

DEBUNKING ANTIBIOTIC MYTHS FOR THE INFECTIOUS DISEASES CLINICIAN



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The logo for UW Medicine is located on the right side of the slide, enclosed in a white circle. It features the text "UW Medicine" in a large, serif font, with "UW SCHOOL OF MEDICINE" in a smaller, sans-serif font below it, separated by horizontal lines.

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ORIGINS



MYTH: CEFAZOLIN SHOULD BE AVOIDED FOR CNS INFECTIONS

The screenshot shows the UpToDate interface. At the top, the search bar contains 'bacterial meningitis' and the user is logged in as 'University of Pittsburgh'. The article title is 'Treatment of bacterial meningitis caused by specific pathogens in adults'. On the left, a sidebar lists 'APPROACH TO THERAPY' and 'THERAPY FOR SPECIFIC PATHOGENS' with sub-items: Streptococcus pneumoniae, First-line regimens, Alternative agents, Neisseria meningitidis, Haemophilus influenzae, and Listeria monocytogenes. The main text discusses *Staphylococcus aureus* meningitis, stating that vancomycin should be used initially for suspected or proven MRSA, and that if susceptibility testing reveals methicillin-susceptible *S. aureus* (MSSA), therapy should be changed to nafcillin or oxacillin. A blue highlight is placed over the text: 'Cefazolin should not be used for MSSA meningitis because it does not adequately penetrate into the CNS.' The text continues with 'If the organism is methicillin resistant, vancomycin should be continued. (See "Vancomycin: Parenteral dosing, monitoring, and adverse effects in adults".)

UpToDate. Accessed 8-31-2023.

ORIGIN

Development of Meningitis During Cephalothin Therapy

RICHARD J. MANGI, M.D., RONALD S. KUNDARGI, M.B., B.S., RICHARD QUINTILIANI, M.D.,
VINCENT T. ANDRIOLE, M.D., F.A.C.P., New Haven, Connecticut

- “unpredictable CSF levels”
 - Cite studies with CSF concentrations ranging from 0 – 64.5 µg/mL
- 3 previously reported cases developing pneumococcal (1) or meningococcal (2) meningitis 18-60 hours into cephalothin therapy
- 5 additional cases (cephalothin dose)
 - *Pneumococcus* after 40h (1g q4h)
 - *Neisseria meningitidis* after 42h (500mg q6h)
 - *Klebsiella spp* after 24h (1g q4h)
 - *Listeria monocytogenes* after 96h (1g q4h)
 - *Pneumococcus* after 120h (1.5g q6h)

From our experience, we have made the following conclusions about the use of cephalothin for the treatment of bacterial meningitis. For meningococcal meningitis, cephalothin is unreliable, and chloramphenicol is the agent of choice for patients allergic to penicillin (28). Pneumococcal meningitis has been successfully treated with cephalothin at a dosage of 6 to 12 grams daily (2, 3, 27). We believe 6 grams a day is definitely inadequate: we prefer chloramphenicol. If cephalothin must be used we would recommend 12 to 16 grams daily. For patients with Gram-negative meningitis, the choice of antibiotic should depend on the organism's sensitivity. Our experience suggests that chloramphenicol, ampicillin, and intrathecal gentamicin are all superior to cephalothin.

DOES ANY CEPHALOSPORIN “GET TO” THE CSF?

TABLE 1. CSF penetration and clinical use of different classes of antibiotics^a

Compound (reference[s] for CSF penetration)	AUC _{CSF} /AUC _S ^b		Relationship of CSF concn to MIC with usual doses	Compound(s) with broad clinical experience for CNS infections	Description
	Uninflamed or mildly inflamed meninges	Strong meningeal inflammation			
Cephalosporins	0.007–0.1	0.15	CSF concn with uninflamed meninges close to the MICs of moderately susceptible bacteria; because of binding to plasma proteins, AUC ratio for ceftriaxone is approx 1 order of magnitude lower than that of cefotaxime	Cefazolin, cefotaxime, ceftriaxone, ceftazidime, cefepime, ceftiofime	Low toxicity; daily dose can be increased up to 12–24 g (cefotaxime)
Cefazolin (111)					
Cephaloridine (46)					
Cefuroxime (112, 229)					
Cefotaxime (96, 175, 194, 195, 230)	0.12	0.04, 0.17			
Ceftriaxone (47, 118, 141, 162, 175, 195, 236)	0.007				
Ceftazidime (24, 70, 83, 156, 160, 172, 265)	0.057				
Cefixime (165)		0.103			
Cefepime (213)		0.145, 0.31			
Cefpirome (73, 181, 262)					

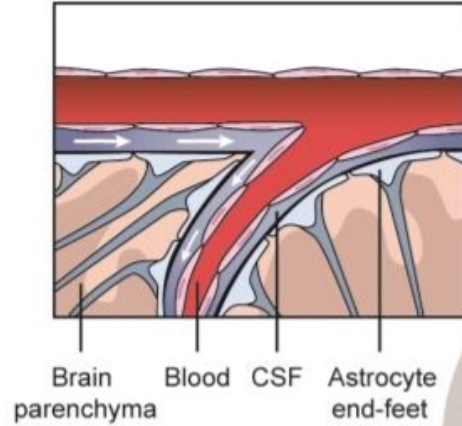
THIS BLEW MY MIND



7. Echinocandins

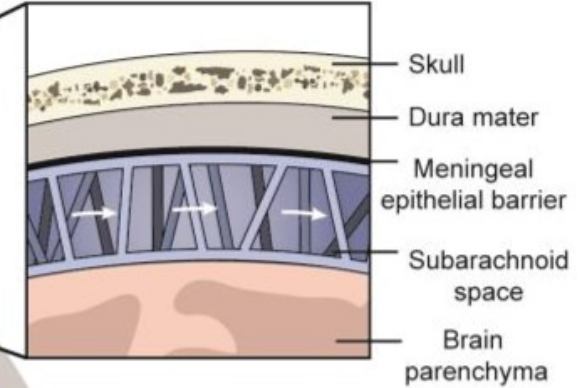
The CNS pharmacokinetics of each of the three available echinocandin compounds, caspofungin, micafungin and anidulafungin, has been studied in detail using a non-infected rabbit model [50-52]. In each instance, the investigators have reported **undetectable CSF concentrations** even using dose levels far exceeding those used in current clinical regimens. However, these same investigations found **brain parenchymal concentrations in the range of 10 – 20% of those measured in serum.** For example, Groll *et al.* performed extensive tissue distribution studies with anidulafungin in healthy rabbits [51]. Although a CSF assay for anidulafungin did not identify a measurable amount of drug, brain parenchymal concentrations ranged 0.24 – 3.9 µg/g over a dose range of 0.5 – 10 mg/kg [51]. **These tissue concentrations exceed the MIC₉₀ of fungal pathogens in the echinocandin spectrum and would be anticipated to be sufficient for treatment success.** This same research group has undertaken similar

Glymphatic circulatory system



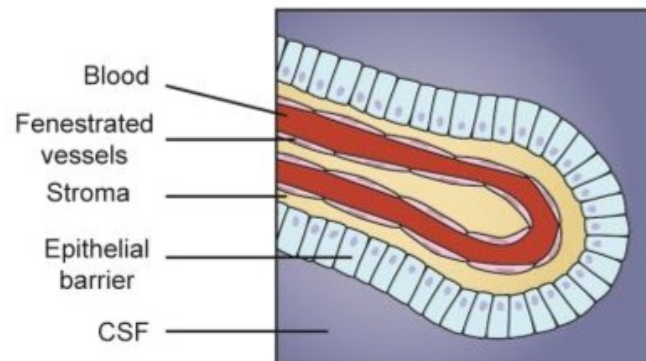
1 Meningeal barrier

Arachnoid epithelium



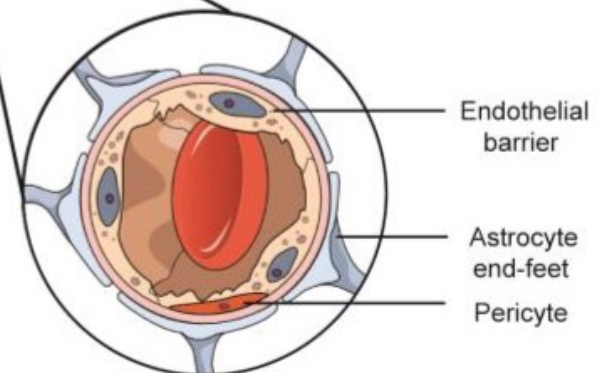
3 Blood CSF barrier

Choroid plexus epithelium



2 Blood brain barrier

Capillary endothelium





In Our Central Nervous System Era

CEFAZOLIN PROBABLY “GETS THERE”

0148-396X/83/1202-0142\$02.00/0

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Vol. 12, No. 2, 1983

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Penetration of Nafcillin, Methicillin, and Cefazolin into Human Brain Tissue

Peter T. Frame, M.D., Chatrchai Watanakunakorn, M.D., Robert L. McLaurin, M.D., and Ghahreman Khodadad, M.D.

Division of Infectious Diseases, Department of Internal Medicine (P.T.F.), and Division of Neurosurgery, Department of Surgery (R.L.M.), University of Cincinnati College of Medicine, Cincinnati; Division of Infectious Diseases, Department of Internal Medicine (C.W.), St. Elizabeth Hospital Medical Center, Youngstown; and Surgical Service (G.K.), Veterans Administration Hospital, Cincinnati, Ohio

- 27 patients getting a craniotomy
- Brain tissue + serum antibiotic concentrations obtained

Drug	Tissue specimens with detectable drug	Tissue concentrations (µg/g, [mean])
Nafcillin	11/13 (85%)	0.36-11.0 [2.7]
Methicillin	14/18 (78%)	0.56-5.0 [2]
Cefazolin	10/11 (91%)	2.0-40.0 [10.6]

SOME CLINICAL DATA

Clinical Microbiology and Infection

journal homepage: www.clinicalmicrobiologyandinfection.com

Should we reconsider cefazolin for treating staphylococcal meningitis? A retrospective analysis of cefazolin and cloxacillin cerebrospinal fluid levels in patients treated for staphylococcal meningitis

P. Le Turnier^{1,†}, M. Gregoire^{2,3,†}, G. Deslandes², K. Lakhal⁴, C. Deschanvres¹, R. Lecomte¹, J.-P. Talarmin⁵, V. Dubée⁶, R. Bellouard², D. Boutoille^{1,7}, A.-G. Leroy^{7,8}, B.J. Gaborit^{1,7,*} on behalf of the NAMAP study group[‡]

- 17 patients
- 8 cefazolin vs 9 cloxacillin
 - 4 cefazolin patients also received levofloxacin
- Median cefazolin dose = 8g continuous infusion
- Median CSF concentration = 2.8 mg/L [2.1, 5.2]
- All patient cured without recurrence



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High-Dosage Cefazolin Achieves Sufficient Cerebrospinal Diffusion To Treat an External Ventricular Drainage-Related *Staphylococcus aureus* Ventriculitis

Matthieu Grégoire,^{a,b} Benjamin Gaborit,^{c,d} Colin Deschanvres,^c Raphaël Lecomte,^c Guillaume Deslandes,^a Éric Dailly,^{a,e} Xavier Ambrosi,^f Ronan Bellouard,^{a,e} Nathalie Asseray,^c Karim Lakhal,^f David Boutoille^{c,d}

- 1 patient
- 10g continuous infusion → step down to 8g
 - Received levofloxacin too
- MSSA ventriculitis
- Median CSF concentration = 11.9 mg/L (10g), 6.1 mg/L (8g)

COUNTERPOINT

> Clin Infect Dis. 2023 Sep 19;ciad559. doi: 10.1093/cid/ciad559. Online ahead of print.

Cefazolin for the Treatment of Central Nervous System Infections

Allan R Tunkel ¹

Affiliations + expand

PMID: 37724584 DOI: 10.1093/cid/ciad559

- Effectiveness of antibiotic for treatment of bacterial meningitis is not just related to CSF penetration
- Rapid bactericidal activity required for optimal therapy → increased rate of neurological complications if CSF isn't rapidly cleared of bacteria
- Ceftriaxone > cefuroxime for children with bacterial meningitis¹
- Very limited clinical data on use of cefazolin for treatment of staphylococcal meningitis
- Some patients received combination therapy in Le Turnier reference
- Cefazolin is appropriate for spinal epidural abscess

COUNTERPOINT

> Clin Infect Dis. 2023 Sep 19;ciad559. doi: 10.1093/cid/ciad559. Online ahead of print.

Cefazolin for the Treatment of Central Nervous System Infections

Allan R Tunkel ¹

Affiliations + expand

PMID: 37724584 DOI: 10.1093/cid/ciad559

- Effectiveness of antibiotic for treatment of bacterial meningitis is not just related to CSF penetration **(agree)**
- Rapid bactericidal activity required for optimal therapy → increased rate of neurological complications if CSF isn't rapidly cleared of bacteria **(time to activity therapy critical, bactericidal vs static is more lab than clinical phenom)**
- Ceftriaxone > cefuroxime for children with bacterial meningitis¹ **(87% had gram-negative meningitis, no MSSA)**
- Very limited clinical data on use of cefazolin for treatment of staphylococcal meningitis **(because we were taught we couldn't use it 😊)**
- Some patients received combination therapy in Le Turnier reference **(cloxacillin arm also received combo; some patients received cefazolin monotherapy with cure)**
- Cefazolin is appropriate for spinal epidural abscess **(agree!)**

FACT: CEFAZOLIN IS PROBABLY REASONABLE FOR CNS INFECTIONS

- Cefazolin is a reasonable treatment option for susceptible CNS infections
- Clinical data are limited and the most data is with MSSA
- I wouldn't give cefazolin to my mom if she had a gram-negative CNS infection
- Studies describe higher brain **tissue** concentrations for cefazolin than nafcillin
- Many studies describe adequate CSF concentrations (if CSF concentrations matter)
- High-dose, continuous infusion might be the answer, but optimal dose is to be determined
- **2g IV q6h or 8-10g continuous infusion might be the way to go for now**

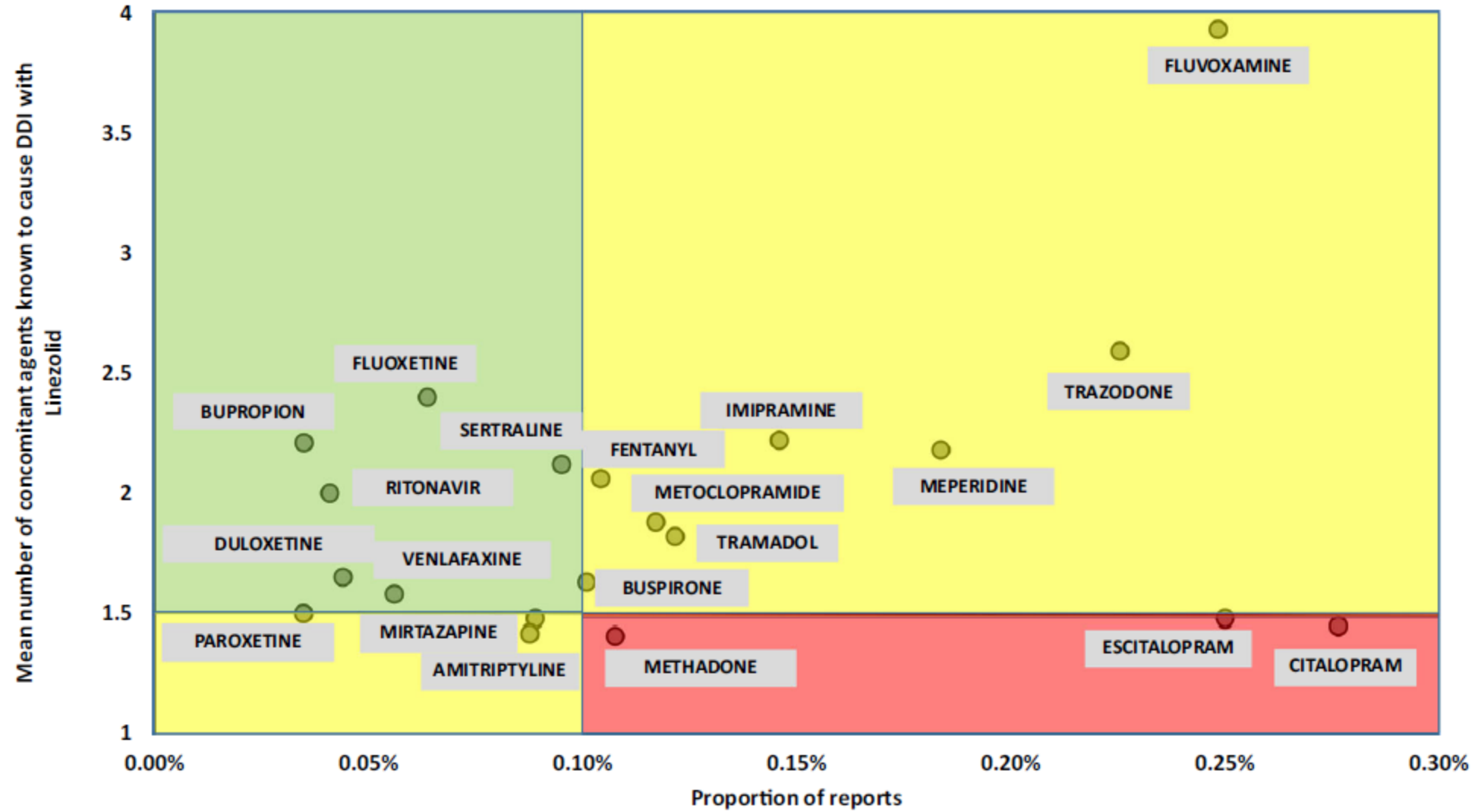
Bassaris HP, et al. Curr Ther Res Clin Exp. 1976.
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Le Turnier P, et al. Clin Microbiol Infect. 2020.
Nau R, et al. Eur J Clin Pharmacol. 1993.
Antosz K, et al. Pharmacotherapy. 2022.

MYTH: LINEZOLID MUST BE AVOIDED IN PATIENTS RECEIVING SSRIS

Monoamine Oxidase Inhibition: Linezolid is a reversible, nonselective inhibitor of monoamine oxidase. Therefore, linezolid has the potential for interaction with adrenergic and serotonergic agents.

Serotonin Syndrome

Spontaneous reports of serotonin syndrome associated with the co-administration of ZYVOX and serotonergic agents, including antidepressants such as selective serotonin reuptake inhibitors (SSRIs), have been reported (see PRECAUTIONS, Drug Interactions).



Association of Linezolid With Risk of Serotonin Syndrome in Patients Receiving Antidepressants

Anthony D. Bai, MD; Susan McKenna, BScPhm; Heather Wise, BScPhM; Mark Loeb, MD, MSc; Sudeep S. Gill, MD, MSc



- Retrospective, population-based cohort study using Canadian database
- 1134 adults 66 years or older from 2014-2021
 - 19% also taking an antidepressant
 - SSRI, SNRI, TCA, MAOI, Bupropion, Trazodone, or others
 - Also collected data on other serotonergic meds
- Most overlap = 7 days (IQR 5-10 days)
- Primary outcome = SS requiring healthcare visit (outpatient or hospitalization) within 30 days of linezolid
- **Less than 6 patients had SS** (cannot report exact number due to privacy)
- Less cases in group with concomitant antidepressants
- Maybe more altered mental status (11.6% vs 6.9%, risk difference 4.8 (0.7 to 10.1))

Review

➤ [Eur J Clin Pharmacol.](#) 2023 Jul;79(7):875-883. doi: 10.1007/s00228-023-03500-9.

Epub 2023 May 2.

Linezolid-associated serotonin toxicity: a systematic review

Fawzy Elbarbry¹, Nicholas Moshirian²

Affiliations + expand

PMID: 37129603 DOI: [10.1007/s00228-023-03500-9](#)

➤ [Int J Antimicrob Agents.](#) 2023 Jul;62(1):106843. doi: 10.1016/j.ijantimicag.2023.106843.

Epub 2023 May 7.

Real-world evaluation of linezolid-associated serotonin toxicity with and without concurrent serotonergic agents

Wesley D Kufel¹, Katie A Parsels², Bruce E Blaine³, Jeffrey M Steele⁴, Robert W Seabury⁴, Elizabeth A Asiago-Reddy⁴

Affiliations + expand

PMID: 37160238 DOI: [10.1016/j.ijantimicag.2023.106843](#)

Review

➤ [Pharmacy \(Basel\).](#) 2023 Nov 20;11(6):182. doi: 10.3390/pharmacy1106018

The Association of Serotonin Toxicity with Combination Linezolid-Serotonergic Agent Therapy: A Systematic Review and Meta-Analysis

Savanna SanFilippo^{1 2}, Jacques Turgeon³, Veronique Michaud³, Ronald G Nahass⁴, Luigi Brunetti^{1 2}

Affiliations + expand

PMID: 37987392 PMCID: [PMC10661260](#) DOI: [10.3390/pharmacy11060182](#)

FACT: LINEZOLID AND SSRI CO-ADMINISTRATION IS OKAY; COUNSEL AND MONITOR THE PATIENT

UPMC Health System Safe Practice Guideline Topic:
Linezolid Interaction Guideline
Date: 06/25/2023

LINEZOLID INTERACTIONS AND SIDE EFFECTS

1. Use of linezolid with concomitant serotonergic agents other than MAOI's is not an absolute contraindication.
2. Patients on more than 1 serotonergic agent can also receive linezolid provided it is clinically appropriate and the patient is monitored for signs of serotonin syndrome
3. There are no food restrictions for inpatients receiving linezolid
4. Therapeutic drug monitoring for linezolid should be considered in patients requiring long term linezolid (greater than 2 weeks) or requiring greater than 1 week in the setting of renal failure.

MYTH: NO DOSE ADJUSTMENT IS NEEDED FOR LINEZOLID IN PATIENTS WITH RENAL IMPAIRMENT

*“Renal Insufficiency: The pharmacokinetics of the parent drug, linezolid, are not altered in patients with any degree of renal insufficiency; however, the two primary metabolites of linezolid may accumulate in patients with renal insufficiency, with the amount of accumulation increasing with the severity of renal dysfunction. The clinical significance of accumulation of these two metabolites has not been determined in patients with severe renal insufficiency. Because similar plasma concentrations of linezolid are achieved regardless of renal function, no dose adjustment is recommended for patients with renal insufficiency. **However, given the absence of information on the clinical significance of accumulation of the primary metabolites, use of linezolid in patients with renal insufficiency should be weighed against the potential risks of accumulation of these metabolites.**”*

ACCUMULATION IN RENAL IMPAIRMENT

TABLE 1 Concentrations of linezolid and its major metabolites stratified by renal impairment

Variable	Total (<i>n</i> = 39)	Study group	
		No renal impairment (<i>n</i> = 17)	Renal impairment ^b (<i>n</i> = 22)
No. of serum samples	138	41	97
No. of samples/patient	3 (2–4)	2 (2–3)	4 (2–6)
Concentration (mg/liter) ^a			
Linezolid	10.8 (6.3–17.4)	7.6 (4.4–14.3)	12.3 (8.0–18.1)
PNU-142300	4.4 (2.5–6.6)	1.6 (0.8–3.1)	5.2 (3.8–10.9)
PNU-142586	11.4 (6.2–19.4)	4.9 (2.7–7.0)	13.8 (9.7–24.6)
Time since last dose (h)	7.5 (3.6–9.7)	7.6 (3.6–9.8)	7.5 (3.5–9.6)

^aData are presented as medians (IQR).

^bRenal impairment defined as eGFR of <60 ml/min/1.73 m².

THIS IS SEEN IN CIRRHOSIS, TOO

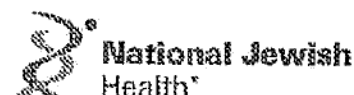
	Cases* (n = 26)	Controls† (n = 26)	<i>P</i>
PK/PD data			
Cmin, ss (mg/L), median (IQR)	20.6 (17.4)	2.7 (11.3)	<0.001
Cmax, ss (mg/L), median (IQR)	34.1 (22.7)	16.5 (11.6)	0.001
Cmin, ss < 2 mg/L, n (%)	0 (0)	10 (38.5)	0.002
Cmin, ss > 10 mg/L, n (%)	20 (76.9)	7 (26.9)	<0.001
100% time > MIC, n (%)	26 (100)	16 (61.5)	0.002
Toxicity data			
Anemia‡, n (%)	7/25 (28.0)	6/25 (24)	0.747
Thrombocytopenia§, n (%)	13/25 (52.0)	8/24 (33.3)	0.187
Final platelet count, median (IQR)§	81 (87)	203 (14)	0.001
Final platelet count <100.000/mm ³ §, n (%)	17/25 (68.0)	4/24 (16.7)	<0.001

TDM THRESHOLDS FOR LINEZOLID EFFICACY AND TOXICITY

Pharmacokinetic Measurement	Lower Threshold (Efficacy)	Upper Threshold (Toxicity)
Time spent above the MIC (T>MIC)	>82–98% ⁴⁰ or >85% ⁴²	N/A
Duration of therapy	N/A	Usually >14–28 days ^{42,83,91}
Area under the concentration versus time curve from 0 to 24 hours (AUC)	>160–400 mg × h/L depending on the MIC of the infecting pathogen ^{33,40,42}	>280–300 mg × h/L ^{33,42} or >400–800 mg × h/L ⁸⁷ depending on the duration of therapy and severity of illness; the proposed higher end of this range may be tolerable for less than 2 weeks ⁸⁷
AUC:MIC	>100 (may vary with infection site) ^{23,40,42,43}	Depends on duration of therapy and pathogen MIC
Trough concentration (C _{min})	>2 mg/L (may be higher depending on the MIC of the infecting pathogen) ⁴⁸	>7–8 mg/L ^{46,48}

FACTS

- 2-fold increase in risk of thrombocytopenia with eGFR < 60
- Linezolid myelosuppression is very likely exposure dependent
- PK/toxicodynamic model associates a C_{min} of 8.06 mg/IL as the threshold for 50% decrease in platelet precursor cells
- Consider tdm in patients with renal dysfunction, dose adjustment may be necessary



Advanced Diagnostic Laboratories
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ClinRefLabs@njhealth.org njlabs.org
CAP# 2178901 CLIA # 06D0644307

Client Name: UPMC CLINICAL REFERENCE LAB
Physician: GENERAL, PHYSICIAN
Submitter ID #: G3370645605

Infectious Disease Pharmacokinetics Laboratory

(p): 303.398.1422

(f): 303.270.2124

Drug Level	Conc.	Unit	Flags
Linezolid Level by HPLC	25.48	mcg/mL	

Crass RL, et al. AAC. 2019.
Boak LM, et al. AAC. 2014.

Apple Podcasts Preview



50 min

PLAY ►

Dosing Consult: Linezolid Therapeutic Drug Monitoring Breakpoints

Health & Fitness

[Listen on Apple Podcasts ↗](#)



In the second episode of Breakpoints' Dosing Consult series, Drs. Ryan Crass (@crasspofungin) and Amit Pai (@DosingMatters) join Dr. Jillian Hayes (@thejillianhayes) to break down the 5 Ws and 1 H of linezolid TDM.

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Bibliography

MYTH: CLINDAMYCIN IS A FIRST-LINE DRUG FOR PREVENTION OF SURGICAL SITE INFECTIONS IN PATIENTS WITH ALLERGIES

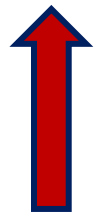
FACT



ANCEF FOR ALL

Implications of Penicillin / β -lactam Allergy

Use of second-line, non- β -lactam antibiotics



- Vancomycin
- Aztreonam
- Fluoroquinolones
- Clindamycin

Just 1 dose of clindamycin is associated with increased risk of *C. difficile* infection



14%

Risk of death¹

> 3-fold

Risk for adverse outcome³

69%

Risk of MRSA⁴

26%

Risk of Cdiff⁴

50%

Risk of Surgical Site Infection⁵

+ \$609

Drug costs during hospitalization⁶

Penicillin allergy label is a key modifiable risk factor

Surgical Prophylaxis Choices Aren't All Equal

Surgery 170 (2021) 777–782

Contents lists available at ScienceDirect

Surgery

journal homepage: www.elsevier.com/locate/surg

ELSEVIER

INFECTION/INFLAMMATION

Comparison of immediate hypersensitivity reactions to preoperative antibiotics in patients labeled as penicillin allergic

Spencer Fosnot, PharmD^a, Katelyn Currier, PharmD^a, Jay Pendell, PharmD^a, Meghan N. Jeffres, PharmD^{a,*}

^a University of Colorado Anschutz Medical Campus, Skaggs School of Pharmacy and Pharmaceutical Sciences, Aurora, CO

ARTICLE INFO

Article history:
Accepted 26 February 2021
Available online 8 April 2021

ABSTRACT

Background: Cefazolin is routinely recommended as the first-line agent for surgical antibiotic prophylaxis because it prevents more surgical site infections than second-line antibiotics. Clinicians often avoid administering cefazolin to patients who are labeled as penicillin allergic due to concerns of cross-

690 patients with reported penicillin allergies who had surgery

Hypersensitivity

Cefazolin: 3 (0.9%)

Clindamycin: 4 (1.4%)

Vancomycin: 1 (1.1%)

Cefazolin vs. second-line antibiotics for surgical site infection prevention after total joint arthroplasty among patients with a beta-lactam allergy

Norvell et al., 2023 | *Open Forum Infectious Diseases*

Retrospective Cohort



Should patients allergic to beta-lactams receive cefazolin for surgical site infection prophylaxis?



COHORT 1: Labeled as allergic to PCN/CEPH, received cefazolin for prophylaxis of SSI for TJA (hip, knee)

n = 809

COHORT 2: Labeled as allergic to PCN/CEPH, received clindamycin and/or vancomycin for prophylaxis of SSI for TJA (hip, knee)

n = 319

Included: Adults, primary total knee or hip arthroplasty, labeled allergic to PCN/CEPH

Surgical Site Infection
(superficial, PJI)



0.9%

3.8%

p = <.01

Interoperative Hypersensitivity Reaction



0.2%

1.3%

p = 0.6

Patients allergic to beta-lactams receiving cefazolin instead of clindamycin and/or vancomycin had fewer surgical site infections without an increase in immediate intraoperative hypersensitivity reactions. Cefazolin should be considered first-line regardless of penicillin allergy.



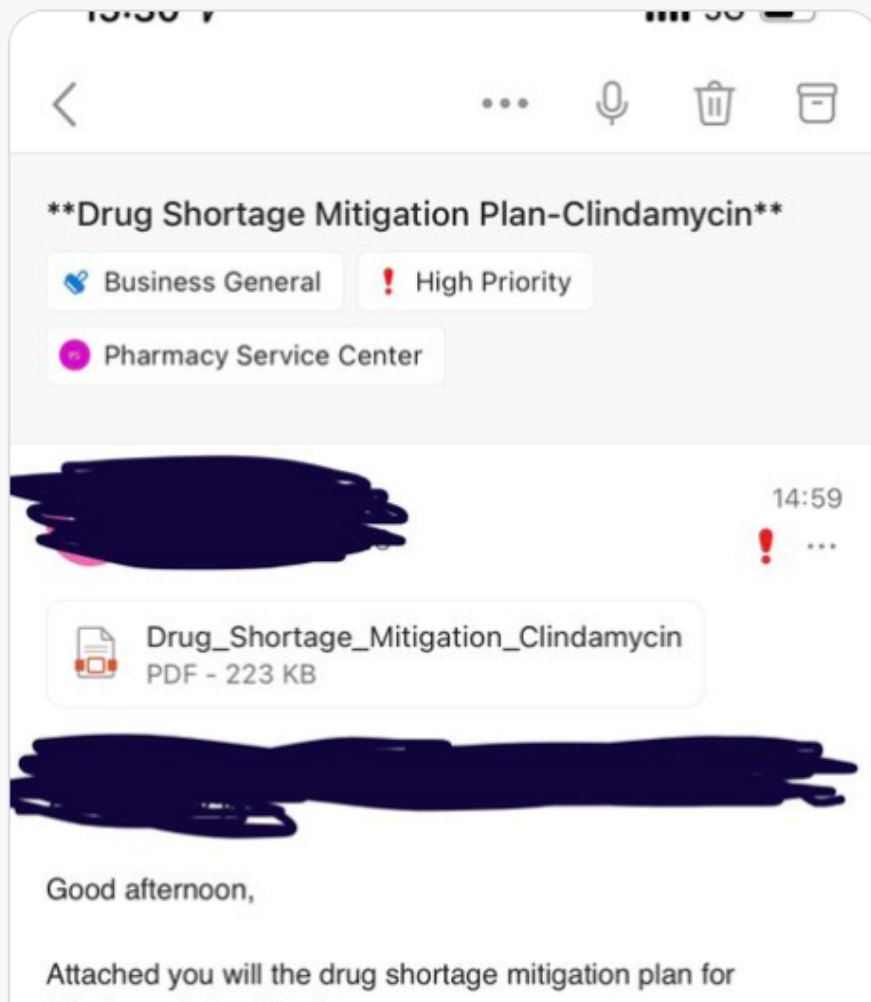
Erin McCreary @ErinMcCreary · Apr 13, 2022

Promote



I'm a big believer in finding the silver lining of drug shortages but this one is the holy grail: finally the date everyone realizes there is almost no role for **clindamycin** in the care of patients with infectious diseases

(zosyn+linezolid for nec fasc don't @ me)



MYTH: ORAL FOSFOMYCIN IS AN EXCELLENT DRUG FOR UNCOMPLICATED CYSTITIS

CLINICAL THERAPEUTICS®/VOL. 21, NO. 11, 1999

Comparison of Single-Dose Fosfomycin and a 7-Day Course of Nitrofurantoin in Female Patients with Uncomplicated Urinary Tract Infection

Gary E. Stein, PharmD

Department of Medicine, Michigan State University, East Lansing, Michigan

- Oral
- Once dose
- Rapidly bactericidal?
- Not systemically absorbed (low collateral damage)
- Early RCT of 521 patients (female, cystitis, >80% E. coli) found no difference compared to 7-days nitrofurantoin

AND THEN, THE INFAMOUS ECCMID 2018 LATE BREAKERS

- 513 women with uncomplicated cystitis
- 5 days of nitrofurantoin at 28 days =
 - Greater clinical resolution (70% vs 58%, $P = 0.004$)
 - Greater microbiologic resolution (74% vs 63%, $P = 0.04$)
 - Same drug-related ADEs

JAMA | Original Investigation

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

Angela Huttner, MD; Anna Kowalczyk, MS; Adi Turjeman, MSc; Tanya Babich, MSc; Caroline Brossier, RN; Noa Eliakim-Raz, MD; Katarzyna Kosiek, MD, PhD; Begoña Martinez de Tejada, MD, PhD; Xavier Roux, MD; Shachaf Shiber, MD; Ursula Theuretzbacher, PhD; Elodie von Dach, PhD; Dafna Yahav, MD; Leonard Leibovici, MD; Maciek Godycki-Cwirko, MD, PhD; Johan W. Mouton, MD, PhD; Stephan Harbarth, MD



Erin McCreary @ErinMcCreary · Apr 22, 2018

AWESOME presentation by @AngelaHuttner at #ECCMID2018 on effect of 5-day nitrofurantoin vs single-dose fosfomycin for uncomplicated UTIs in women. Check out the full publication, hot off the press!
[jamanetwork.com/journals/jama/...](http://jamanetwork.com/journals/jama/)

Clinical response in patients with *Escherichia coli* infections

E. coli in baseline urine culture		
	Nitrofurantoin	Fosfomycin
Number of patients randomized	255	258
Clinical response at day 28		
Patients with day 28 data available	109	115
Clinical resolution (%)	80 (76)	55 (48)
Clinical failure (%)	19 (18)	54 (48)
Indeterminate, no improvement (%)	4 (4)	2 (2)
Clinical response at day 14		
Patients with day 14 data available	105	114
Clinical resolution (%)	88 (84)	67 (59)
Clinical failure (%)	14 (13)	45 (39)
Indeterminate, no improvement (%)	3 (3)	2 (2)

*Chi square test, one degree of freedom.

Microbiologic response in patients with *Escherichia coli* infections

E. coli in baseline urine culture		
	Nitrofurantoin	Fosfomycin
Number of patients randomized	255	258
Microbiologic response at day 28		
Patients with day 28 data available	109	115
Microbiologic resolution (%)	74 (68)	63 (55)
Microbiologic failure (%)	26 (24)	52 (45)
Indeterminate, no improvement (%)	5 (5)	2 (2)
Microbiologic response at day 14		
Patients with day 14 data available	105	114
Microbiologic resolution (%)	80 (77)	63 (55)
Microbiologic failure (%)	25 (24)	51 (45)
Indeterminate, no improvement (%)	5 (5)	2 (2)

*Chi square test, one degree of freedom.

1

43

62



WHAT CHANGED?

- Increasing resistance
- Improved AST showcasing issues with non-E. coli bugs
 - Requires G6P supplementation for agar dilution
 - Other methods have issues
- Glucose-6-phosphate (G6P) is not present in human urine
 - Antibacterial activity and pharmacodynamics of fosfomycin impaired *in vivo*

Oteo J, et al. JAC. 2010.

Fu Z, et al. Front Microbiol. 2015.

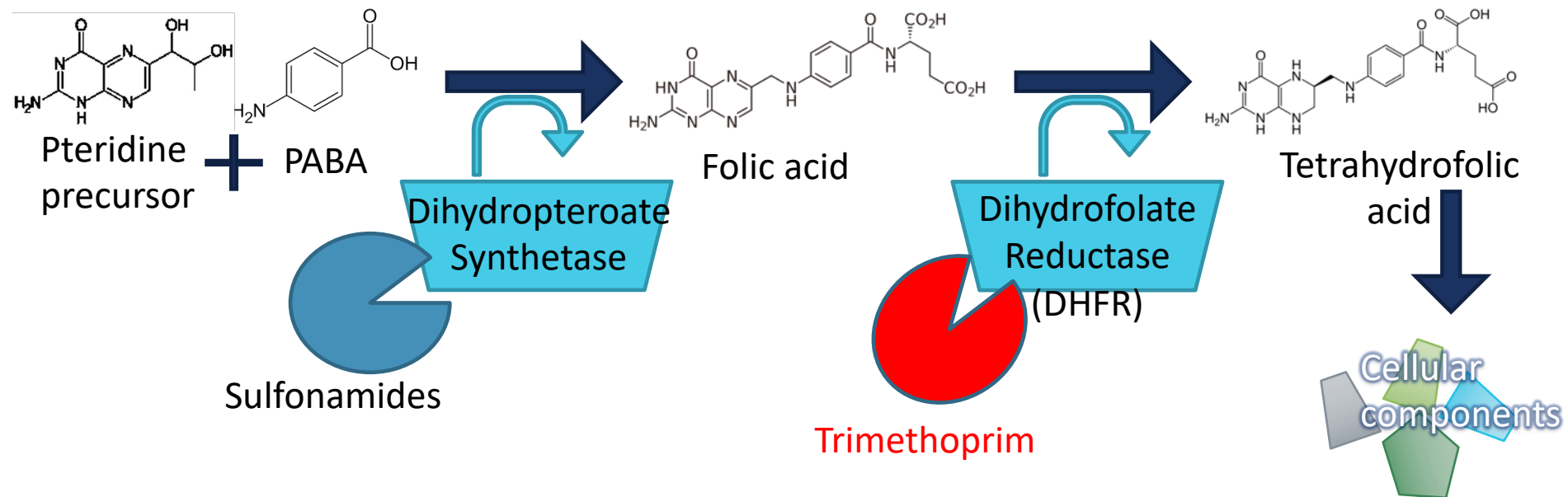
Wenzler E, et al. AAC. 2020.

Doern CD. Clinical Microbiology Newsletter. 2020.

FACT: ORAL FOSFOMYCIN IS THE BEST ASB DRUG IN THE WORLD

- Oral packets actually quite costly
- Same eGFR limitations as nitrofurantoin
- AST is a nightmare
- RCT evidence fairly convincing it's not nitrofurantoin
- Does it work in the urine??
- Every now and then we'll try to for an ESBL to avoid carbapenem outpatient

MYTH: TRIMETHOPRIM-SULFAMETHOXAZOLE DOES NOT HAVE *IN VITRO* ACTIVITY AGAINST *S. PYOGENES*



- Early studies did not control thymidine content of test media: ↑thymidine ↓sulfa inhibitory effect

What if I told you...

TABLE 2 (Continued)

Organism (no. of isolates) and drug ^g	MIC ₅₀ (μg/ml)	MIC ₉₀ (μg/ml)	MIC range (μg/ml)	% of isolates with breakpoint according to ^a :					
				CLSI			EUCAST		
				S	I	R	S	I	R
Beta-hemolytic streptococci (1,493) ^h									
Solithromycin	0.015	0.03	0.004–0.5	—	—	—	—	—	—
Telithromycin	0.015	0.12	0.008–>32	—	—	—	96.9	0.7	2.4
Azithromycin	0.12	>32	0.03–>32	75.2	0.4	24.4	75.0	0.2	24.8
Clindamycin	≤0.25	>2	≤0.25–>2	84.9	1.1	14.0	86.0	—	14.0
Penicillin	≤0.06	≤0.06	≤0.06–0.12	100.0	—	—	100.0	—	0.0
Amoxicillin-clavulanate	≤1	≤1	≤1–2	—	—	—	100.0	—	0.0
Ceftriaxone	≤0.06	0.12	≤0.06–0.5	100.0	—	—	100.0	—	0.0
Linezolid	1	1	≤0.12–1	100.0	—	—	100.0	0.0	0.0
Moxifloxacin	≤0.12	0.25	≤0.12–4	—	—	—	99.5	0.0	0.5
Tetracycline	≤0.5	>8	≤0.5–>8	53.5	1.7	44.8	17.5	1.0	46.5
TMP-SMX	≤0.5	≤0.5	≤0.5–>4	—	—	—	98.9	0.3	0.9
Vancomycin	0.25	0.5	≤0.12–1	100.0	—	—	100.0	—	0.0

^g TMP-SMX, trimethoprim-sulfamethoxazole.

^h Organisms include *Streptococcus pyogenes* (689 isolates), *Streptococcus agalactiae* (579), and *Streptococcus dysgalactiae* (225).

FACT: TMP/SMX IS PRETTY GOOD FOR SKIN INFECTIONS (INCLUDING CELLULITIS)

Comparison in
cellulitis and
abscesses

Group	Clindamycin	TMP-SMX	Difference (95% CI)
Overall ITT	212/264 (80.3%)	202/260 (77.7%)	-2.6 (-10.2 to 4.9)
Cellulitis	110/136 (80.9%)	110/114 (76.5%)	-1.3 (-15.1 to 6.1)
Abscess	63/80 (78.8%)	64/80 (80%)	1.3 (-12.9 to 15.4)
Mixed	39/47 (83%)	28/35 (80%)	-3.0 (-23.0 to 17.0)

Vs. placebo for
abscesses >5 cm

Group	TMP-SMX	Placebo	Difference (95% CI)
MITT	507/630 (80.5%)	454/617 (73.6%)	6.9 (3.2 to 11.2)

Vs. placebo for
abscesses <5 cm

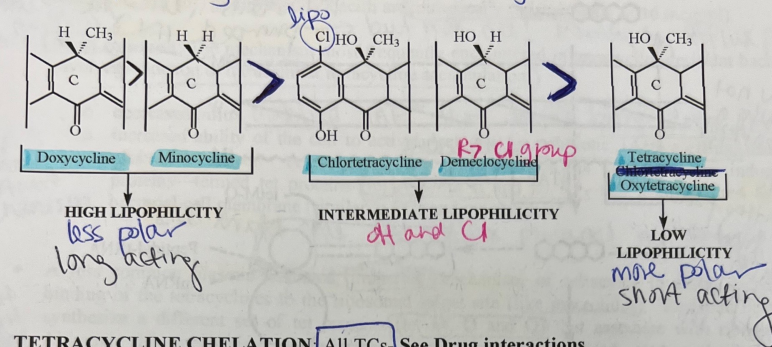
Group	Clindamycin	TMP-SMX	Placebo
MITT	221/266 (83.1%)	215/263 (81.7%)	117/257 (68.9%)

Both drugs better than placebo, no significant difference between them

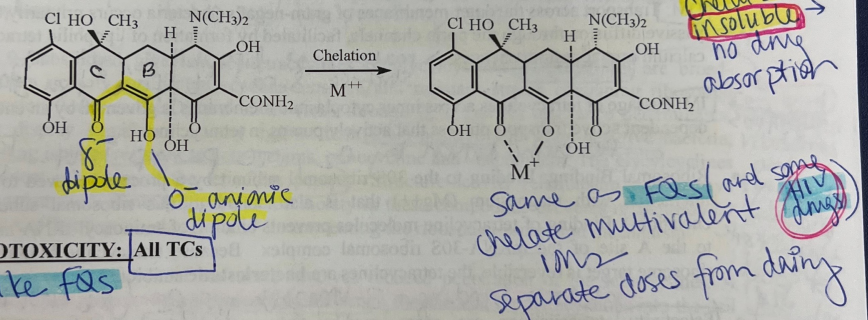
Myth: Doxycycline is contraindicated in pregnancy and pediatric patients less than 8 years old

TETRACYCLINE LIPOPHILICITY: Variable: Primary organ of Elimination

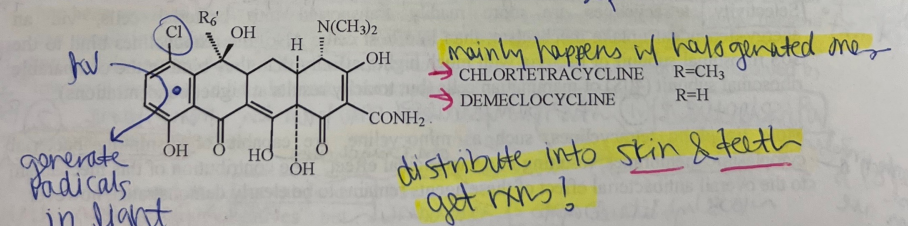
lipophilicity tends parallel hydroxylation trends



TETRACYCLINE CHELATION: All TCs - See Drug interactions



PHOTOTOXICITY: All TCs



What does all of this tell us about the tetracyclines that remain in significant use in the US???

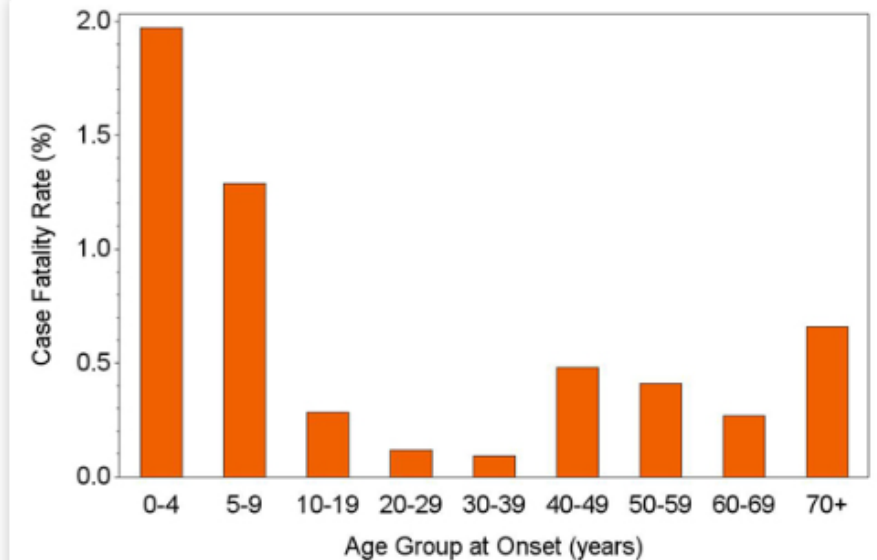
Use M & D not T

- ① no 6' OH
less polar, more stable
- ② no D ring, halogens
- ③ optimally lipophilic

FACT: PLEASE TREAT RICKETTSIAL DISEASES WITH DOXY

- Doxycycline has structural modifications that improve antibacterial activity, decrease calcium binding, and diminish ADRs compared to tetracycline
- AAP says ≤ 21 days of doxy is acceptable
- Pregnancy teams at FDA, WHO reviewing

Case Fatality Rate of Spotted Fever Rickettsiosis by Age Group, 2008-2013



Case fatality rate by age-group for spotted fever rickettsioses (including RMSF) in the United States, 2008-2012.

The current label allows for the use of doxycycline in pediatric rickettsial patients because other antibiotics are not likely to be effective for treatment. However, clearer language on the drug label may help avoid hesitation in prescribing life-saving doxycycline to children, and reinforce CDC and AAP RMSF treatment recommendations. Despite the current label warning, it is important for healthcare providers to know that doxycycline has not been shown to cause tooth staining in the dose and duration used to treat rickettsial diseases. Early administration of doxycycline in adults and children can prevent severe illness and save lives.

MYTH: RIFAMPIN AND GENTAMICIN ARE ESSENTIAL FOR TREATMENT OF STAPHYLOCOCCUS SPP. PROSTHETIC VALVE ENDOCARDITIS

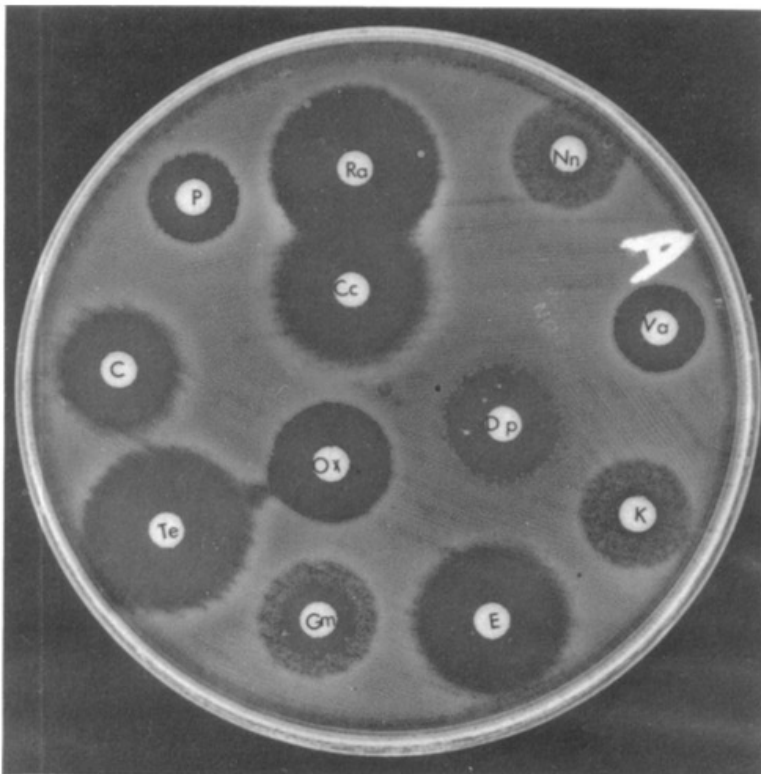


FIG. 3. Photograph of a Mueller-Hinton agar plate seeded with an undiluted homogenate from a vegetation of an animal receiving 6 days of intramuscular gentamicin. Standard Kirby-Bauer antibiotic disks placed on the agar include penicillin (P), oxacillin (Ox), methicillin (Dp), chloramphenicol (C), tetracycline (Te), erythromycin (E), clindamycin (Cc), vancomycin (Va), rifampin (Ra), and the aminoglycosides, tobramycin (Nn), gentamicin (Gm), and kanamycin (K).

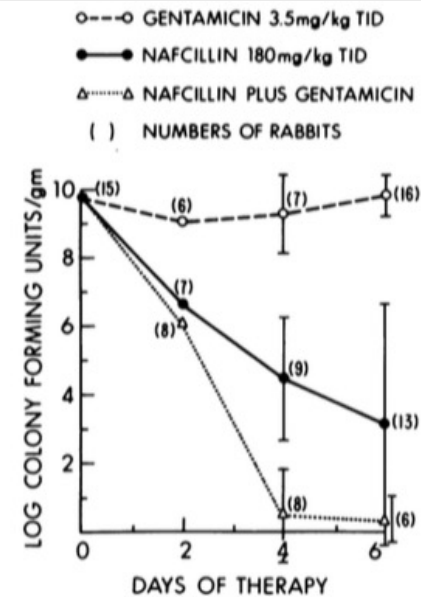


FIG. 2. Rate of killing of *S. aureus* in valvular vegetations in rabbits receiving intramuscular nafcillin, gentamicin, or the combination, three times daily, and in untreated controls. Results express the mean \pm standard deviation.

TABLE 1. Time for sterilization of infected valves

Antibiotic	No. of rabbits with sterile valves/total at:		
	2 days	4 days	6 days
Gentamicin	0/6	0/7	0/16
Nafcillin	1/7	0/9	6/13
Nafcillin + gentamicin	1/8	7/8	5/6

	PWID		NOT PWID	
	Nafcillin (n=24)	NAF + GEN (n=24)	Nafcillin (n=11)	NAF + GEN (n=19)
Valve				
Left	5	2	9	13
Both	6	5	1	4
Right	13	17	1	2
Outcomes				
Bacteremia	3.4 ± 1.2	2.9 ± 1.1	4.1 ± 1.4*	2.8 ± 1.4*
Days febrile	7 (0-20)^	3 (0-20)^	5 (3-20)	7 (0-22)
Days of leukocytosis	11.7 ± 6.6~	6.7 ± 6.5~	NR	NR

1982 RCT of
nafcillin x6 weeks +
gentamicin x2 weeks
vs nafcillin x6 weeks in
native valve IE

#IDTWITTER TO THE CAUSE



Open Forum Infectious Diseases

MAJOR ARTICLE



Deconstructing the Dogma: Systematic Literature Review and Meta-analysis of Adjunctive Gentamicin and Rifampin in Staphylococcal Prosthetic Valve Endocarditis

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Background. Based primarily on in vitro and animal models, with little data directly addressing patient outcomes, current guidelines recommend treating staphylococcal prosthetic valve endocarditis (PVE) with antibiotic combinations including gentamicin and rifampin. Here, we synthesize the clinical data on adjunctive rifampin and gentamicin in staphylococcal PVE.

Methods. We conducted a systematic review and meta-analysis of PubMed- and Cochrane-indexed studies reporting outcomes

FACT: THE BASIS FOR THIS IS... UNDERWHELMING

Study	Outcome N	Backbone* n (%)	Gent+ backbone n (%)	Rif+ backbone n (%)	Rif+ Gent+ backbone n (%)	Relapse/ Recurrence n (%)	Hospital LOS days
Karchmer 1983	Failure n=23	NR	NR	5/15 (33.3)	2/8 (25)	NR	NR
Karchmer 1983	Failure n=46	5/10 (50)	3/13 (23.1)	5/15 (33.3)	2/8 (25)	NR	NR
Ramos- Martinez 2018	1-yr mortality n=94	NR	NR	8/17 (47.1)	38/77 (49.4)	No Gent: 0/17 (0) Gent: 0/77 (0)	NR
Le Bot 2021	1-yr mortality n=180	NR	25/79 (31.6)	NR	38/101 (37.6)	No RIF: 7/79 (8.9) RIF: 6/101 (5.9)	No RIF: 31.2^ RIF: 42.3



1 hr 1 min

PLAY ▶

Who You Gonna Call? Mythbusters! Antibiotic Myths for Infectious Diseases Clinicians

Breakpoints

Health & Fitness

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Episode Notes

Drs. Jason Gallagher (@JGPharmD) and Melissa Johnson (@IDPharmacist) join Dr. Erin McCreary (@ErinMcCreary) to discuss one of the most talked about papers of the year: Antibiotic Myths for the Infectious Diseases Clinician. Tune in to hear these common myths debunked!

Antibiotic Myths for the Infectious Diseases Clinician: <https://academic.oup.com/cid/advance-article-abstract/doi/10.1093/cid/ciad357/7194976?redirectedFrom=fulltext>

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DEBUNKING ANTIBIOTIC MYTHS FOR THE INFECTIOUS DISEASES CLINICIAN



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