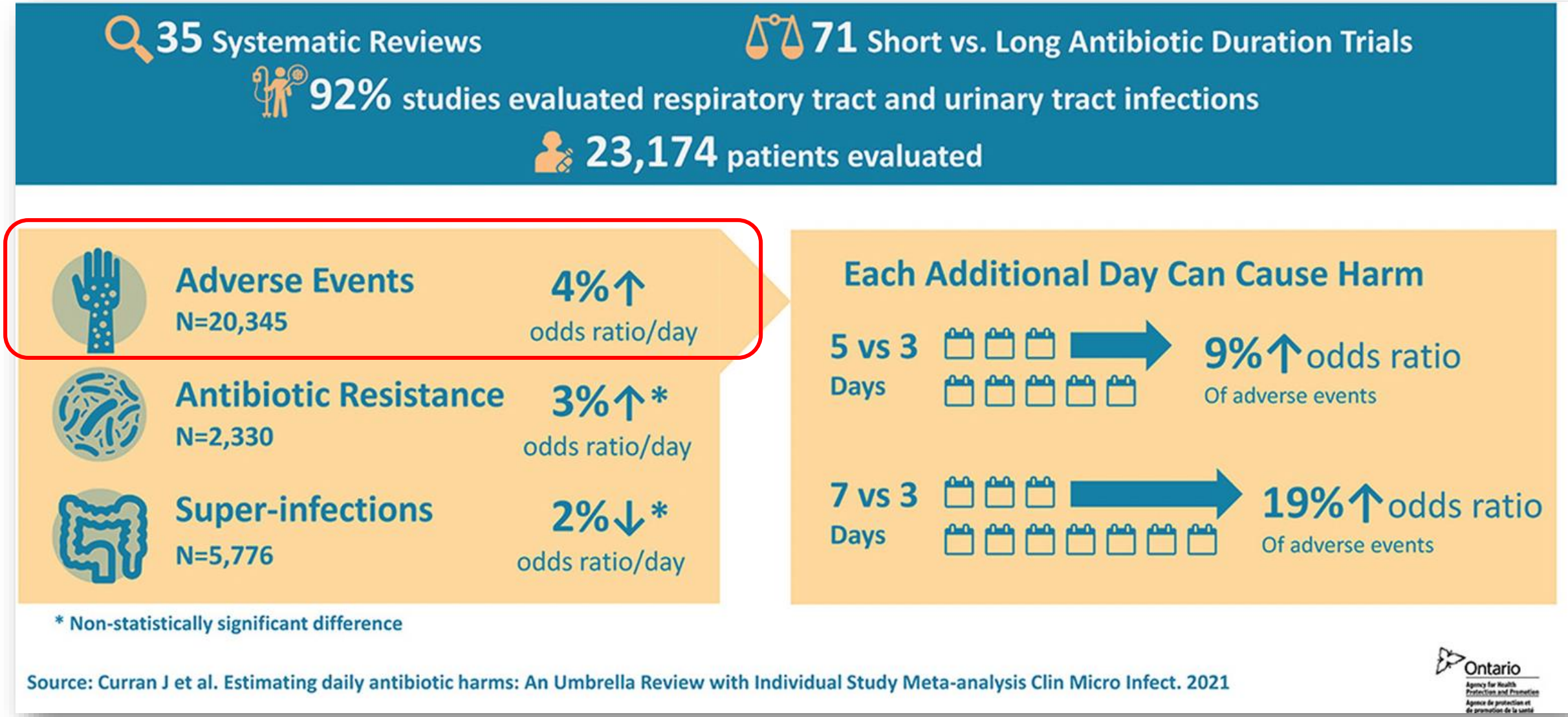
JOURNAL ARTICLE

Short-course Antibiotic Therapy—Replacing Constantine Units With "Shorter Is Better" FREE

Noah Wald-Dickler, Brad Spellberg ✉

Clinical Infectious Diseases, Volume 69, Issue 9, 1 November 2019, Pages 1476–1479,
https://doi.org/10.1093/cid/ciy1134
Published: 07 January 2019 **Article history** ▾

Clinical Infect Dis 2019.


35 Systematic Reviews
71 Short vs. Long Antibiotic Duration Trials
92% studies evaluated respiratory tract and urinary tract infections
23,174 patients evaluated
Adverse Events
N=20,345
4%↑
odds ratio/day
Antibiotic Resistance
N=2,330
3%↑*
odds ratio/day
Super-infections
N=5,776
2%↓*
odds ratio/day
Each Additional Day Can Cause Harm
5 vs 3
Days
9%↑odds ratio
Of adverse events
7 vs 3
Days
19%↑odds ratio
Of adverse events
* Non-statistically significant difference
Source: Curran J et al. Estimating daily antibiotic harms: An Umbrella Review with Individual Study Meta-analysis Clin Micro Infect. 2021
Ontario

Antibiotics: Take-home points

- Growing data support the importance of limiting antibiotic use
  - Resistance
  - Alteration in the microbiome
- Strategies to reduce use in clinical practice include shared decision making and delayed antibiotic prescribing
- Linezolid access and use should increase with reduced cost
- Fluoroquinolones may rarely cause severe side effects, but still useful
- Duration of therapy – shorter usually better!

Thank you!