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MAJOR ARTICLE

Antibiotic Myths for the Infectious Diseases Clinician

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Antimicrobials are commonly prescribed and often misunderstood. With over 50% of hospitalized patients receiving an antimicrobial agent at any point in time, judicious and optimal use of these drugs is paramount to advancing patient care. This narrative will focus on myths relevant to nuanced consultation from infectious diseases specialists, particularly surrounding specific considerations for a variety of antibiotics.

Keywords: Cefazolin, Trimethoprim-sulfamethoxazole, Linezolid, Clindamycin

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INTRODUCTION

Antimicrobial use is commonly informed by past practices instead of evidence,[1] with "pearls" propagated over time.[2] Consequently, medical paradigms may be constructed and followed without foundation until unique patients or logistical implications arise that challenge the status quo. One such example is the historical avoidance of the entire beta-lactam class of antibiotics for patients with reported penicillin allergies; however, this practice is proven to be unfounded and harmful.[3,4]

Core principles of antimicrobial use advocate for appropriate dose, duration, and route of the optimal agent(s) for each disease.[5] This author group, comprised of infectious diseases clinicians and consultants in academic and community hospitals, previously published 10 common myths of infectious diseases diagnosis and management in adult patients, focused on clinicians practicing in hospital medicine.[6] The group then identified remaining myths and dogma from their shared experiences, conference presentations, and academic community social channels and listservs. A voting process occurred to gain consensus on 8 myths related to optimizing antibiotic use for infectious diseases providers for a focused review. Herein, those 8 myths related to the nuanced prescribing of antimicrobial agents are elucidated. This analysis provides infectious diseases specialists with the history, current literature, and remaining unknowns for each myth.

Myth: Cefazolin should be avoided for central nervous system (CNS) infections

A commonly used tertiary medical reference states "Cefazolin should not be used for… meningitis because it does not adequately penetrate into the CNS."[7] The source of this recommendation is from 1973, when Mangi et al described a case series of breakthrough meningitis cases in patients receiving cephalothin for invasive streptococcal infections.[8] The authors suggested these occurrences were due to poor penetration of cephalothin across the blood-brain barrier. Another early study found undetectable cefazolin CSF concentrations after a single 1-gram dose.[9] Given this information, it has since been taught that clinicians should avoid cefazolin for CNS infections.

However, a few years later, Frame et al found higher concentrations in brain tissue after a single 2g infusion of cefazolin than a 2g infusion of nafcillin (4.3 µg/g vs 1.3 µg/g, respectively).[10] Furthermore, Novak et al described 15 patients with extra-ventricular devices receiving prophylactic doses of cefazolin 2g intravenously (IV) every 8 hours.[11] Cohort-extrapolated median C_{max} and C_{min} in CSF were 2.97 and 1.59 mg/L. Gregoire et al found that 8g or 10g daily of cefazolin via continuous infusion led to median CSF concentrations of 6.1mg/L or 11.9 mg/L, respectively, in a patient who experienced clinical success after receiving 6 weeks of cefazolin plus levofloxacin for MSSA neurosurgical meningitis.[12] Le Turnier et al found similar median concentrations of cefazolin when using 6-12g continuous infusions (2.8 mg/L, IQR 2.1-5.2).[13] These concentrations are higher than the Clinical Laboratory and Standards Institute (CLSI) breakpoints for *Staphylococcus aureus* and Enterobacterales of ≤ 2 mg/L and above the

European Committee on Antimicrobial Susceptibility Testing (EUCAST) epidemiologic cutoff of MIC ≤2 mg/L for methicillin-susceptible *Staphylococcus aureus* (MSSA).[14]

The pharmacokinetics of antibiotics in the CSF are poorly defined. Since drug entry into the CSF is delayed compared to other body fluids and compartments (a phenomenon known as system hysteresis), the ratio of drug in CSF to plasma may increase after initiation of the drug infusion.[15,16] Therefore, the ratio of the area-under-the-curve (AUC) of CSF to serum at steady state (AUC_{CSF}/AUC_{SS}) is the most accurate means of characterizing drug penetration into the CSF and single point CSF concentrations may not have interpretative utility. The AUC_{CSF}/AUC_{SS} for cephalosporins typically ranges from 0.007 - 0.17, which is quite low; however, high doses of cephalosporins such as ceftriaxone are preferred therapy for many CNS infections despite this "poor" penetration.

In conclusion, cefazolin is a reasonable option for treatment of CNS infections with susceptible pathogens. A recent narrative review on the treatment of cefazolin for CNS infections (including 11 reports describing cefazolin treatment of spinal epidural abscesses in a total of 104 patients) recommends 2g IV every 6 hours or a continuous infusion of 8-10 grams daily instead of the traditional 1-2g IV every 8 hours dosing scheme to optimize pharmacokinetic/pharmacodynamic (PKPD) properties.[17] Clinical studies would help determine the optimal cefazolin dose for CNS infections.

Myth: Linezolid must be avoided in patients receiving selective serotonin reuptake inhibitors (ssris)

Linezolid is an oxazolidinone-class antibacterial with *in vitro* activity against multidrug-resistant gram-positive bacteria and favorable pharmacokinetics.[18] However, its reversible, nonselective inhibition of monoamine oxidase, an enzyme responsible for breaking down serotonin in CNS, has led to cautious use in patients receiving serotonergic agents to avoid serotonin syndrome (SS).[19] The Food and Drug Administration (FDA) recommends an impractical 14-day (5-weeks for fluoxetine) washout period in patients receiving these agents.[19]

Butterfield et al assessed 4,265 patients in clinical trials of gram-positive infections taking serotonergic agents and receiving either linezolid or a comparator. Using one set of criteria, 9/2208 (0.41%) linezolid and 3/2057 (0.14%) comparator patients experienced SS; by different criteria, the incidences were 3/2208 (0.14%) and 1/2057 (0.05%), respectively. SS was uncommon overall and not significantly higher with linezolid.[20] This result has been replicated, and SS has not been linked to a specific duration of linezolid therapy since it occurs so rarely.[21] Gatti et al. evaluated 669 FDA post-marketing reports of SS mentioning linezolid. Linezolid co-administered with citalopram constituted 69/699 (10.3%) of reports; however, the denominator of total exposures of this combination amongst US patients (and therefore true incidence of this reaction) is unknown.[22] Inferring from pharmacological properties including lipophilicity, large volume of distribution, and potent serotonin reuptake transporter inhibition, the authors suggest

linezolid plus citalopram, escitalopram, and methadone may be more likely to cause SS than other drug combinations. More recently, Bai et al. evaluated 1134 elderly patients in Canada receiving linezolid, 215 (19%) of whom were also taking an antidepressant.[21] SS occurred in less than 6 patients. Similarly, Kufel et al. evaluated 1743 patients receiving linezolid, 1168 (67%) of whom also received anywhere from 1-5 additional serotonergic agents.[23] Only 2 patients (0.11%) had possible serotonin toxicity.

In summary, SS is exceedingly rare even when linezolid is combined with serotonergic agents. The risk/benefit profile of linezolid use in patients receiving serotonergic drugs is acceptable. Patients receiving serotonergic agents should be monitored closely while receiving linezolid, but it is not necessary to avoid concomitant administration of linezolid when required.

Myth: No dose adjustment is needed for linezolid in patients with renal insufficiency

Linezolid is administered as 600mg IV or orally (PO) twice daily, with no dose adjustment for renal dysfunction recommended in the package insert. In early clinical trials and observational experiences of patients receiving short-course linezolid, incidence of thrombocytopenia was low (less than 3%).[18,24,25] However, with expanded clinical use, myelosuppression is more frequently observed. An investigation of the relationship between linezolid exposure and renal dysfunction revealed a strong correlation between renal clearance and linezolid clearance among a small number of patients. Interestingly, it was found that an increased linezolid exposure (defined by total AUC or trough concentrations) was associated with thrombocytopenia.[26]

Building on this experience, Crass et al examined the risk for thrombocytopenia among 341 patients receiving linezolid.[27] Ninety-two (27.0%) patients developed thrombocytopenia; 47 (13.8%) developed severe thrombocytopenia. The frequency of both thrombocytopenia (42.9% versus 16.8%; $P < 0.001$) and severe thrombocytopenia (19.5% versus 10.1%; $P = 0.02$) was greater among patients with renal impairment. Renal impairment, defined as eGFR < 60 ml/min/1.73m^2, was independently associated with thrombocytopenia in a multivariable analysis (adjusted hazard ratio [aHR], 2.37; 95% confidence interval [CI], 1.52 to 3.68). The authors suggest empirical linezolid dose reduction to 300mg IV or PO every 12 hours provides the best balance of safety and efficacy, achieving therapeutic concentrations in 65% of simulated patients with eGFR < 60mL/min.[27]

Although recommendations to adjust linezolid dosing for renal dysfunction have not been added to its product label, it may be prudent to consider dose adjustment or therapeutic drug monitoring (TDM). Experts recommend dosing linezolid to an $AUC_{0–24}$/MIC ratio of 80–120 for optimal efficacy and maintaining troughs less than 7 mg/L for safety.[28]

Myth: Clindamycin is a first-line drug for prevention of surgical site infections in patients with reported penicillin allergies

Clindamycin is a protein synthesis inhibitor used for a broad range of indications, including site infection (SSI) prophylaxis. As a lincosamide, it does not share any chemical structure with beta-lactam antibiotics, making clindamycin the historically preferred choice for SSI prophylaxis in patients with reported penicillin allergies.[29]

Cefazolin, the first-line prophylactic agent for most surgical procedures, is traditionally avoided in patients with reported penicillin allergies since historical references quote cross-reactivity rates of 5-10% between penicillin allergies and reactions to first-generation cephalosporins.[30,31] However, cefazolin does not share a side chain with any other beta-lactam antibiotic and the likelihood of cefazolin allergy in a patient with reported penicillin allergy is extremely rare.[3] Indeed, in a meta-analysis of 77 studies yielding 6,147 patients, the frequency of dual allergy, including penicillin and cefazolin, was 0.7%.[3] In a study of 690 patients with reported penicillin allergy who received cefazolin, clindamycin, or vancomycin, hypersensitivity reactions were similar across all three antibiotics (3 (0.9%), 4 (1.4%), and 1 (1.1%), respectively).[32] Most recently, Norvell et al described use of cefazolin or clindamycin and/or vancomycin as surgical prophylaxis in patients with reported penicillin allergies.[33] There were fewer SSIs (0.9% vs. 3.8%, $p < .001$) including prosthetic joints infections (0.1% vs. 1.9%) amongst cefazolin-treated patients. More interoperative hypersensitivity reactions occurred in patients receiving clindamycin and/or vancomycin compared to cefazolin (1.3% vs 0.2%).

Additionally, clindamycin resistance has increased amongst methicillin-resistant *S. aureus* (MRSA) isolates globally. In the United States, *Streptococcus pyogenes* resistance to clindamycin reached 24.2% in 2018, and resistance in *S. agalactiae* has risen to over 40%, making clindamycin unreliable against common causes of cellulitis and SSIs.[35]

For these reasons, the Joint Task Force on Practice Parameters (formed by two leading allergy and immunology groups in 2022) updated its guidance to suggest structurally dissimilar cephalosporins (e.g., cefazolin or ceftriaxone) as first-line antibiotic agents of choice for surgical prophylaxis in patients with a history of anaphylaxis to penicillin.[36] The need for clindamycin in surgical prophylaxis is now extremely limited.

Myth: Trimethoprim-sulfamethoxazole does not have *in vitro* activity against *S. Pyogenes*

A common teaching point in managing skin and skin structure infections (SSSI) is that pustular infections are staphylococcal in origin, and non-pustular cellulitis is streptococcal, primarily *Streptococcus pyogenes*. Cephalexin is often recommended for either type of SSSI since it displays *in vitro* activity against MSSA and *S. pyogenes*. However, the rise of community-associated MRSA in the 2000s led to alternative regimens for these infections, including tetracyclines and trimethoprim-sulfamethoxazole (T/S).[37] The common misnomer that T/S is

inactive *in vitro* against *S. pyogenes* led to using T/S plus beta-lactams in combination for uncultured SSSI.[38]

The misunderstanding about T/S resistance in *S. pyogenes* is mainly laboratory-based.[39] Through their effects on different steps of folic acid synthesis and utilization, trimethoprim and sulfamethoxazole prevent the biosynthesis of the nucleic acid thymidine in bacteria. Some species of bacteria can utilize exogenous thymidine when endogenous production is inhibited. There are differences between streptococci in this ability: while absent in *Streptococcus pneumoniae* and many viridans group streptococci, it occurs in *S. pyogenes* and *S. agalactiae*.[40] Agar used for *in vitro* cultures of streptococci previously contained thymidine, serving as an exogenous source to intentionally isolate *S. pyogenes* from upper respiratory samples.[40] Currently recommended thymidine-depleted media eliminates this issue. When tested appropriately and using EUCAST breakpoints, all 370 *S. pyogenes* isolates in the US SENTRY database tested susceptible to T/S with an MIC_{90} </= 0.12 mcg/mL (2020-21, North America only).

While these microbiological data are reassuring, recent clinical studies also support the ability of T/S to treat SSSIs primarily caused by *S. pyogenes*. For example, in a multicenter randomized clinical trial containing 524 patients with uncomplicated SSSIs (280 (53.4%) had cellulitis without abscess), cure rate for T/S treatment was 88.2% in the evaluable population.[41] *Streptococcus pyogenes* was rarely isolated as expected, but cure rates were similar between agents for those with cellulitis alone. A 2017 systematic review of T/S for SSSIs, including those caused by *S. pyogenes*, also concluded that T/S is useful for the treatment of both staphylococcal and streptococcal skin infections.[42] Collectively, these data indicate the utility of T/S monotherapy for SSSIs.

Myth: Oral fosfomycin is an excellent drug for uncomplicated cystitis

Fosfomycin is a unique antibiotic that interferes with cell wall synthesis of gram-positive and gram-negative bacteria. Guidelines recommend fosfomycin first-line for acute uncomplicated cystitis in women.[43,44]

Efficacy data for fosfomycin are conflicting. In 1999, a 749-patient trial found single-dose fosfomycin had similar efficacy as a 7-day course of nitrofurantoin.[45] A meta-analysis of 27 clinical trials also found that fosfomycin had similar cure rates to fluoroquinolones, T/S, or nitrofurantoin for cystitis in pregnant and non-pregnant patients.[46] However, a more recent randomized, open-label, controlled trial of 513 women with uncomplicated cystitis found 5 days of nitrofurantoin treatment resulted in greater clinical and microbiologic resolution at 28 days compared to fosfomycin (70% vs 58%, P= 0.004).[47]

The IDSA guidelines state that fosfomycin may cause less ecological adverse effects than other antibacterial options.[44] However, a longitudinal Spanish study noted that a 340% increase in fosfomycin use from 1997 to 2009 was accompanied by an increase in fosfomycin resistance

from 4% to 11%.[48] Increased fosfomycin use has also been connected to increases in fosfomycin-resistant, ESBL-producing *E. coli*.[43,49] More concerningly, fosfomycin requires glucose-6-phosphate (G6P) to exert bacterial killing; this enzyme is not present in human urine.[50] Therefore, minimum inhibitory concentrations determined in the presence of G6P in the laboratory may not accurately reflect the *in vivo* activity of the drug, and the appropriate susceptibility breakpoint may need reassessment. Furthermore, fosfomycin susceptibility testing is challenging, and is currently only recommended for *E. coli* and *Enterococcus faecalis*.[51]

While fosfomycin is appealing due to the "one and done" FDA-approved dosing for uncomplicated cystitis, the most recent randomized, clinical data do not support its use compared to nitrofurantoin. Additionally, critical evaluations are ongoing to determine if fosfomycin is reliably active at the infection site and to understand the clinical susceptibility breakpoint. If fosfomycin is utilized for uncomplicated cystitis, patients should be carefully assessed for cure.

Myth: Rifampin and gentamicin are essential for treatment of *Staphylococcus* spp. Prosthetic valve endocarditis

Invasive *Staphylococcus* spp. infections, particularly prosthetic valve endocarditis (PVE), are associated with high morbidity and mortality.[52] The IDSA guidelines for MRSA infection recommend addition of gentamicin and rifampin for treatment of MRSA PVE based on small, retrospective studies of patients with coagulase-negative staphylococci infections.[37] Additionally, gentamicin may act synergistically with several other antibiotics against *Staphylococcus aureus* in *in-vitro* and animal models.[53]

However, clinical studies, including a randomized controlled trial by Cosgrove et al, did not demonstrate any benefit in patient outcomes when gentamicin was added to the PVE treatment regimen.[54] Instead, the authors observed increased acute renal injury with gentamicin. Subsequent studies on staphylococcal PVE found no difference in mortality with the addition of gentamicin.[55]

The recommendation for rifampin in patients with MRSA PVE comes from a post-hoc analysis of a *Staphylococcus aureus* bacteremia cohort where rifampin-based combinations were associated with a lower hazard ratio for mortality at 30 days (0.6, CI 0.3-1.1) and reduced late complications (10.6% vs 4.5%, p=0.03).[56] However, this sample was small and a purely observational association and only 12.6% of the population had endocarditis. In a recent multi-national observational study, rifampin did not impact 1-year mortality or infection relapse and hospital length of stay was longer for rifampin recipients.[57] A meta-analysis of adjunctive rifampin and gentamicin for staphylococcal PVE identified only 4 studies and did not show benefit.[58]

Rifampin and gentamicin each have issues complicating their use, which necessitates re-examining the basis of their utility. The problems introduced with drug interactions and toxicities outweigh the utility of these antibiotics in endocarditis.

MYTH: Doxycycline is contraindicated in pregnancy and pediatric patients less than 8 years old

Tetracycline is associated with maternal hepatotoxicity, inhibition of bone growth, and tooth discoloration with prolonged exposure in patients under age 8.[71] Therefore, use in pregnant women and children is restricted.[72,73] Doxycycline was developed later and contains structural modifications that improve antibacterial activity, decrease calcium binding, and diminish adverse events compared to tetracycline.[74,75] However, it carries the same FDA warnings as tetracycline due to the 'tetracycline class effect' established in 1970. Thus, many prescribers avoided doxycycline in children less than 8, even when it was recommended first-line for treatment such as in Rickettsial diseases.[76,77]

Recent evidence suggests that doxycycline can be used safely in pregnant women and young children in select scenarios and that withholding doxycycline for certain diseases in these populations may lead to harm.[78] Case fatality rates for Rocky Mountain Spotted Fever and ehrlichiosis are significantly higher in children under 8 years of age compared to every other age group.[79] One study of 58 children who received doxycycline before age 8 compared to 213 unexposed children found no difference in teeth staining.[80] A large, retrospective study of infants with fetal doxycycline exposure found no increased risk of congenital malformations and teratogenic risk compared to unexposed infants.[81] The American Academy of Pediatrics states that short-course doxycycline (≤21 days) is acceptable since it has been shown to pose minimal risk of dental staining.[82,83] The Pregnancy Team at the FDA stated, "while there are no controlled studies of doxycycline use in pregnant women to show safety, an expert review of published data on experiences with doxycycline use during pregnancy by the Teratogen Information System concluded therapeutic doses during pregnancy are unlikely to pose a substantial teratogenic risk…but the data are insufficient to state that there is no risk."[84]

These data indicate that in the cases of serious infections without equivalently efficacious treatment alternatives, such as Rickettsial diseases, the benefits of using doxycycline outweigh the risks for pediatric patients. Clinical trials of doxycycline in pregnancy and early childhood are indicated, including pharmacokinetic and longitudinal studies to evaluate the impact of doxycycline use on long bone growth and dental discoloration.[83]

CONCLUSION

Clinicians are often presented with medical statements that are either more opinion than robust evidence, or wherein the evidence has evolved yet perception remains unchanged. This narrative highlights the need for vigilance as evidence bases evolve. Today's teaching point may end up as tomorrow's myth.

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