Antibiotic Mindfulness - Becoming Better Stewards of a Precious Resource

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1

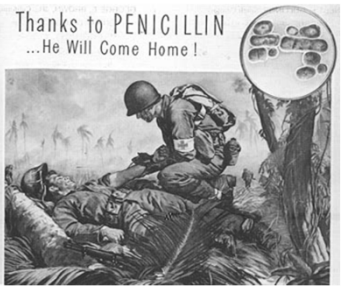
What Is Stewardship?

Merriam-Webster:

"The careful and responsible management of something entrusted to one's care"

"The responsible overseeing and protection of something considered worth caring for and preserving"

2

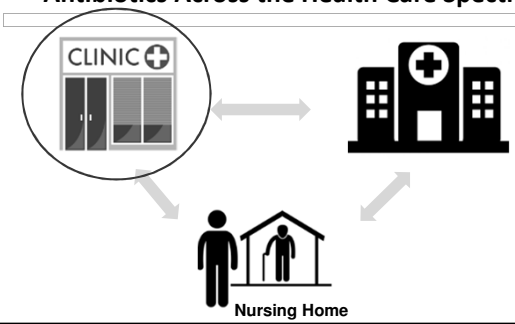


"Because infectious diseases have been largely controlled in the United States, we can now close the book on infectious diseases."

- William Stewart, MD
U.S. Surgeon General, 1967

3

Antibiotics Across the Health Care Spectrum



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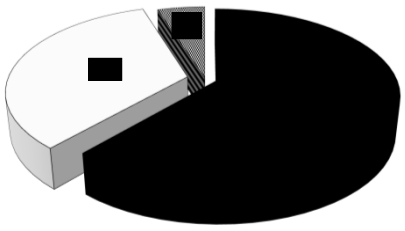
Antibiotic Expenditures in U.S. by Treatment Setting, 2009 Total Cost $10.7 billion)



■ Community ☐ Hospital ▨ Nursing Home

5

Conspicuous Consumption

- 5 out of every 6 Americans will receive a course of antibiotics annually
- 160-258 million antibiotic Rx (≈ 3 million kg) / yr
- Avg American child will receive 10-20 courses of antibiotics before age 18
- Not atypical for a 2 y.o. to have spent ≈ 3 mos of their life on antibiotics

Wenzel RP and Edmond MB. *N Engl J Med.* 2000;343:1961-1963
Spellberg and Bartlett. *N Engl J Med.* 2013; 368;299-302
Hicks and Taylor. *N Engl J Med.* 2013; 368; 1461-1462

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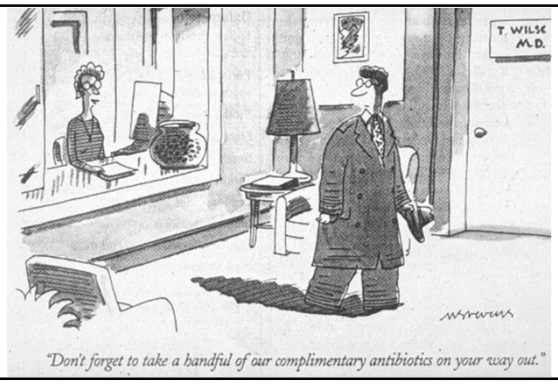

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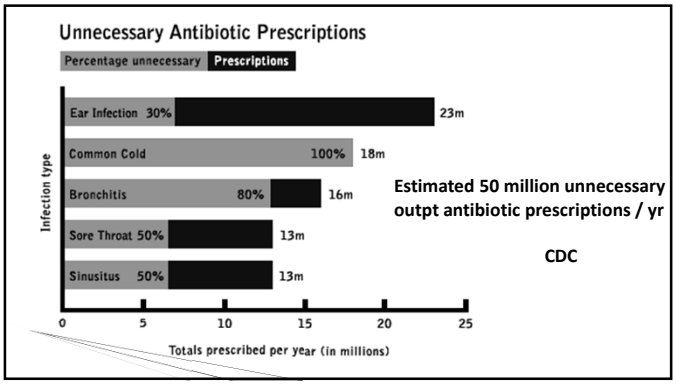

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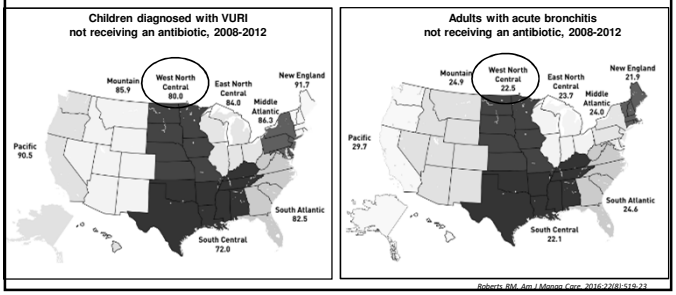
A Tale of Two Countries: Rate of Outpatient Antibiotic Use, 2014

835 / 1000 population / yr **328 / 1000 population / yr**

9

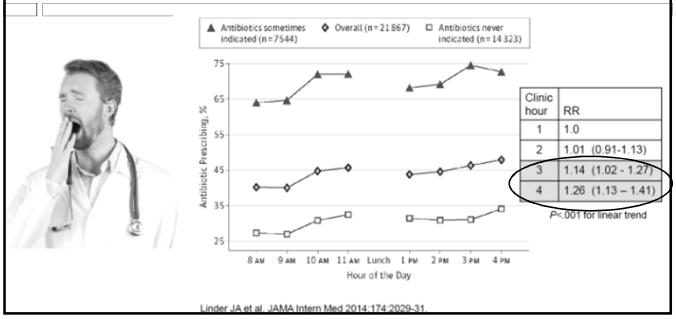
Geographic Variability in HEDIS Measures Related to Appropriate Antibiotic Use



Roberts RM. Am J Manag Care. 2016;22(8):519-23.

10

Antibiotic Prescribing Increases with Fatigue



Linder JA et al. JAMA Intern Med 2014;174:2029-31.

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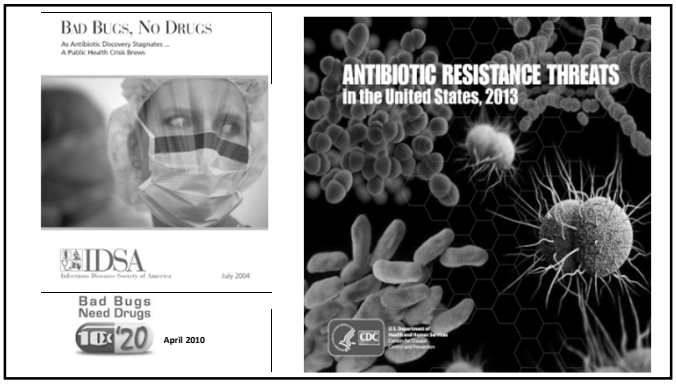

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CDC Hazard Level for Antibiotic Resistance Threats - 2013

Concerning	Serious	Urgent
VRSA	MRSA	*Clostridium difficile* (C. diff)
Ery-R GABHS	VRE	Carbapenem-R Enterobacteriaceae
Clinda-R GBBHS	MDR-Pseudomonas	Drug-resistant *N. gonorrhoeae*
	ESBL-Enterobacteriaceae	
	DR-Campylobacter	
	DR-Salmonella	
	Fluconazole-R Candida sp	
	MDR-Acinetobacter	
	MDR/XDR TB	

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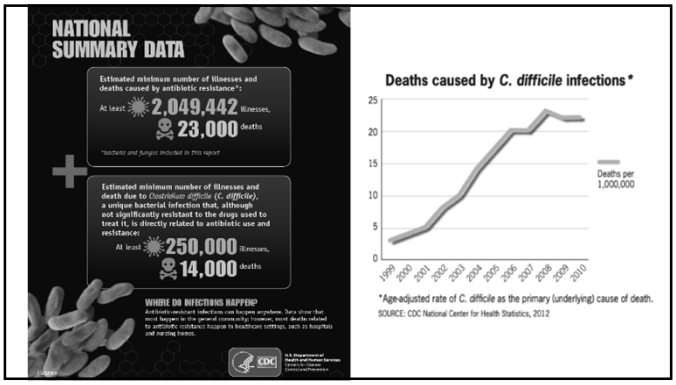

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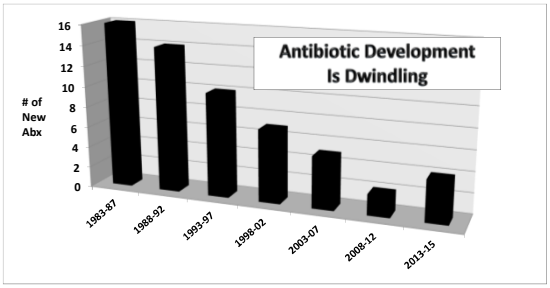
Approved Antibiotics in U.S. 1983 - 2015



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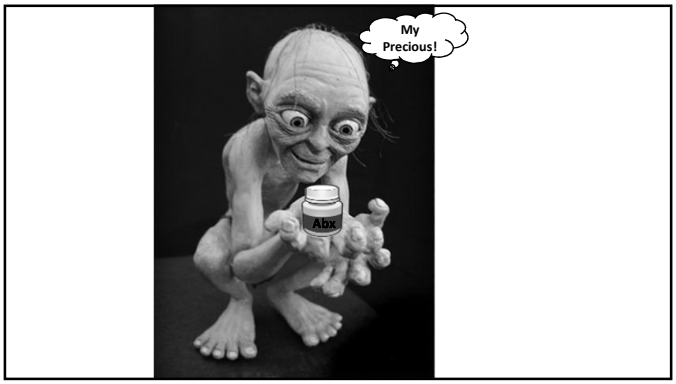

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Frequency of ADEs due to Antibiotics in Outpatient Setting

- Up to 1:4 will experience some ADE with an antibiotic
- 142,505 estimated emergency department visits/year due to untoward effects of antibiotics (~ 1:1000 abx prescriptions)
  - Antibiotics account for 19.3% of drug related adverse events
    - 78.7% for allergic events
    - 19.2% for adverse events (e.g. diarrhea, vomiting)
  - Approximately 50% due to penicillin & cephalosporin classes
  - 6.1% required hospital admission

2004-2005 NEISS-CADES project
Bourgeois, et al. Pediatrics. 2009;124;e744-50
Linder. Clin Infect Dis. 2008 Sep 15;47(6):744-6
Vangay, et al. Cell host & Microbe 2015;17;553-64
Shehab N et al. Clin Infect Dis. 2008;47:735

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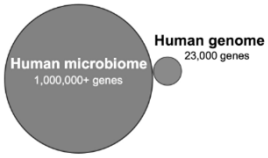
Human Microbiome

10^{13} Human Cells
10^{14} Bacterial Cells



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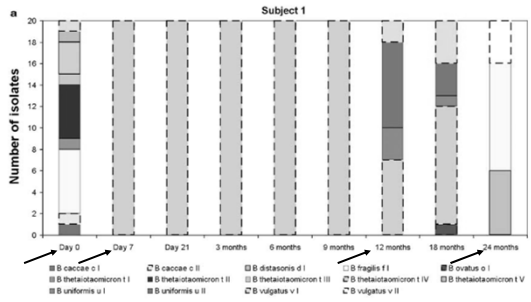
Diversity of Bacteroides Species in Gut After 7 day Course of Clindamycin



Microbiology (2010), 156, 3216–3223

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"Dysbiosis"

- Obesity
- Auto-immune dz
- Metabolic syndrome
- Diabetes
- IBD
- Asthma
- Allergy
- Autism

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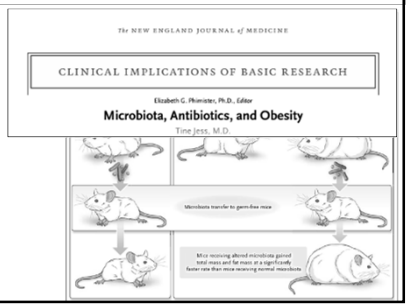
Do These Antibiotics Make Me Look Fat??

Mice given low dose penicillin before weaning become obese

Germ free mice exposed to the microbiome of the obese mice become obese



Cox et al. Cell 2014

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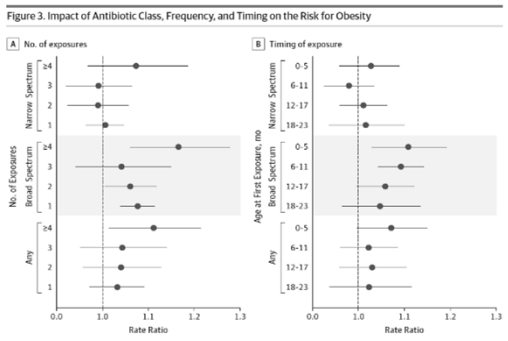

JAMA Pediatr. 2014;168(11):1063-1069

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BMJ Journals

Gut

Long-term use of antibiotics and risk of colorectal adenoma

Yin Cao[1, 2, 3], Kana Wu[3], Raaj Mehta[1, 2], David A Drew[1, 2], Mingyang Song[1, 2, 3], Paul Lochhead[1, 2], Long H Nguyen[1, 2], Jacques Izard[4], Charles S Fuchs[5, 6, 7], Wendy S Garrett[8, 9, 10], Curtis Huttenhower[9, 11], Shuji Ogino[8, 12, 13], Edward L Giovannucci[3, 12, 14], Andrew T

- Prevalence of colorectal adenomas on screening colonoscopy in the Nurses Health Study based on ≥ 2mos of antibiotic exposure at a younger age
- **36% increased risk** if received age 20-39
- **69% increased risk** if received age 40-59

Cao Y, *et al. Gut* 2017;**0**:1–7. doi:10.1136/gutjnl-2016-313413

23

Are doctors just being stupid?

Or Evil?

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Risks of not recognizing and treating early serious infection

Risks of over-diagnosis and treatment

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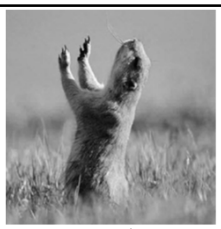

True Believer

We must come to the belief that casually writing for an antibiotic is not a benign act!

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Call for Antimicrobial Stewardship - Preserve a Precious Resource

CDC Centers for Disease Control and Prevention

IDSA

SHEA The Society for Healthcare Epidemiology of America

American Academy of Pediatrics

American Society of Consultant Pharmacists

shm Society of Hospital Medicine — Hospitalists. Transforming Healthcare. Revolutionizing Patient Care.

IDSOG

SIDP Society of Infectious Diseases Pharmacists

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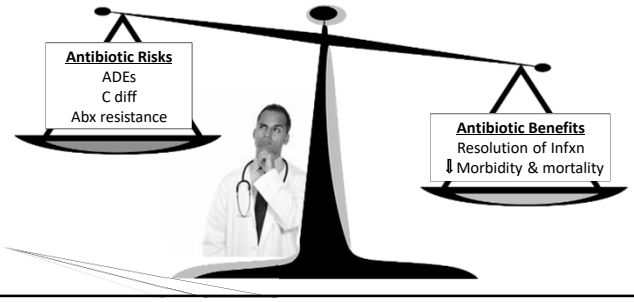
What Is Antimicrobial Stewardship?

Right Drug, Right Dose, Right Duration, Right Time, Every Time



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Antibiotic Time-Out

1. Does my patient really need an antibiotic?
2. If I am going to give an antibiotic, what is the most appropriate choice?
3. Can I revisit the situation in a couple days to assess clinical progress, cultures, and ability to adjust my antibiotics?
4. Have I set an appropriate duration of therapy?

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Antibiotic Time-Out

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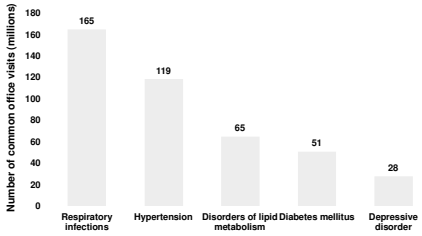
Respiratory Infections are the # 1 Reason for Office Visits



Source: Verispan PDDA 2004

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Nearly Two-thirds of all Oral Solid Antibiotic Prescriptions are for Sinusitis and Bronchitis

Source: SDI, FANDxRx. Based on all tablets/capsule antibiotics for the 52 weeks ending April 6, 2005

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How Do You Clinically Distinguish Bacterial Sinusitis From a VURI??

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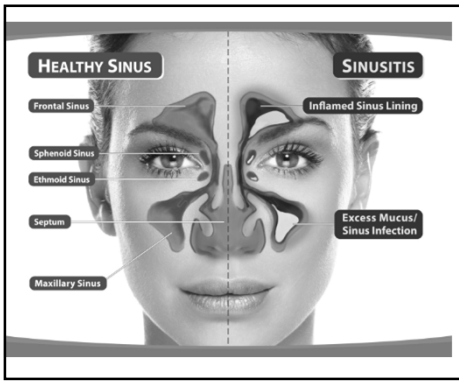

17 million Antibiotic Prescriptions Annually in U.S.

95% of patients at Sanford with acute uncomplicated sinusitis

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Predicting Acute Maxillary Sinusitis in General Practice

- 174 pts in GP office referred with suspected sinusitis
- 122 (70%) had "sinusitis" on CT scan and referred for antral puncture
- 92 (53%) had purulent/mucopurulent secretions (sinusitis)
  - 75% had positive culture for pathogen (only 39% of original suspected group!)
- No sx's, signs, historical features had any statistical correlation with dx of sinusitis

Hansen GJ. BMJ July 1995

35

Acute Uncomplicated Rhinosinusitis – Antibiotics Only If:

- Symptoms lasting ≥ 7-10 days, or
- 3-4 days of severe symptoms or high fever, or
- "Double-sickening" – start worsening after initial improvement

Guidelines from the AAO-Head and Neck Surgery 2015
Choosing Wisely - Abx for sinusitis
UK National Health Service

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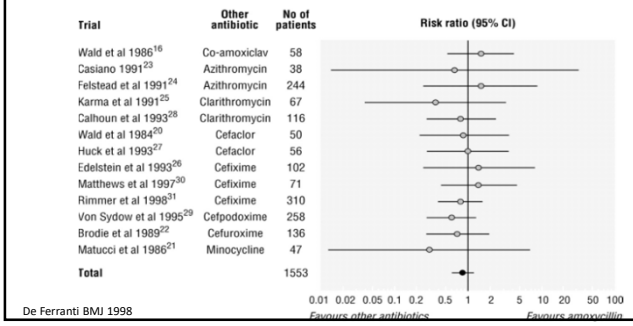
Benefits of Abx for Sinusitis Modest, and Increases AEs

- Cochrane review of 4 RCTs with Abx vs Placebo
  - 91% vs 86% cure or improvement at 7-15d
  - No benefit in duration of pain
  - Complication rates not different
  - Higher chance of adverse events (OR: 1.87-2.10). NNH - 8.1.

Ahovuo-Saoranta A, Rautakorpi UM, Borisenko OV, . Antibiotics for acute maxillary sinusitis in adults. Cochrane Database Syst Rev. 2014;11

37

Meta-Analysis of Amoxicillin vs Broad Spectrum Abx for Sinusitis



De Ferranti BMJ 1998

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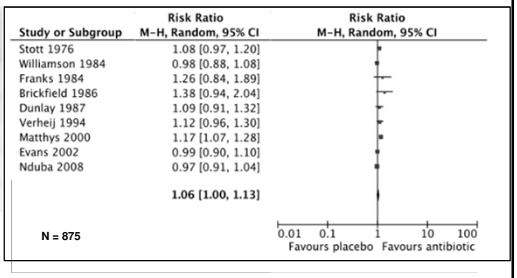
Acute Bronchitis: Meta-Analysis of Abx v. Placebo



Cochrane Review 2012

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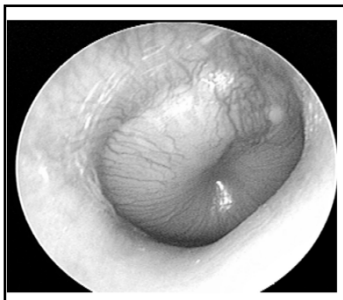

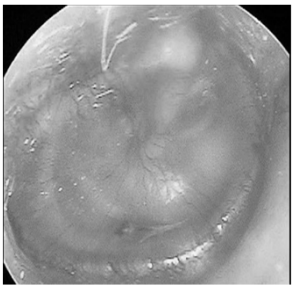

Acute Suppartive Otitis Media **Otitis Media with Effusion**

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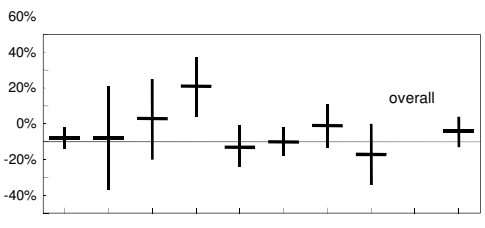
OME: Efficacy of Abx vs Placebo



Williams,JAMA 1993;270:1344

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Antimicrobials for AOM

- Meta-analysis of 5400 children from 33 randomized trials
- Endpoint: complete resolution in 7-14d
- Response Rate
  - Placebo 81%
  - Antibiotics 94.7%
  - Beta lactamase stable Abx No difference

Rosenfeld. J Ped 1994

42

AAP Recommendations for Watchful Waiting in AOM

- Child ≥ 2 mos old, or ≥ 6 mos if dx uncertain, and…
- Non-severe AOM
  - Unilateral disease
  - Mild pain < 48 hrs
  - Temp < 102.2 degrees F
- Consideration with parent for watchful waiting for 48-72 hrs

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TABLE 5. Comparative AOM Outcomes for Initial Observation Versus Antibacterial Agent*

AOM Outcome	Initial Antibacterial Therapy	Initial Observation	*P* Value
Symptomatic relief at 24 hours[37,72]	60%	59%	NS
Symptomatic relief at 2–3 days[72]	91%	87%	NS
Symptomatic relief at 4–7 days[72]	79%	71%	NS
Clinical resolution at 7–14 days[72]	82%	72%	NS
Pain duration, mean days[73]	2.8	3.3	NS
Crying duration, mean days[73]	0.5	1.4	<.001
Analgesic use, mean doses[66]	2.3	4.1	.004
Fever duration, median days[66]	2.0	3.0	.004
Incidence of mastoiditis or suppurative complications[1]	0.59%	0.17%	NS
Persistent MEE at 4–6 weeks[72]	45%	48%	NS
Persistent MEE at 3 months[72]	21%	26%	NS
Antibacterial-agent–induced diarrhea or vomiting[74]	16%	—	—
Antibacterial-agent–induced skin rash[74]	2%	—	—

* NS indicates not significant.

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Pharyngitis

- Grp A Strep Only in:
  - 37% of children
  - 18% of adults
- No antibiotics without a positive test

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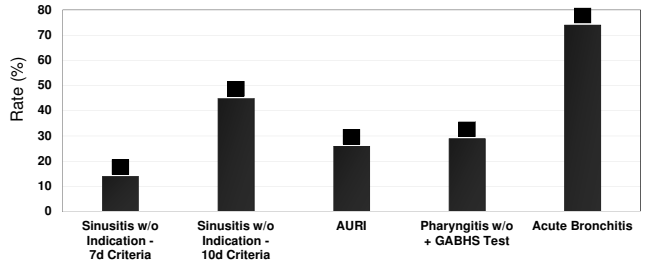
Rate of Unnecessary Antibiotic Prescribing in URIs Sanford Health - 2017-2018, N = 99,107



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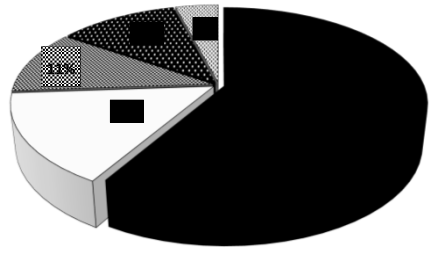
Antibiotic Use in Sinusitis Sanford Health, 2017-18, N=21,226



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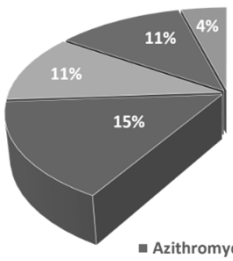
Second Line Antibiotic Use in 41% of Sinusitis Sanford Health, 2017-18, N=21,226



68% Have No PCN-Allergy

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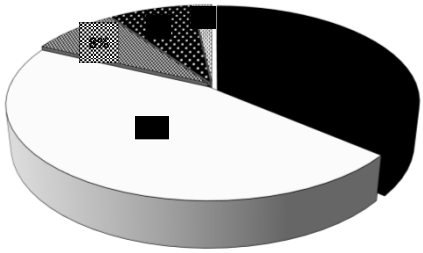
What Antibiotics Are Used in Bronchitis/Pharyngitis/AURI

Sanford Health, June 2017 - May 2018, N=32,360



■ Penicillins □ Macrolides ▨ CPs ▪ TCNs ⊠ FQs

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Appropriate Antibiotic

Condition	1st Line Antibiotic	2nd Line Antibiotic
Acute Otitis Media	Amoxicillin (80-90mg/kg/d)	Cefdinir, Cefuroxime, Cefpodoxime
Acute Bacterial Sinusitis	Amoxicillin Amoxicillin clavulanate	Doxycycline
Pharyngitis	Penicilliin V Benzathine Penicillin	Cephalexin Clindamycin

MIA: "Z-Pak" - Azithromycin and Quinolones

Are alternative in some pharyngitis/otitis guidelines if Type-I IgE PCN allergy

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Fluoroquinolone Risk

FDA BLACK BOX WARNING

Condition	Relative Risk
Achilles tendon rupture	
Current exposure overall	4.3 (95% CI, 2.4-7.8)
Age 60-79	6.4 (95% CI, 3.0-13.7)
Age > 80	20.4 (95% CI, 4.6-90.1)

Since 2016, the FDA has advised that the serious risk for side effects associated with fluoroquinolone antibacterial drugs generally outweigh the benefits for patients with acute sinusitis, acute bronchitis, and uncomplicated urinary tract infections who have other treatment options.

7/10/18, new FDA label changes:
- ***Hypoglycemia - potentially leading to coma***
- ***Mental health side effects: attention, disorientation, agitation, nervousness, delirium***

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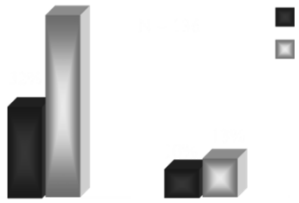
Bacteriologic Failure by Tympanocentesis Day 4-6 in Rx of AOM



Dagan. PIDJ Apr 2000

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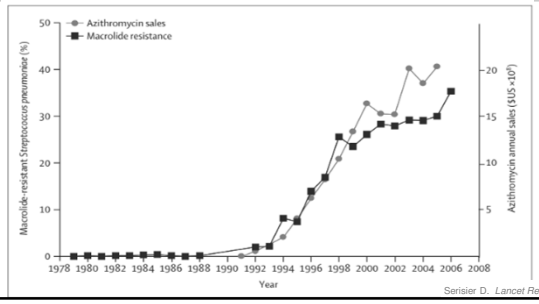
Azithromycin Global Sales and Pneumococcal Macrolide Resistance



Serisier D. *Lancet Resp Med* 2013

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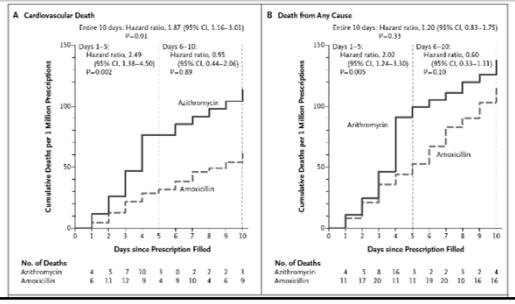
Cumulative Incidence of CV Death and any Death in Patients Who Took Azithromycin



Ray W. *NEJM* 2012

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Antibiotic Time-Out

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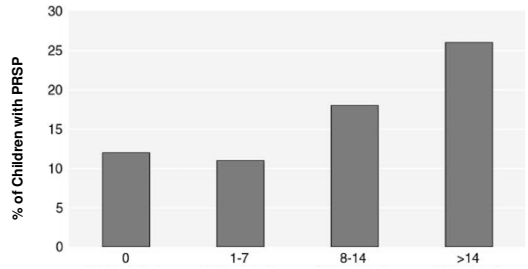
Antibiotic Exposure/Duration in Children and Risk of Carrying Penicillin-Resistant Pneumococcus



Nasrin D. BMJ 2002

56

Duration of Therapy
It May Be Shorter Than You Think!

Disease	Duration of Treatment (days) Short	Long
Pharyngitis	3-6	10
Acute Sinusitis	5-7	10
COPD exacerbation	≤ 5	≥ 7
CAP	3-5	7-10
HCAP, HAP	≤ 8	10-15
Cellulitis	5-6	10
UTI – Cystitis	5 days (macrodantin) 3 days (TMP-SMX, quinolones)	7
UTI – Pyelonephritis	5 days (quinolones)	14 days (TMP-SMX, or Beta lactam)
Peritonitis	4-7 days after source control	10

Altimimi S. Cochrane Database 2012
Spellberg B. JAMA Int Med 2016

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Conclusions

- Most URIs are viral, not bacterial
- Even when we think they're bacterial, we are usually wrong
- Even when they are bacterial, they frequently will get better on their own
- Amoxicillin, usu at high dose, w or w/o clavulanate, is the DOC for most URIs
- Giving Azithromycin is essentially giving a placebo
  - Rare exceptions are for atypical infections (mainly LRTI) and Pertussis
- Shorter courses work most of the time and lessen risk of resistance

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Patient Education Resources

- CDC's Get Smart Patient Education (office posters, fact sheets, viral "prescription pads"
  - https://www.cdc.gov/getsmart/community/materials-references/print-materials/hcp/index.html
- ABIM/Consumer Reports Choosing Wisely patient education handouts (excellent!)
  - http://www.choosingwisely.org/wp-content/uploads/2018/02/Colds-Flu-And-Other-Respiratory-Illnesses-In-Adults-IDSA.pdf

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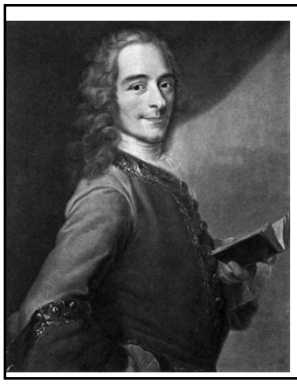

The art of medicine is to amuse the patient while nature cures the disease

Voltaire

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