The Rise and Fall of the Z-Pak:
Updates in Antibiotic Guidelines for Common Urgent Care Conditions Worth Knowing

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Disclosure

I have no financial interests or relationships to disclose.

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Learning Objectives

1. Understand recent changes away from azithromycin use in antibiotic guidelines for the treatment of common bacterial infections encountered in Urgent Care
2. Develop familiarity with the few remaining indications of azithromycin
3. Identify the common and less common, but dangerous, adverse reactions associated with azithromycin

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Can we accurately gauge patient expectations?

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INFECTIOUS DISEASE/ORIGINAL RESEARCH

Antibiotic Use for Emergency Department Patients With Upper Respiratory Infections: Prescribing Practices, Patient Expectations, and Patient Satisfaction

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EMERGEncy ID NET Study Group

From Olive View–University of California Los Angeles Medical Center, Sylmar, CA (Ong, Nakase, Moran, Talan); Temple University School of Medicine, Philadelphia, PA (Karras); and the Centers for Disease Control and Prevention (Kuenhert).

Study objective: Physicians often prescribe antibiotics to patients even when there is no clear indication for their use. Previous studies examining antibiotic use in acute bronchitis and upper respiratory infections have been conducted in primary care settings. We evaluate the factors that physicians in the emergency department (ED) consider when prescribing antibiotics (eg, patient expectations) and the factors associated with patient satisfaction.

Methods: Ten academic EDs enrolled adults and children presenting with symptoms consistent with upper respiratory infection. Enrolled patients were interviewed before their physician encounter and were reinterviewed before discharge and 2 weeks later. Physicians were interviewed about factors that influenced their management decisions, including their perceptions of patients' expectations. Patients with a single diagnosis of uncomplicated acute bronchitis or upper respiratory infection were included for analysis.

Results: Of 272 patients enrolled, 68% of bronchitis patients and 9% of upper respiratory infection patients received antibiotics. Physicians were more likely to prescribe antibiotics when they believed that patients expected them (odds ratio [OR] 5.3; 95% confidence interval [CI] 2.9 to 9.6), although they were able to correctly identify only 27% of the patients who expected antibiotics. Satisfaction with the ED visit was reported by 87% of patients who received antibiotics and 89% of those not receiving antibiotics. Satisfaction with the visit was reported by 92% of patients who believed they had a better understanding of their illness but only by 72% of those who thought they had no better understanding (OR 4.4; 95% CI 2.0 to 8.4).

Conclusion: Physicians in our academic EDs prescribed antibiotics to 68% of acute bronchitis patients and to fewer than 10% of upper respiratory infection patients. Physicians were more likely to prescribe antibiotics to patients who they believed expected them, although they correctly identified only about 1 in 4 of those patients. Patient satisfaction was not related to receipt of antibiotics but was related to the belief they had a better understanding of their illness. [Ann Emerg Med. 2007;50:213-220.]

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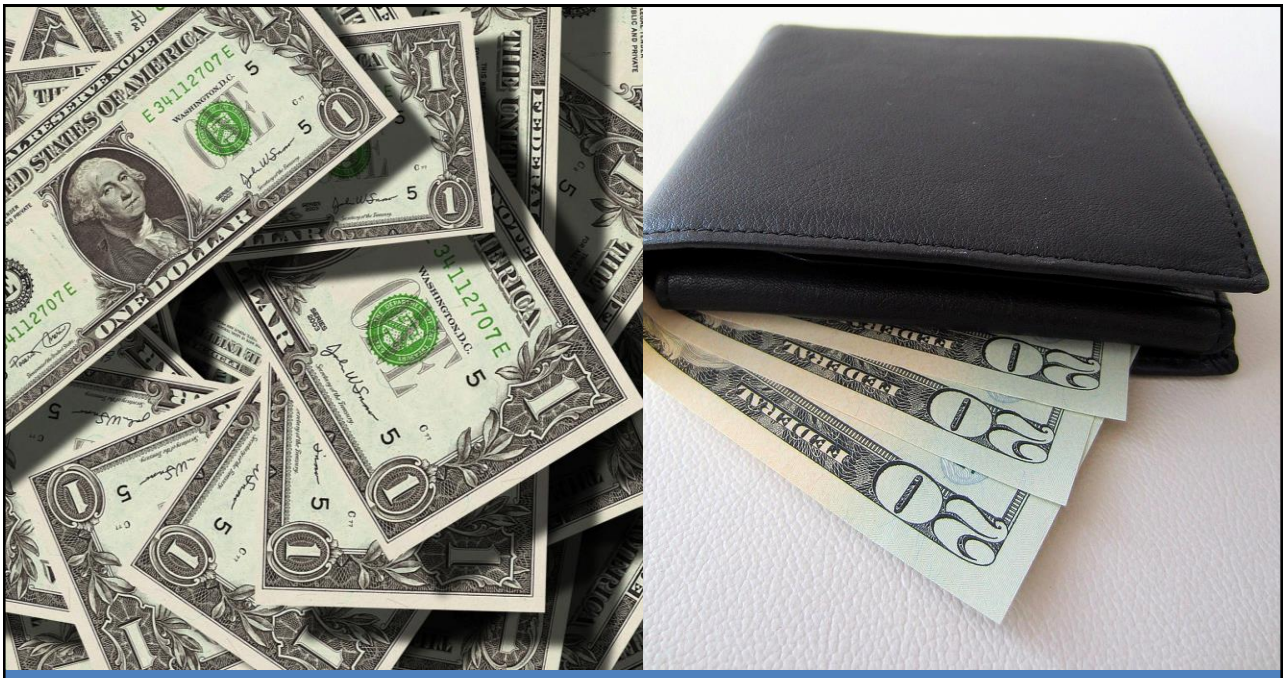

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ORIGINAL INVESTIGATION

ONLINE FIRST

The Cost of Satisfaction

A National Study of Patient Satisfaction, Health Care Utilization, Expenditures, and Mortality

Joshua J. Fenton, MD, MPH; Anthony F. Jerant, MD; Klea D. Bertakis, MD, MPH; Peter Franks, MD

Scan for Author Audio Interview

Background: Patient satisfaction is a widely used health care quality metric. However, the relationship between patient satisfaction and health care utilization, expenditures, and outcomes remains ill defined.

Methods: We conducted a prospective cohort study of adult respondents (N = 51 946) to the 2000 through 2007 national Medical Expenditure Panel Survey, including 2 years of panel data for each patient and mortality follow-up data through December 31, 2006, for the 2000 through 2005 subsample (n = 30 428). Year 1 patient satisfaction was assessed using 5 items from the Consumer Assessment of Health Plans Survey. We estimated the adjusted associations between year 1 patient satisfaction and year 2 health care utilization (any emergency department visits and any inpatient admissions), year 2 health care expenditures (total and for prescription drugs), and mortality during a mean follow-up duration of 3.9 years.

Results: Adjusting for sociodemographics, insurance status, availability of a usual source of care, chronic disease burden, health status, and year 1 utilization and expenditures, respondents in the highest patient satisfaction quartile (relative to the lowest patient satisfaction quartile) had lower odds of any emergency department visit (adjusted odds ratio [aOR], 0.92; 95% CI, 0.84-1.00), higher odds of any inpatient admission (aOR, 1.12; 95% CI, 1.02-1.23), 8.8% (95% CI, 1.6%-16.6%) greater total expenditures, 9.1% (95% CI, 2.3%-16.4%) greater prescription drug expenditures, and higher mortality (adjusted hazard ratio, 1.26; 95% CI, 1.05-1.53).

Conclusion: In a nationally representative sample, higher patient satisfaction was associated with less emergency department use but with greater inpatient use, higher overall health care and prescription drug expenditures, and increased mortality.

Arch Intern Med. 2012;172(5):405-411.
Published online February 13, 2012.
doi:10.1001/archinternmed.2011.1662

WHILE MOST HEALTH care quality metrics assess care processes and health outcomes, patient experience or satisfaction is considered a complementary measure of health care quality.[1] Patient satisfaction data may empower consumers to compare health plans

See also page 435

See Invited Commentary at end of article

and physicians,[1,2] and both the Centers for Medicare & Medicaid Services and the National Committee on Quality Assurance require participating health plans to publicly report patient satisfaction data.[3] Health plans use patient satisfaction surveys to evaluate physicians and to determine incentive compensation, and consumer-oriented Web sites often report patient satisfaction ratings as the sole physician comparator.

Satisfied patients are more adherent to physician recommendations and more loyal to physicians,[4,5] but research suggests a tenuous link between patient satisfaction and health care quality and outcomes.[3,6,7] Among a vulnerable older population, patient satisfaction had no association with the technical quality of geriatric care,[8] and evidence suggests that satisfaction has little or no correlation with Health Plan Employer Data and Information Set quality metrics.[3,7]

In addition, patients often request discretionary services that are of little or no medical benefit, and physicians frequently accede to these requests, which is associated with higher patient satisfaction.[9,10] Physicians whose compensation is more strongly linked with patient satisfaction are more likely to deliver discretionary services, such as advanced imaging for acute low back pain.[11]

Author Affiliations: Department of Family and Community Medicine and Center for Healthcare Policy and Research, University of California–Davis, Sacramento.

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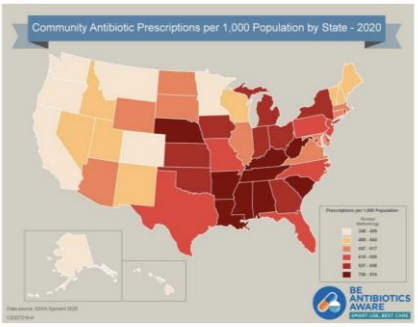
Region	NUMBER OF ANTIBIOTIC PRESCRIPTIONS (MILLIONS)	ANTIBIOTIC PRESCRIPTIONS PER 1,000 PERSONS, RATE
Northeast	41.1	721
Midwest	49.5	719
South	106.2	825
West	39.5	502

1. Antibiotic prescriptions per 1000 persons by state (sextiles) for all ages — United States,



Some of Us Have It Easier Than Others

Source: CDC, 2022

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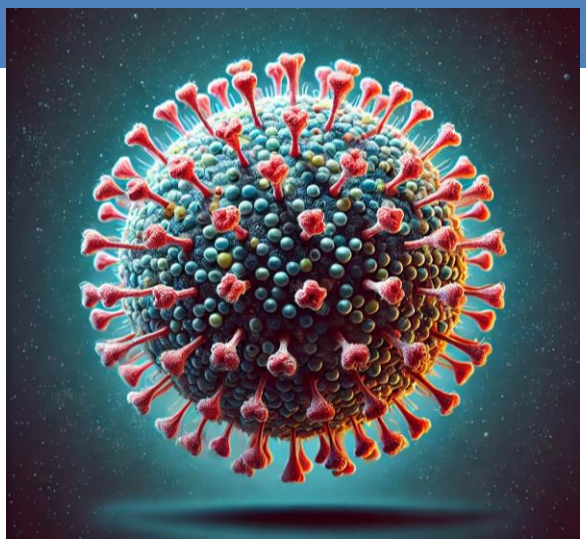

Did COVID Usher In a New Era of Antibiotic Stewardship?

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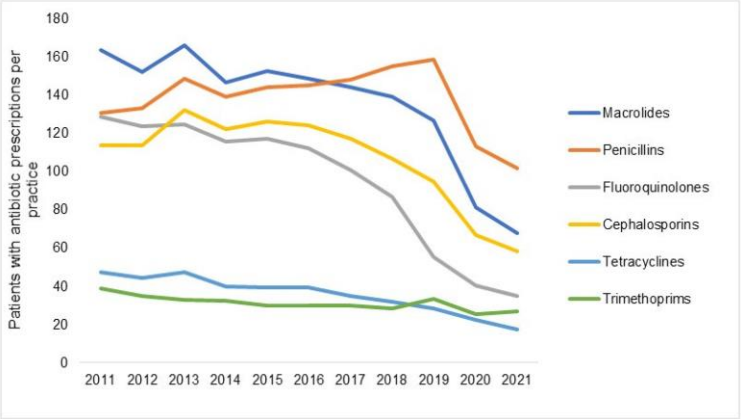
COVID-19 & Antibiotic Utilization



Tanislav C, Rosenbauer J, Kostev K. The COVID-19 Pandemic Enhanced the Decade-Long Trend of the Decreasing Utilization of Antibiotics. *Antibiotics*. 2023; 12(5):927.

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PROVIDER SPECIALTY	NUMBER OF ANTIBIOTIC PRESCRIPTIONS (MILLIONS)	ANTIBIOTIC PRESCRIPTIONS PER PROVIDER, RATE
Primary Care Physicians	110.8	466
Physician Assistants and Nurse Practitioners	62.9	363
Surgical Specialties	19.5	219
Dentistry	25.1	205
Emergency Medicine	14.8	457
Dermatology	7.1	628
Obstetrics/Gynecology	6.3	167
Other	22.9	110
All Providers	269.4	295

Source: CDC, 2015

Table 3. Oral antibiotic prescribing by provider specialty — United States, 2020

Provider Specialty	Number of Antibiotic Prescriptions (Millions)	Antibiotic Prescriptions Per Provider, Rate
Primary Care Physicians	64.1	270
Physician Assistants & Nurse Practitioners	62.3	360
Surgical Specialties	15.3	172
Dentistry	23.4	191
Emergency Medicine	9.5	295
Dermatology	5.6	496
Obstetrics/Gynecology	4.6	123
Other	17.0	82
All Providers[a]	201.9	221

[a] Total may not add to all oral prescriptions (201.9 million) due to rounding.

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Total Annual Azithromycin Prescriptions

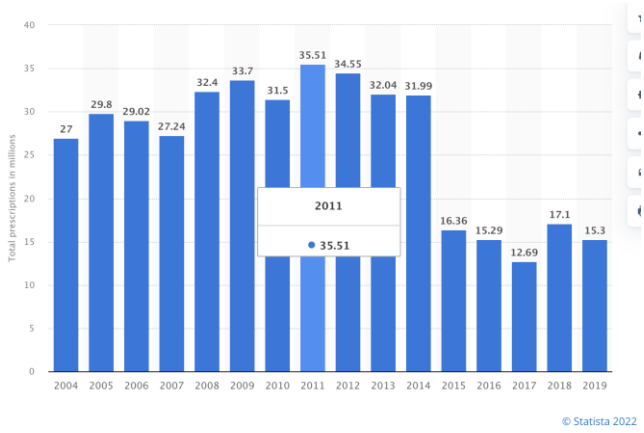

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Table 2. Top oral antibiotic classes and agents—United States, 2020

Characteristics: Antibiotic class	Number of Antibiotic Prescriptions (Millions)	Antibiotic Prescriptions Per 1,000 Persons, Rate
Penicillins	43.2	131
Cephalosporins	30.2	92
Macrolides	29	88
Tetracycline	22.7	69
B-lactams, increased activity	21	64
Characteristics: Antibiotic agent	**Number of Antibiotic Prescriptions (Millions)**	**Antibiotic Prescriptions Per 1,000 Persons, Rate**
Amoxicillin	39.3	119
Azithromycin	27.6	84
Amoxicillin\clavulanic acid	21	64
Cephalexin	19.6	60
Doxycycline	19.5	59

Source: CDC, 2020

ANTIBIOTIC CLASS	NUMBER OF ANTIBIOTIC PRESCRIPTIONS (MILLIONS)	ANTIBIOTIC PRESCRIPTIONS PER 1,000 PERSONS, RATE
Penicillins	53.2	159
Macrolides	36.1	108
Cephalosporins	36.0	108
B-lactams, increased activity	28.7	86
Tetracyclines	27.1	81

ANTIBIOTIC AGENT	NUMBER OF ANTIBIOTIC PRESCRIPTIONS (MILLIONS)	ANTIBIOTIC PRESCRIPTIONS PER 1,000 PERSONS, RATE
Amoxicillin	49.8	149
Azithromycin	34.9	105
Amoxicillin clavulanic acid	28.7	86
Doxycycline	24.1	72
Cephalexin	21.0	63

Source: CDC, 2022

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Table 3. Oral antibiotic prescribing by provider specialty[a] – United States, 2022

PROVIDER SPECIALTY	NUMBER OF ANTIBIOTIC PRESCRIPTIONS (MILLIONS)	ANTIBIOTIC PRESCRIPTIONS PER PROVIDER, RATE
Physician Assistants and Nurse Practitioners	84.4	165
Primary Care Physicians	70.0	179
Dentistry	25.2	127
Surgical Specialties	16.4	115
Emergency Medicine	12.0	182
Dermatology	5.4	299
Obstetrics/Gynecology	4.5	81
Other	18.5	27
All Healthcare Professionals	236.4	114

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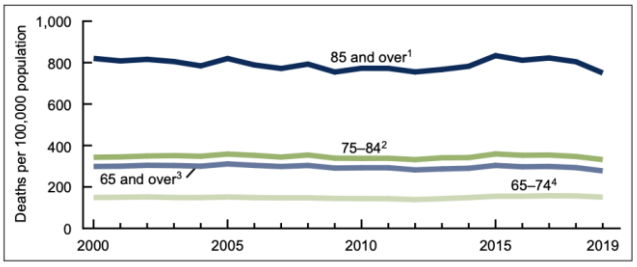
Sepsis Related Mortality By Year

Figure 1. Sepsis-related death rates for adults aged 65 and over, by age group: United States, 2000–2019



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Pneumonia Related Mortality by Year

Year	Deaths	Population	Crude Rate Per 100,000	Age Adjusted Rate Per 100,000
1999	63,730	279,040,168	22.8	23.5
2000	65,313	281,421,906	23.2	23.7
2001	62,034	284,968,955	21.8	22.2
2002	65,681	287,625,193	22.8	23.2
2003	65,163	290,107,933	22.5	22.6
2004	59,664	292,805,298	20.4	20.4
2005	63,001	295,516,599	21.3	21.0
2006	56,326	298,379,912	18.9	18.4
2007	52,717	301,231,207	17.5	16.8
2008	56,284	304,093,966	18.5	17.6
2009	53,692	306,771,529	17.5	16.5
2010	50,097	308,745,538	16.2	15.1
2011	53,826	311,591,917	17.3	15.7
2012	50,636	313,914,040	16.1	14.4
2013	56,979	316,128,839	18.0	15.9
2014	55,227	318,857,056	17.3	15.1
2015	57,062	321,418,820	17.8	15.2
2016	51,537	323,127,513	15.9	13.5
2017	55,672	325,719,178	17.1	14.3
2018	59,120	327,167,434	18.1	14.9
Total	1,153,761	6,088,633,001	18.9	17.7

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The Rise of the Z-Pak…

- Synthetic Macrolide developed by Pliva Pharmaceuticals, Yugoslavia in 1981
- Licensed to Pfizer in 1991 – Z-Pak is born…
- Activity at 50S Ribosomal Subunit
- Clinically Favorable Profile
  - Delivered by phagocytes
  - Active at low pH
  - Long tissue half-life
- Rapidly became among top 5 most commonly prescribed antibiotics…

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Azithromycin Resistance

- Population Level:
  - Rapid Emergence of Resistance of *S. pneumoniae* (& *S. pyogenes)* in 90's
  - Ribosomal Methylation (erm) or Efflux Pumping (mef)
  - Range of *S. PNA R*esistance from 10 – > 90% based on region
- Individual Level:
  - Asymptomatic Pneumococcal Carriage Rates up to 90%

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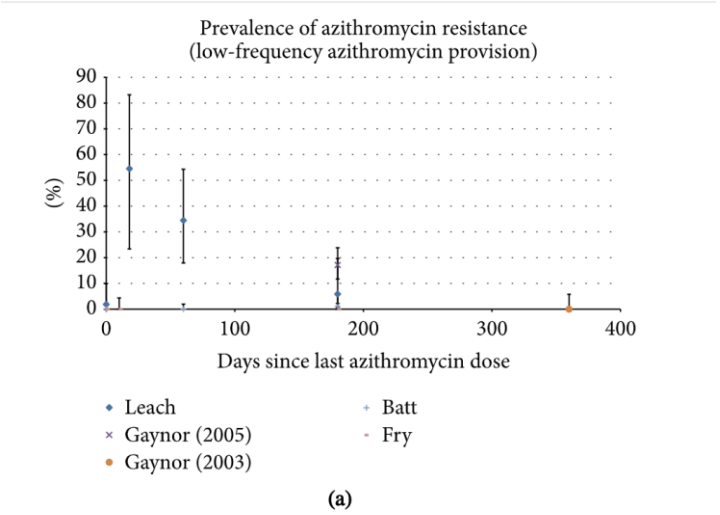
Pneumococcal Resistance

Derek K-H. Ho et al, "Antibiotic Resistance in *Streptococcus pneumoniae* after Azithromycin Distribution for Trachoma", *Journal of Tropical Medicine*, vol. 2015, Article ID 917370, 8 pages, 2015. https://doi.org/10.1155/2015/917370



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"Gimme a Z-Pak to Knock It Down"

Common Z-Pak Requests:

- Sinusitis
- Cough/Bronchitis
- AOM - in PCN allergy
- Strep - in PCN allergy
- Chlamydia

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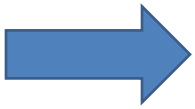

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use ZITHROMAX® safely and effectively. See full prescribing information for ZITHROMAX.

ZITHROMAX (azithromycin) 250 mg and 500 mg tablets, for oral use
ZITHROMAX (azithromycin) for oral suspension
Initial U.S. Approval: 1991

RECENT MAJOR CHANGES

Warnings and Precautions, Cardiovascular Death (5.5) 11/2021

INDICATIONS AND USAGE

ZITHROMAX is a macrolide antibacterial drug indicated for mild to moderate infections caused by designated, susceptible bacteria:

- Acute bacterial exacerbations of chronic bronchitis in adults (1.1)
- Acute bacterial sinusitis in adults (1.1)
- Uncomplicated skin and skin structure infections in adults (1.1)
- Urethritis and cervicitis in adults (1.1)
- Genital ulcer disease in men (1.1)
- Acute otitis media in pediatric patients (6 months of age and older) (1.2)
- Community-acquired pneumonia in adults and pediatric patients (6 months of age and older) (1.1, 1.2)
- Pharyngitis/tonsillitis in adults and pediatric patients (2 years of age and older) (1.1, 1.2)

Limitation of Use:
Azithromycin should not be used in patients with pneumonia who are judged to be inappropriate for oral therapy because of moderate to severe illness or risk factors. (1.3)
To reduce the development of drug-resistant bacteria and maintain the effectiveness of ZITHROMAX (azithromycin) and other antibacterial drugs, ZITHROMAX (azithromycin) should be used only to treat infections that are proven or strongly suspected to be caused by susceptible bacteria. (1.4)

DOSAGE AND ADMINISTRATION

- **Adult Patients (2.1)**

Infection	Recommended Dose/Duration of Therapy
Community-acquired pneumonia (mild severity) Pharyngitis/tonsillitis (second-line therapy) Skin/skin structure (uncomplicated)	500 mg as a single dose on Day 1, followed by 250 mg once daily on Days 2 through 5.
Acute bacterial exacerbations of chronic bronchitis (mild to moderate)	500 mg as a single dose on Day 1, followed by 250 mg once daily on Days 2 through 5 or 500 mg once daily for 3 days.
Acute bacterial sinusitis	500 mg once daily for 3 days.
Genital ulcer disease (chancroid) Non-gonococcal urethritis and cervicitis	One single 1 gram dose.
Gonococcal urethritis and cervicitis	One single 2 gram dose.

- **Pediatric Patients (2.2)**

Infection	Recommended Dose/Duration of Therapy
Acute otitis media (6 months of age and older)	30 mg/kg as a single dose or 10 mg/kg once daily for 3 days or 10 mg/kg as a single dose on Day 1 followed by 5 mg/kg/day on Days 2 through 5.
Acute bacterial sinusitis (6 months of age and older)	10 mg/kg once daily for 3 days.
Community-acquired pneumonia (6 months of age and older)	10 mg/kg as a single dose on Day 1 followed by 5 mg/kg once daily on Days 2 through 5.
Pharyngitis/tonsillitis (2 years of age and older)	12 mg/kg once daily for 5 days.

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Acute Bacterial Sinusitis (ABRS)

- *Acute Sinusitis*: Inflammation in the nasal cavity and paranasal sinuses lasting <4 weeks
- ABRS def (IDSA):
  - 10 days of illness **w/o improvement**
  - **Severe symptoms** (facial pain, purulent discharge) **AND** Fevers >39C x **3-4d**
  - **"Double sickening"** (new onset fever, facial pain, headache after URI)
- <2% of cases are bacterial **& 80%** of ABRS resolves w/I 2 weeks w/o ABX !!
- Consider risk of complications: Advanced age, diabetes, immunosuppression

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ABRS: What Do the Guidelines Say?

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Distribution of pathogens in acute bacterial rhinosinusitis in adults

Pathogen	Incidence (%)
Streptococcus pneumoniae	20 to 43
Haemophilus influenzae	22 to 36
Moraxella catarrhalis	2 to 16
Staphylococcus aureus	10 to 13
Streptococcus pyogenes	3

Distribution of pathogens in acute bacterial rhinosinusitis based upon culture results.

Data from:

1. Hadley JA, Meages R, Desrosiers M, et al. Moxifloxacin five-day therapy versus placebo in acute bacterial rhinosinusitis. Laryngoscope 2010; 120:1057.
2. Rosenfeld RM, Piccirillo JF, Chandrasekhar SS, et al. Clinical practice guideline (update): Adult sinusitis. Otolaryngol Head Neck Surg 2015; 152:S1.

- AAO-HNS (2015) & IDSA (2012) & ACP/CDC High Value Care Task Force (2016)

1. Treat only ABRS
2. Treat Immediately (IDSA) or Watch & Wait x 7 days (AAO-HNS)
   - Watchful waiting only if immunocompetent and good follow-up
3. **"Azithromycin/macrolides NOT recommended for empiric therapy due to high rates of S. pneumoniae resistance"**

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ABRS: What Do the Guidelines Say?

- **Amoxicillin/Clavulanate 875mg BID** (NOT amoxicillin alone – Resistance in H. flu and M. catarrhalis)
- **Doxycycline 100mg BID (PCN allergy/alternate first line)**
- Cefpodoxime 200mg BID

***Levofloxacin 500mg daily (only if unable to tolerate other alternatives due to FQ risks)*

Duration: 5-7 days

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Community-Acquired Pneumonia (CAP)

- **Clinical diagnosis** with constellation of findings: fever, dyspnea, cough, sputum production, abnormal lung sounds, abnormal cxr findings
- *"Clinicians should not perform testing or initiate antibiotic therapy in patients with bronchitis unless pneumonia is suspected."* **ACP/CDC High Value Care Task Force, 2016**
- **Remember to educate:** Up to 3-4 weeks of cough is expected with bronchitis
- **Azithromycin is NOT recommended for outpatients (or inpatients) with COVID-19.**

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CAP: What Do the Guidelines Say?

2019 ATS/IDSA Joint Guideline Updates on Treatment of CAP:

- **Amoxicillin 1g TID -OR- Doxycycline 100mg BID x 5 days** (healthy, <65yo w/o recent antibiotic use)
- *Azithromycin/Macrolide ONLY Recommended if Local S. Pneumoniae resistance <25%*
- **Dual Therapy for >65 and/or co-morbidities and/or recent antibiotic use:**
  - Amox/clav -OR- 3rd gen cephalosporin **PLUS** Doxycycline -OR- Macrolide
  - ** *Monotherapy with respiratory fluoroquinones (e.g. levofloxacin)*

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Penicillins in Urgent Care

- Strep Pharyngitis
  - Preferred first line: Penicillin VK (or Amoxicillin)
  - *Macrolide resistant S. pyogenes*
- Acute Otitis Media
  - Preferred first line: Amoxicillin (+/- Clavulanate)
  - *Macrolide resistant S. pneumoniae*

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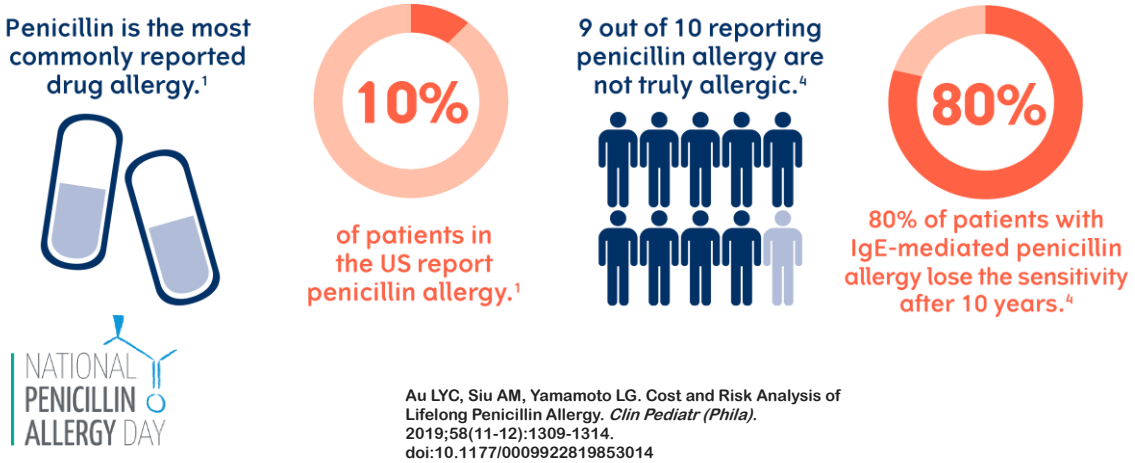
"I'm Allergic to Penicillin"



Au LYC, Siu AM, Yamamoto LG. Cost and Risk Analysis of Lifelong Penicillin Allergy. *Clin Pediatr (Phila).* 2019;58(11-12):1309-1314. doi:10.1177/0009922819853014

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Consequences of 'Penicillin Allergy'

- Higher Lifelong Healthcare Spending
- Higher Rates of Broad Spectrum & Quinolone Abx Exposure
- Higher Rates of *C. difficile*

Au LYC, Siu AM, Yamamoto LG. Cost and Risk Analysis of Lifelong Penicillin Allergy. *Clin Pediatr (Phila)*. 2019;58(11-12):1309-1314. doi:10.1177/0009922819853014

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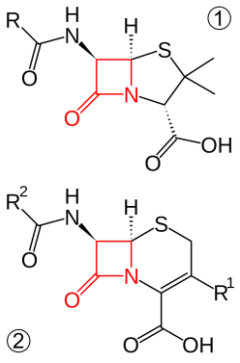
Guidelines: De-Label When Able

Penicillin Risk Assessment

1. Allergy vs. Adverse Reaction/Intolerance (e.g. GI upset) ➔ PCN and Amoxicillin Safe
2. Mild/Delayed Hypersensitivity (e.g. maculopapular rash) ➔ PO Test Dose of PCN or Cephalosporin
   - **Cephalosporin/Penicillin Cross Reactivity (mostly) Myth**
     - *97% w/ true PCN allergy tolerate cephalosporins*
   - **Refer to Allergist for Formal Testing**
1. Immediate/IgE Mediated (e.g. hives, anaphylaxis) ➔ PO Test Dose of 3rd generation cephalosporin
2. Non-Allergic Severe Reaction (e.g. TEN, SJS, DRESS) ➔ Avoid ALL B-lactams



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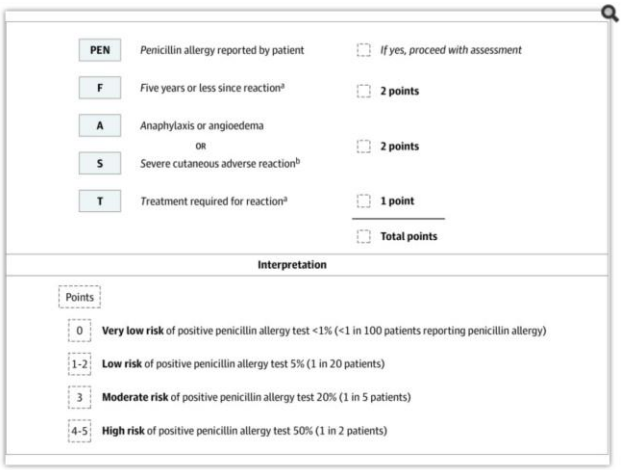
Penicillin Allergy Risk : 'PEN-FAST'



PEN	Penicillin allergy reported by patient	☐ *If yes, proceed with assessment*
F	Five years or less since reaction[a]	☐ **2 points**
A	Anaphylaxis or angioedema	
OR		☐ **2 points**
S	Severe cutaneous adverse reaction[b]	
T	Treatment required for reaction[a]	☐ **1 point**
		☐ **Total points**

Interpretation

Points	
0	**Very low risk** of positive penicillin allergy test <1% (<1 in 100 patients reporting penicillin allergy)
1-2	**Low risk** of positive penicillin allergy test 5% (1 in 20 patients)
3	**Moderate risk** of positive penicillin allergy test 20% (1 in 5 patients)
4-5	**High risk** of positive penicillin allergy test 50% (1 in 2 patients)

Trubiano JA, Vogrin S, Chua KYL, et al. Development and Validation of a Penicillin Allergy Clinical Decision Rule. *JAMA Intern Med*. 2020;180(5):745-752. doi:10.1001/jamainternmed.2020.0403

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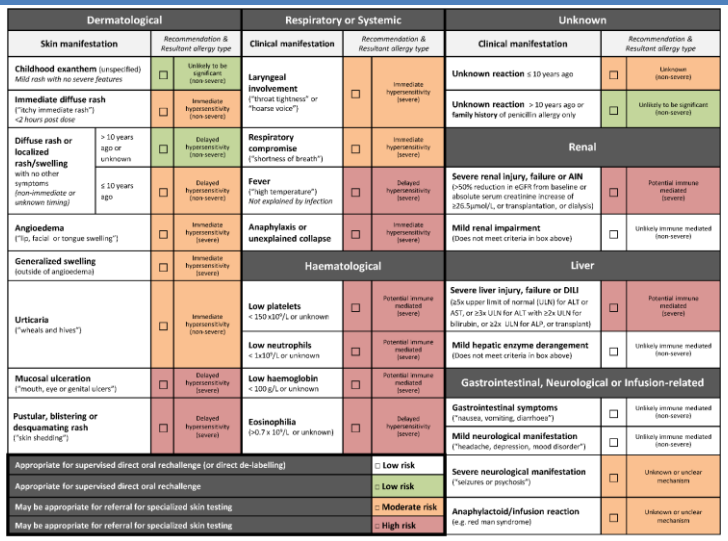
De-Labeling Guidelines

Chua, KY et al. "The Penicillin Allergy Delabeling Program: A Multicenter Whole-of-Hospital Health Services Intervention and Comparative Effectiveness Study." *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America* vol. 73,3 (2021): 487-496.



Dermatological				Respiratory or Systemic			Unknown		
Skin manifestation		Recommendation & Resultant allergy type		Clinical manifestation	Recommendation & Resultant allergy type		Clinical manifestation	Recommendation & Resultant allergy type	
Childhood exanthem (unspecified) *Mild rash with no severe features*		☐	Unlikely to be significant (non-severe)	**Laryngeal involvement** ("throat tightness" or "hoarse voice")	☐	Immediate hypersensitivity (severe)	**Unknown reaction** ≤ 10 years ago	☐	Unknown (non-severe)
Immediate diffuse rash ("itchy immediate rash") *<2 hours post dose*		☐	Immediate hypersensitivity (non-severe)				**Unknown reaction** > 10 years ago or **family history** of penicillin allergy only	☐	Unlikely to be significant (non-severe)
Diffuse rash or localized rash/swelling with no other symptoms *(non-immediate or unknown timing)*	> 10 years ago or unknown	☐	Delayed hypersensitivity (non-severe)	**Respiratory compromise** ("shortness of breath")	☐	Immediate hypersensitivity (severe)	**Renal**		
	≤ 10 years ago	☐	Delayed hypersensitivity (non-severe)	**Fever** ("high temperature") *Not explained by infection*	☐	Delayed hypersensitivity (severe)	**Severe renal injury, failure or AIN** (>50% reduction in eGFR from baseline or absolute serum creatinine increase of ≥26.5μmol/L, or transplantation, or dialysis)	☐	Potential immune mediated (severe)
Angioedema ("lip, facial or tongue swelling")		☐	Immediate hypersensitivity (severe)	**Anaphylaxis or unexplained collapse**	☐	Immediate hypersensitivity (severe)	**Mild renal impairment** (Does not meet criteria in box above)	☐	Unlikely immune mediated (non-severe)
Generalized swelling (outside of angioedema)		☐	Immediate hypersensitivity (severe)	**Haematological**			**Liver**		
Urticaria ("wheals and hives")		☐	Immediate hypersensitivity (non-severe)	**Low platelets** < 150 x10⁹/L or unknown	☐	Potential immune mediated (severe)	**Severe liver injury, failure or DILI** (≥5x upper limit of normal (ULN) for ALT or AST, or ≥3x ULN for ALT with ≥2x ULN for bilirubin, or ≥2x ULN for ALP, or transplant)	☐	Potential immune mediated (severe)
				Low neutrophils < 1x10⁹/L or unknown	☐	Potential immune mediated (severe)	**Mild hepatic enzyme derangement** (Does not meet criteria in box above)	☐	Unlikely immune mediated (non-severe)
Mucosal ulceration ("mouth, eye or genital ulcers")		☐	Delayed hypersensitivity (severe)	**Low haemoglobin** < 100 g/L or unknown	☐	Potential immune mediated (severe)	**Gastrointestinal, Neurological or Infusion-related**		
Pustular, blistering or desquamating rash ("skin shedding")		☐	Delayed hypersensitivity (severe)	**Eosinophilia** (>0.7 x 10⁹/L or unknown)	☐	Delayed hypersensitivity (severe)	**Gastrointestinal symptoms** ("nausea, vomiting, diarrhoea")	☐	Unlikely immune mediated (non-severe)
							Mild neurological manifestation ("headache, depression, mood disorder")	☐	Unlikely immune mediated (non-severe)
Appropriate for supervised direct oral rechallenge (or direct de-labelling)			☐ Low risk				**Severe neurological manifestation** ("seizures or psychosis")	☐	Unknown or unclear mechanism
Appropriate for supervised direct oral rechallenge			☐ Low risk						
May be appropriate for referral for specialized skin testing			☐ Moderate risk				**Anaphylactoid/infusion reaction** (e.g. red man syndrome)	☐	Unknown or unclear mechanism
May be appropriate for referral for specialized skin testing			☐ High risk						

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Chlamydia

Chlamydia trachomatis - most common bacterial sexually transmitted genital infections

2nd Most Common Reportable Disease & 20% Inc since 2015

Intracellular Reproduction

Presentation ranges from Asymptomatic -> Dysuria/Discharge -> PID

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Chlamydia: What Do The Guidelines Say?

- CDC STI Treatment Guidelines, 2021
- Doxycycline 100mg BID x 7 days
- Higher Rate of Laboratory Cure than Azithromycin 1g PO x 1 (up to 20% failure rate)
- Doxy also better for rectal and pharyngeal infection
- Azithromycin 1g x 1 still preferred in pregnancy or if expect non-adherence with doxy

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Toxicity and Adverse Reactions

- **Black box :** "Rare QTc prolongation and ventricular arrhythmias, including torsades de pointes"
- Gastrointestinal – Immediate (vomiting) & Delayed (diarrhea)
- Drug-Drug Interactions
- Liver Injury (can be fatal, but rare)

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Original Investigation | Pediatrics

Association of Inappropriate Outpatient Pediatric Antibiotic Prescriptions With Adverse Drug Events and Health Care Expenditures

Anne M. Butler, PhD; Derek S. Brown, PhD; Michael J. Durkin, MD, MPH; John M. Sahrmann, MA; Katelin B. Nickel, MPH; Caroline A. O'Neil, MA, MPH; Margaret A. Olsen, PhD, MPH; David Y. Hyun, MD; Rachel M. Zetts, MPH; Jason G. Newland, MD, MEd

Abstract

IMPORTANCE Nonguideline antibiotic prescribing for the treatment of pediatric infections is common, but the consequences of inappropriate antibiotics are not well described.

OBJECTIVE To evaluate the comparative safety and health care expenditures of inappropriate vs appropriate oral antibiotic prescriptions for common outpatient pediatric infections.

DESIGN, SETTING, AND PARTICIPANTS This cohort study included children aged 6 months to 17 years diagnosed with a bacterial infection (suppurative otitis media [OM], pharyngitis, sinusitis) or viral infection (influenza, viral upper respiratory infection [URI], bronchiolitis, bronchitis, nonsuppurative OM) as an outpatient from April 1, 2016, to September 30, 2018, in the IBM MarketScan Commercial Database. Data were analyzed from August to November 2021.

EXPOSURES Inappropriate (ie, non-guideline-recommended) vs appropriate (ie, guideline-recommended) oral antibiotic agents dispensed from an outpatient pharmacy on the date of infection.

MAIN OUTCOMES AND MEASURES Propensity score–weighted Cox proportional hazards models were used to estimate hazards ratios (HRs) and 95% CIs for the association between inappropriate antibiotic prescriptions and adverse drug events. Two-part models were used to calculate 30-day all-cause attributable health care expenditures by infection type. National-level annual attributable expenditures were calculated by scaling attributable expenditures in the study cohort to the national employer-sponsored insurance population.

RESULTS The cohort included 2 804 245 eligible children (52% male; median [IQR] age, 8 [4-12] years). Overall, 31% to 36% received inappropriate antibiotics for bacterial infections and 4% to 70% for viral infections. Inappropriate antibiotics were associated with increased risk of several adverse drug events, including *Clostridioides difficile* infection and severe allergic reaction among children treated with a nonrecommended antibiotic agent for a bacterial infection (among patients with suppurative OM, *C difficile* infection: HR, 6.23; 95% CI, 2.24-17.32; allergic reaction: HR, 4.14; 95% CI, 2.48-6.92). Thirty-day attributable health care expenditures were generally higher among children who received inappropriate antibiotics, ranging from $21 to $56 for bacterial infections and from −$96 to $97 for viral infections. National annual attributable expenditure estimates were highest for suppurative OM ($25.3 million), pharyngitis ($21.3 million), and viral URI ($93 million).

CONCLUSIONS AND RELEVANCE In this cohort study of children with common infections treated in an outpatient setting, inappropriate antibiotic prescriptions were common and associated with increased risks of adverse drug events and higher attributable health care expenditures. These

(continued)

Key Points

Question Do adverse events and health care expenditures differ in children given inappropriate vs appropriate oral antibiotic prescriptions for common outpatient infections?

Findings In this cohort study of more than 2.8 million children with commercial insurance, inappropriate antibiotics were associated with increased risk of several adverse drug events (eg, *Clostridioides difficile* infection, severe allergic reaction) and generally higher 30-day all-cause attributable expenditures. National annual expenditure estimates associated with inappropriate antibiotic treatment in the pediatric commercially insured population were highest for suppurative otitis media, pharyngitis, and viral upper respiratory infection.

Meaning Inappropriate antibiotic prescriptions were associated with avoidable adverse drug events and substantial individual- and national-level health care expenditures.

Invited Commentary

Supplemental content

Author affiliations and article information are listed at the end of this article.

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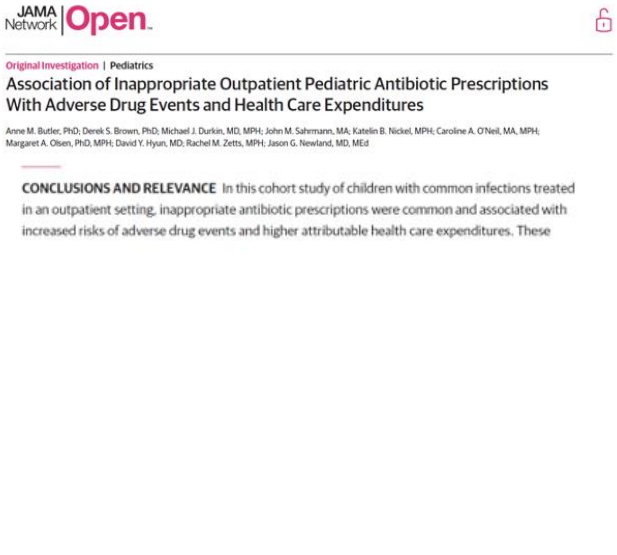
JAMA Network Open. 2022;5(5):e224853. doi:10.1001/jamanetworkopen.2022.24853 May 26, 2022 1/16



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When might Azithromycin be indicated?

1. Traveler's diarrhea
2. COPD Exacerbation
3. Atypical pneumonia
4. Chlamydia in Pregnancy or ?Adherence

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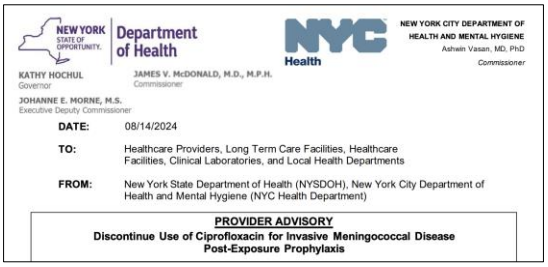

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NEW YORK CITY DEPARTMENT OF HEALTH AND MENTAL HYGIENE
Ashwin Vasan, MD, PhD
Commissioner

DATE: 08/14/2024

TO: Healthcare Providers, Long Term Care Facilities, Healthcare Facilities, Clinical Laboratories, and Local Health Departments

FROM: New York State Department of Health (NYSDOH), New York City Department of Health and Mental Hygiene (NYC Health Department)

PROVIDER ADVISORY
Discontinue Use of Ciprofloxacin for Invasive Meningococcal Disease Post-Exposure Prophylaxis

Drug	Age	Dose	Duration	Other Considerations
Rifampin	<1 month	5 mg/kg, orally, every 12 hours	2 days	Consider consultation with a pediatric infectious disease expert for infants <1 month.
	≥1 month	10 mg/kg (maximum 600 mg), orally, every 12 hours	2 days	Can interfere with efficacy of oral contraceptives and some seizure prevention and anticoagulant medications; may stain soft contact lenses. Not recommended for pregnant people.
Ceftriaxone	<15 years	125 mg, intramuscularly	Single dose	To decrease pain at injection site, dilute with 1% lidocaine.
	≥15 years	250 mg, intramuscularly	Single dose	
Azithromycin	All Ages	10 mg/kg (maximum 500 mg)	Single dose	Alternative agent. In one study, equivalent to rifampin for eradication of ***N. meningitidis*** from nasopharynx.

Meningococcal Prophylaxis?

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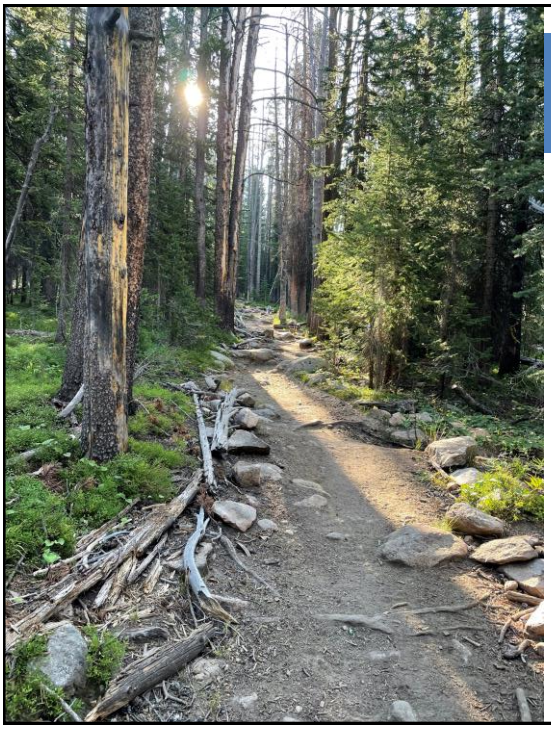

SUMMARY

- ❑ Patient satisfaction poorly correlated w/ Abx Rx
- ❑ Azithromycin stewardship improving…but still overprescribed in UC
- ❑ *S. PNA* & *S. Pyogenes* *r*esistance is common

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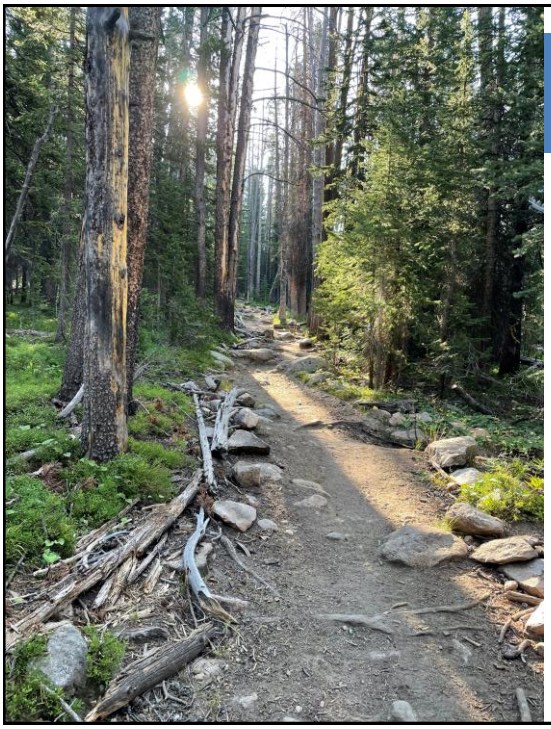

SUMMARY

- ❑ Azithro never recommended for ABRS
- ❑ Azithro monotx is out for CAP
- ❑ PCN “allergy” can usually be de-labeled
- ❑ Doxy is the way to go for Chlamydia
- ❑ Introduce the ‘Fall’ of Azithromycin to explain self-limited illness and risks

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