Alex Crawley, BSP

Antibiotic Harms

Antibiotics are a valuable resource and judicious use is important. For many serious infections (e.g. pneumonia, bacterial meningitis, sexually transmitted infections) the benefits of antibiotics clearly outweigh potential harms. However, for conditions that are primarily viral (e.g. pharyngitis, acute sinusitis, acute bronchitis), the benefits are minimal and likely outweighed by harms.

Of note: antibiotic-related adverse drug events account for 1 out of every 5 visits to the Emergency Department.[1]

How common are overall harms with antibiotics?

- In a meta-analysis (10 trials, 2450 patients) comparing antibiotics to placebo for acute rhinosinusitis, common adverse events (such as **nausea**, **vomiting**, **diarrhea**, or **abdominal pain**) occurred in 27% of patients on antibiotics versus 15% on placebo (NNH = 8-12).[2,5] The antibiotics used in this meta-analysis included **penicillins**, **macrolides**, and **tetracyclines**. Trials examining other populations have found similar numbers of adverse events.[3,4,5]
- A recent meta-analysis comparing amoxicillin or amox/clav to placebo found risk of **yeast infection** (candidiasis) to be about 8x higher in those on antibiotics (NNH = 23).[6]

Overall harms:	**NNH = 8-12**
Yeast infection:	**NNH = 23**

How common are allergic reactions with antibiotics?

- Allergic reactions can occur with any antibiotic; **penicillin** is particularly well studied. About 5-10% of patients will self-report a penicillin allergy;[7,8] however the vast majority of these reactions are delayed reactions, occurring days to weeks after initiating therapy, and do not typically indicate a true allergy.[9] Anaphylaxis occurs in about 0.01% of patients taking penicillin; about 10% of these reactions are fatal (i.e. 0.001% of all patients prescribed penicillin).[10,11,12]

Rash, hives:	**NNH ≈ 20**
Anaphylaxis:	**NNH ≈ 10,000**

How common are serious harms with antibiotics?

Rare but serious adverse events are associated with all antibiotics. Large, long-term randomized controlled trials are uncommon, and so it is difficult to put a precise estimate on how prevalent these events are. However, some adverse events include:

Serious harms:	**NNH from 300 to 30,000**

- ***Clostridium difficile* infection**: associated most often with **clindamycin** (RR≈4), cephalosporins, and fluoroquinolones; risk varies depending on patient factors.[13,14,15]
- **Stevens Johnson Syndrome, Toxic Epidermal Necrolysis, & other severe skin reactions**: these events occur a few times per 100,000 antibiotic prescriptions.[16] Cotrimoxazole in particular has a higher association than most other antibiotics.[17]
- **QT prolongation**: associated most often with macrolides (esp. **clarithromycin** and **erythromycin**) and fluoroquinolones (esp. **levofloxacin** and **moxifloxacin**). Risk of QT prolongation is also dependent on other factors (e.g. cardiac, metabolic, other drugs, etc.). See RxFiles QT Prolongation.
- **Tendon rupture with fluoroquinolones**: one large cohort study found a risk of 3.5% for tendon rupture in adults over the age of 65.[18]
- **Hyperkalemia with cotrimoxazole**: in older adults taking medications which can raise potassium (such as **ACEIs**, **ARBs**, **spironolactone**, or **NSAIDs**), **cotrimoxazole** was associated with sudden death (NNH ≈ 300).[19,20]
- **Contraceptive failure/drug interaction?** Birth control failure is a well-documented event with rifampin. It is thought to be unlikely with other antibiotics, although a backup birth control method is still recommended.

What about antimicrobial resistance?

- Resistance to an antibacterial can develop quickly. For example, strains of *Streptococcus pneumoniae* resistant to **levofloxacin** were documented in the same year levofloxacin was introduced to the market.[21] Rare, but worrisome, reports of bacteria resistant to every available antimicrobial can be found in the literature.[22]

  The good news is that when prescribing patterns change, resistance rates decline.[23,24]

NNH as low as 1???

Every course of antibiotic is likely to result in some emerging resistance which could affect the next choice of antibiotic regimen for that individual, especially if within 3 months of the previous antibiotic. Of course, the NNH for catastrophic resistance would be much higher.

Final Thoughts:

- There are many more harms than can be covered here! For example: serum sickness like reactions, pulmonary fibrosis with nitrofurantoin, tooth discoloration with tetracyclines.
- A quote from the team: *Harms speak louder when there is little or no benefit to offset them!*

ACKNOWLEDGMENTS: We would like to thank those who contributed to the development & review of this discussion document. Alex Crawley, Lynette Kosar, Loren Regier, Brent Jensen, Yvonne Shevchuk, and the rest of the RxFiles Team.

References

1. Shehab N, Patel PR, Srinivasan A, Budnitz DS. Emergency department visits for antibiotic-associated adverse events. Clin Infect Dis. 2008 Sep 15;47(6):735-43.
2. Lemiengre MB, van Driel ML, Merenstein D, Young J, De Sutter AI. Antibiotics for clinically diagnosed acute rhinosinusitis in adults. Cochrane Database Syst Rev 2012;10:CD006089.
3. Smith SM, Fahey T, Smucny J, et al. Antibiotics for acute bronchitis. Cochrane Database of Systematic Reviews 2014, Issue 3.
4. Venekamp, Roderick P., et al. "Antibiotics for acute otitis media in children." *The Cochrane Library* (2013).
5. Rosenfeld, Richard M. "Acute Sinusitis in Adults." *New England Journal of Medicine* 375.10 (2016): 962-970.
6. Gillies M, Ranakusuma A, Hoffmann T, et al. Common harms from amoxicillin: a systematic review and meta-analysis of randomized placebo-controlled trials for any indication. CMAJ : Canadian Medical Association Journal. 2015;187(1):E21-E31. doi:10.1503/cmaj.140848.
7. Lee CE, Zembower TR, Fotis MA, Postelnick MJ, Greenberger PA, Peterson LR, Noskin GA. The incidence of antimicrobial allergies in hospitalized patients: implications regarding prescribing patterns and emerging bacterial resistance. Arch Intern Med. 2000 Oct 9;160(18):2819-22.
8. Joint Task Force on Practice Parameters; American Academy of Allergy, Asthma and Immunology; American College of Allergy, Asthma and Immunology; Joint Council of Allergy, Asthma and Immunology. Drug allergy: an updated practice parameter. Ann Allergy Asthma Immunol. 2010 Oct;105(4):259-273.
9. Johansson SG, Bieber T, Dahl R, Friedmann PS, Lanier BQ, Lockey RF, Motala C, Ortega Martell JA, Platts-Mills TA, Ring J, Thien F, Van Cauwenberge P, Williams HC. Revised nomenclature for allergy for global use: Report of the Nomenclature Review Committee of the World Allergy Organization, October 2003. J Allergy Clin Immunol. 2004 May;113(5):832-6.
10. Bhattacharya S. The facts about penicillin allergy: A review. Journal of Advanced Pharmaceutical Technology & Research. 2010;1(1):11-17.
11. Idsoe O, Guthe T, Willcox RR, de Weck AL. Nature and extent of penicillin side-reactions, with particular reference to fatalities from anaphylactic shock. Bull World Health Organ. 1968;38(2):159-88.
12. Allergic reactions to long-term benzathine penicillin prophylaxis for rheumatic fever. International Rheumatic Fever Study Group. Lancet. 1991 Jun 1;337(8753):1308-10.
13. Smieja M. Current indications for the use of clindamycin: A critical review. *The Canadian Journal of Infectious Diseases*. 1998;9(1):22-28.
14. Brown, Kevin A., et al. "Meta-analysis of antibiotics and the risk of community-associated Clostridium difficile infection." *Antimicrobial agents and chemotherapy* 57.5 (2013): 2326-2332.
15. Slimings C, Riley TV. Antibiotics and hospital-acquired Clostridium difficile infection: update of systematic review and meta-analysis. J Antimicrob Chemother 2014;69:881-891.
16. Chan HL, Stern RS, Arndt KA, Langlois J, Jick SS, Jick H, Walker AM. The incidence of erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis. A population-based study with particular reference to reactions caused by drugs among outpatients. Arch Dermatol. 1990 Jan;126(1):43-7.
17. Mockenhaupt M, Viboud C, Dunant A, et al. Stevens-Johnson syndrome and toxic epidermal necrolysis: assessment of medication risks with emphasis on recently marketed drugs. The EuroSCAR-study. J Invest Dermatol 2008;128:35e44.
18. Daneman, Nick, Hong Lu, and Donald A. Redelmeier. "Fluoroquinolones and collagen associated severe adverse events: a longitudinal cohort study." *BMJ open* 5.11 (2015): e010077.
19. Fralick M, Macdonald EM, Gomes T, Antoniou T, Hollands S, Mamdani MM, Juurlink DN; Canadian Drug Safety and Effectiveness Research Network.. Co-trimoxazole and sudden death in patients receiving inhibitors of renin-angiotensin system: population based study.
20. Antoniou T, Hollands S, Macdonald EM, Gomes T, Mamdani MM, Juurlink DN; Canadian Drug Safety and Effectiveness Research Network. Trimethoprim-sulfamethoxazole and risk of sudden death among patients taking spironolactone. CMAJ. 2015 Mar 3;187(4):E138-43.
21. Antibiotic Resistance Threats in the United States, 2013. Centre for Disease Control. Retrieved from http://www.cdc.gov/drugresistance/pdf/ar-threats-2013-508.pdf October 6, 2016.
22. Souli, Maria, I. Galani, and H. Giamarellou. "Emergence of extensively drug-resistant and pandrug-resistant Gram-negative bacilli in Europe." *Euro surveillance: bulletin Europeen sur les maladies transmissibles= European communicable disease bulletin* 13.47 (2008): 5437-5453.
23. Seppälä, Helena, et al. "The effect of changes in the consumption of macrolide antibiotics on erythromycin resistance in group A streptococci in Finland." *New England Journal of Medicine* 337.7 (1997): 441-446.
24. Mölstad, Sigvard, et al. "Sustained reduction of antibiotic use and low bacterial resistance: 10-year follow-up of the Swedish Strama programme." *The Lancet infectious diseases* 8.2 (2008): 125-132.
25. Lovegrove MC, Geller AI, Fleming-Dutra KE, et al. US Emergency Department Visits for Adverse Drug Events From Antibiotics in Children, 2011-2015. J Pediatric Infect Dis Soc. 2018 Aug 23.