DEBUNKING ANTIBIOTIC MYTHS FOR THE INFECTIOUS DISEASES CLINICIAN

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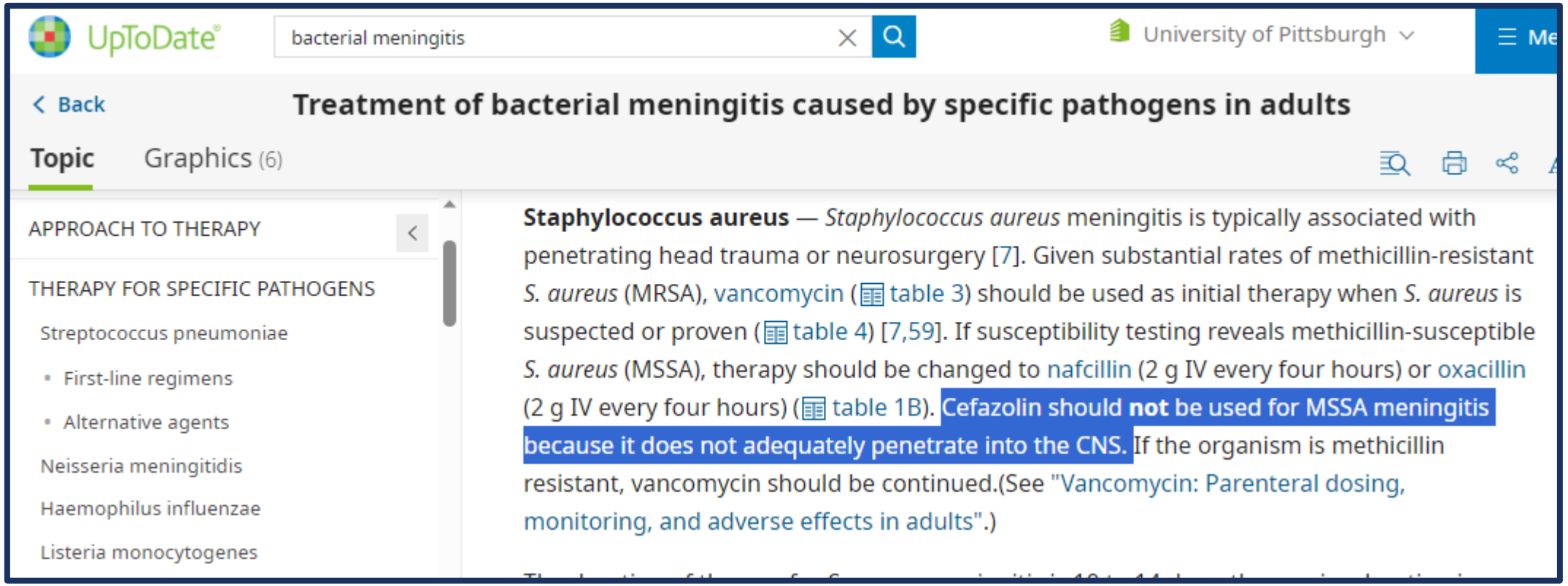
DECLARATIONS

- EKM has served on advisory boards for: Abbvie, Merck, Basilea, Shionogi, Melinta, Ferring, Cidara, Entasis, LabSimply, Pfizer, and GSK, and received speaker honorarium from GSK, Shionogi, and Pfizer.

MYTH: CEFAZOLIN SHOULD BE AVOIDED FOR CNS INFECTIONS



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.

Annals of Internal Medicine. 78:347-351, 1973
Lerner PI. Am J Med Sci. 257:125-131, 1969.
Almond HR. N Engl J Med. 281:218-219, 1969.
Turck M, et al. Ann Intern Med. 63:199-211, 1965.

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, cefpirome	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)					
Cefepime (213)		0.103			
Cefpirome (73, 181, 262)		0.145, 0.31			

Nau R, et al. Clin Microbiol Rev. 2010.

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 MIC_{90} of fungal pathogens in the echinocandin spectrum and would be anticipated to be sufficient for treatment success. This same research group has undertaken similar

Kethireddy S, Andes D. Expert Opin. Drug Metab. Toxicol. (2007) 3(4):573-581.

CEFAZOLIN PROBABLY "GETS THERE"

0148-396X/83/1202-0142$02.00/0
NEUROSURGERY
Vol. 12, No. 2, 1983
Printed in U.S.A.
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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. Deslandes [2], K. Lakhal [4], C. Deschanvres [1], R. Lecomte [1], J.-P. Talarmin [5], V. Dubée [6], R. Bellouard [2], 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

AMERICAN SOCIETY FOR MICROBIOLOGY | Antimicrobial Agents and Chemotherapy®

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 meningitis[1]
- 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

1. Schaad UB, et al. N Engl J Med 1990; 322:141-7

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 meningitis[1] **(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!)**

1. Schaad UB, et al. N Engl J Med 1990; 322:141-7

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**

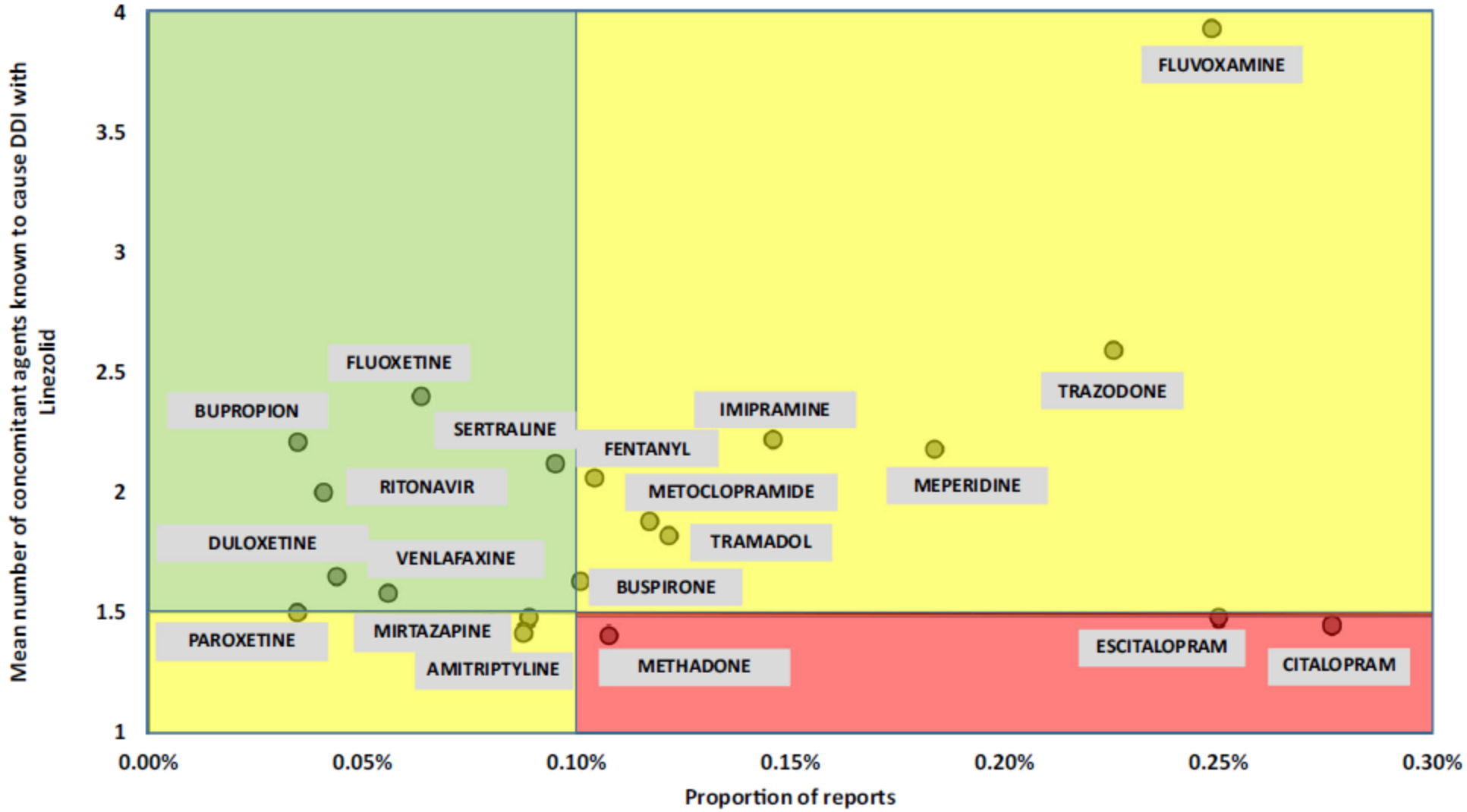
Bassaris HP, et al. Curr Ther Res Clin Exp. 1976.
Frame PT, et al. Neurosurgery. 1983.
Novak AR, et al. OFID. 2022.
Gregoire M, et al. AAC. 2019.
Le Turnier P, et al. Clin Microbiol Infect. 2020.
Nau R, et al. Eur J Clin Pharmacol. 1993.
Antosz K, et al. Pharmacotherapy. 2022.

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).

Zyvox FDA Approval 2002
Package Insert last updated 2011: Zyvox (linezolid) injection label (fda.gov)



Gatti et al. European Journal of Clinical Pharmacology. 2021.

Original Investigation | Pharmacy and Clinical Pharmacology

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
  - qSSRI, 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))

Bal AD, et al. Jama Network Open. 2022.

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."***

Zyvox FDA Approval 2002
Package Insert last updated 2011: Zyvox (linezolid) injection label (fda.gov)

ACCUMULATION IN RENAL IMPAIRMENT

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

Variable	Total (n = 39)	Study group	
		No renal impairment (n =17)	Renal impairment[b] (n = 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)

[a]Data are presented as medians (IQR).
[b]Renal impairment defined as eGFR of <60 ml/min/1.73 m².

Souza E, et al. AAC. 2020.

THIS IS SEEN IN CIRRHOSIS, TOO

	Cases* (n = 26)	Controls† (n = 26)	*P*
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**

Luque S, et al. Therapeutic Drug Monitoring. 2019.

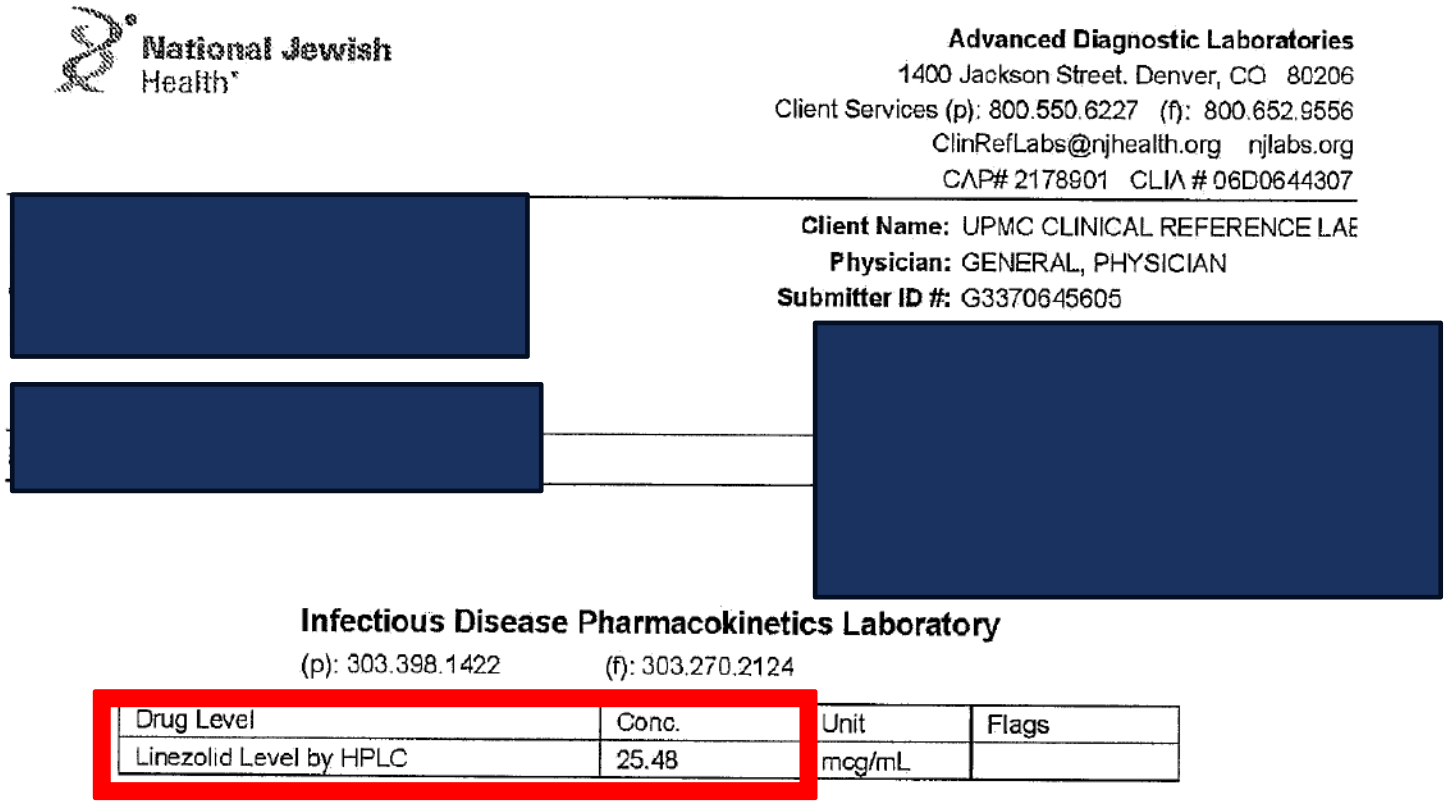
TDM THRESHOLDS FOR LINEZOLID EFFICACY AND TOXICITY

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]

Rao GG, et al. Ther Drug Monit. 2020

FACTS

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



National Jewish Health

Advanced Diagnostic Laboratories
1400 Jackson Street. Denver, CO 80206
Client Services (p): 800.550.6227 (f): 800.652.9556
ClinRefLabs@njhealth.org njlabs.org
CAP# 2178901 CLIA # 06D0644307

Client Name: UPMC CLINICAL REFERENCE LAE
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

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%	> 3-fold	69%	26%	50%	+ $609
Risk of death[1]	Risk for adverse outcome[3]	Risk of MRSA[4]	Risk of Cdiff[4]	Risk of Surgical Site Infection[5]	Drug costs during hospitalization[6]

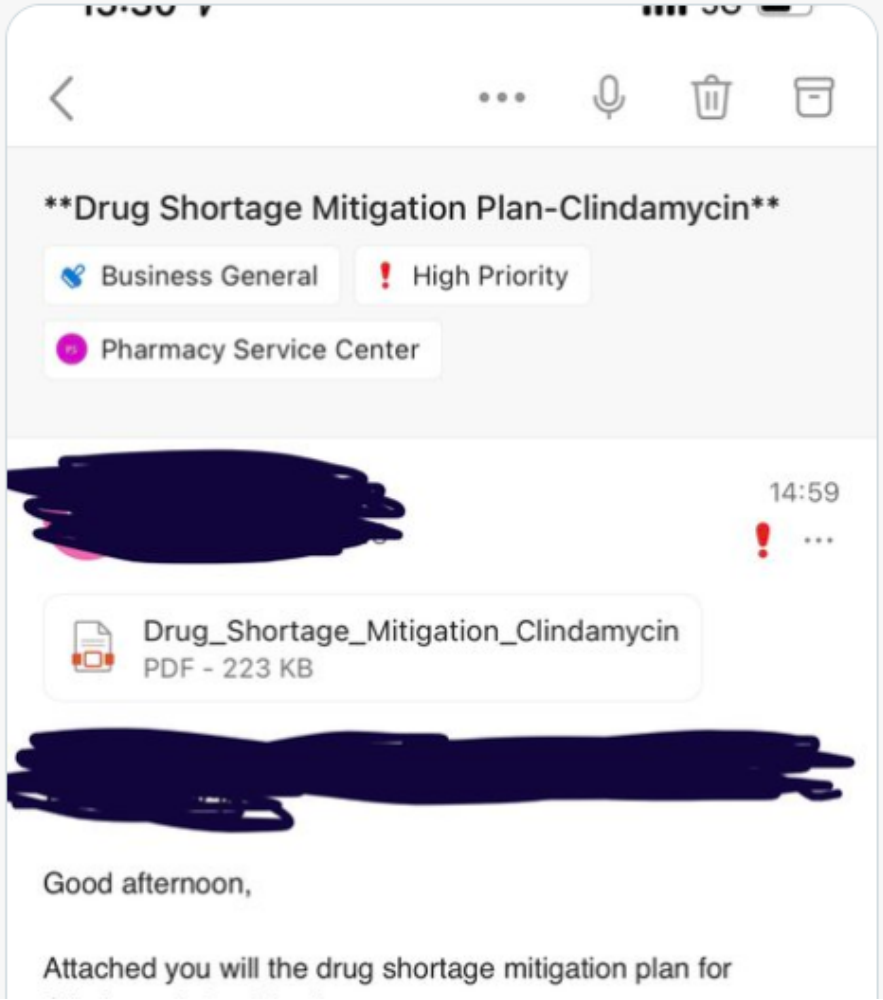
Penicillin allergy <u>label</u> is a key modifiable risk factor

1. Blumenthal KG, et al. J Gen Intern Med. 2019; 34 (9): 1685-7. 2. Sacco KA, et al. Allergy. 2017;72(9):1288–96.. 3. Jeffres MN, et al. J Allergy Clin Immunol Pract. 2016;137(4):1148–53
4. Blumenthal KG, et al. BMJ. 2018;361:k2400 5. Blumenthal KG, et al. Clin Infect Dis. 2018;66:329-336 6. Mattingly TJ, et al. J Allergy Clin Immunol Pract. 2018;6(5):1649-1654.

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

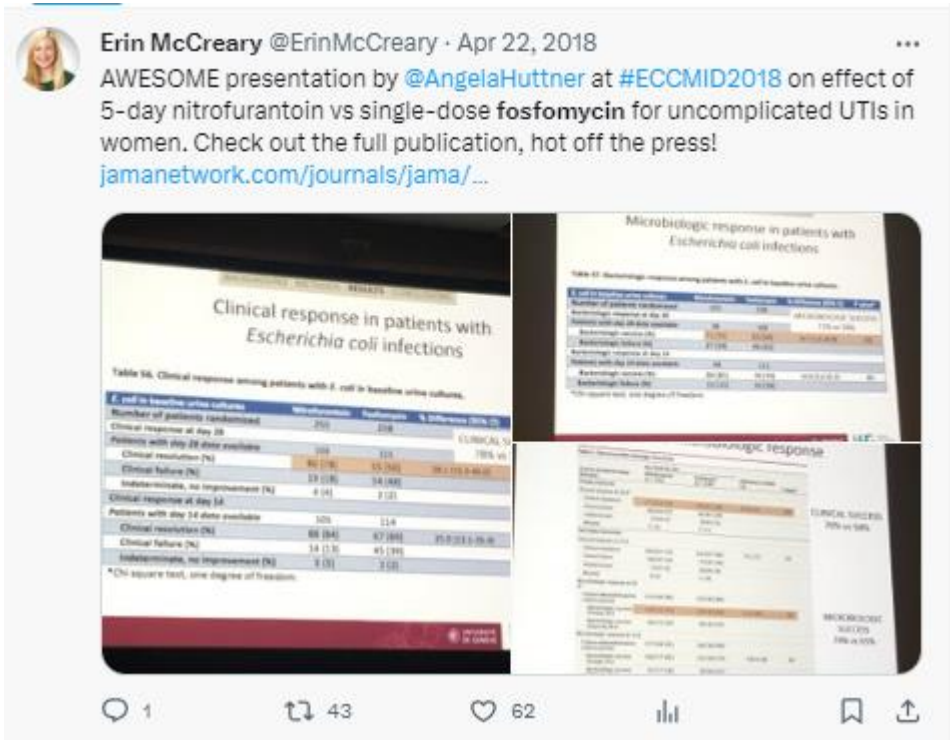
- 513 women with uncomplicated cystitis
- 5 days of nitrofurantoin at 28 days =
  - Greater clinical resolution (70% vs 58%, P= 0.004)
  - Greater microbiologic resolution (74% vs 63%, P = 0.04)
  - Same drug-related ADEs

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-Ćwirko, MD, PhD; Johan W. Mouton, MD, PhD; Stephan Harbarth, MD



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,e t 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

TOP 10 MYTHS REGARDING THE DIAGNOSIS AND TREATMENT OF CELLULITIS

Erin K. McCreary, PHARMD, BCPS,* Melissa E. Heim, PHARMD, BCCCP,† Lucas T. Schulz, PHARMD, BCPS (AQ-ID),* Robert Hoffman, MD,‡ Jeffrey Pothof, MD,§ and Barry Fox, MD||

2. For patients who warrant MRSA coverage but do not need intravenous antibiotics, TMP-SMX, doxycycline, or linezolid can be initiated. Providers should note that while studies have demonstrated the activity of TMP-SMX against β-hemolytic streptococci, overall the activity of TMP-SMX and doxycycline against β-hemolytic streptococci is largely unknown (8,47).
   a. If TMP-SMX or doxycycline is initiated, it is reasonable to consider combination therapy with a β-lactam antibiotic for the treatment of possible mixed MRSA/streptococcal infection (8).

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

McCreary EK, et al. J Emerg Med. 2017;53 (4):485-492.

Open Forum Infectious Diseases

REVIEW ARTICLE

Sulfamethoxazole-Trimethoprim (Cotrimoxazole) for Skin and Soft Tissue Infections Including Impetigo, Cellulitis, and Abscess

Asha C. Bowen,[1,2,3] Jonathan R. Carapetis,[1,2] Bart J. Currie,[3,4] Vance Fowler Jr.,[5] Henry F. Chambers,[6] and Steven Y. C. Tong[3,7]

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

Miller LG, et al. N Engl J Med. 2015;372:1093-103.
Talan DA, et al. N Engl J Med. 2016;374:823-32.

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 S	CLSI I	CLSI R	EUCAST S	EUCAST I	EUCAST 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	[illegible]	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	—	—	[illegible]	—	0.0

[g] TMP-SMX, trimethoprim-sulfamethoxazole.

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

Farrell D, et al. AAC. 2016;60(6):3662-3668.

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REVIEW ARTICLE

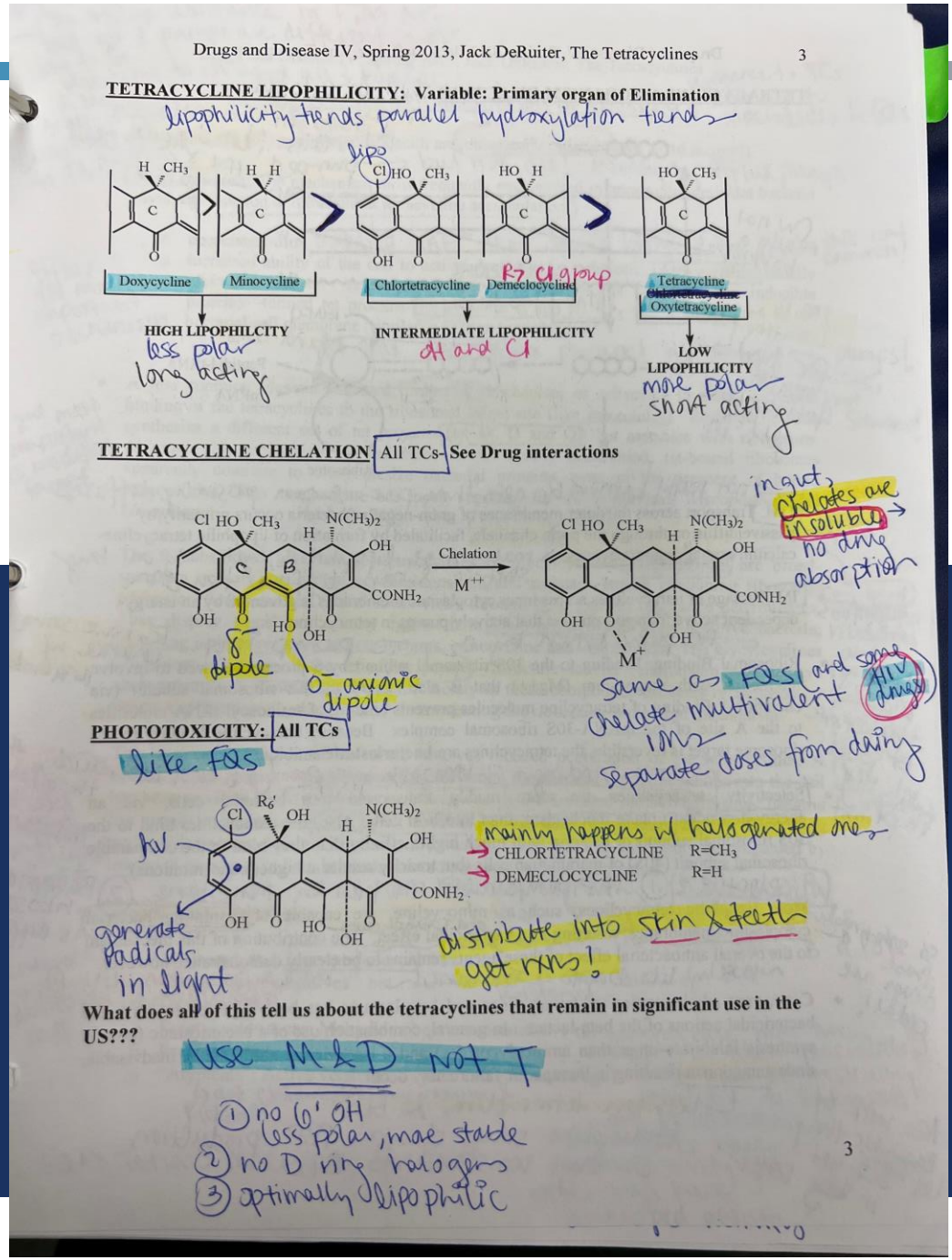
Sulfamethoxazole-Trimethoprim (Cotrimoxazole) for Skin and Soft Tissue Infections Including Impetigo, Cellulitis, and Abscess

Asha C. Bowen,[1,2,3] Jonathan R. Carapetis,[1,2] Bart J. Currie,[3,4] Vance Fowler Jr.,[5] Henry F. Chambers,[6] and Steven Y. C. Tong[3,7]

- Early studies did not control thymidine content of test media
  - ↑thymidine ↓sulfa inhibitory effect
- Nonpurulent cellulitis → β-lactam <u>monotherapy</u>
- **Impetigo, purulent cellulitis, abscess, wound → TMP/SMX <u>monotherapy</u>**
  - >20% of patients had area erythema >75 cm^2
  - Talan 2016
    - 2 DS TMP/SMX PO BID x 7 days = 80% cure of drained abscess
  - Miller 2015
    - 2 SS TMP/SMX PO BID x 10 days = 76.4% cure (abscess, cellulitis, & mixed)

Miller LG, et al. N Engl J Med. 2015;372:1093-103.
Talan DA, et al. N Engl J Med. 2016;374:823-32.

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



Drugs and Disease IV, Spring 2013, Jack DeRuiter, The Tetracyclines 3

TETRACYCLINE LIPOPHILICITY: Variable: Primary organ of Elimination

lipophilicity trends parallel hydroxylation trends

Doxycycline — Minocycline

HIGH LIPOPHILCITY

less polar

long acting

Chlortetracycline — Demeclocycline

R7 Cl group

INTERMEDIATE LIPOPHILICITY

OH and Cl

Tetracycline — Oxytetracycline

LOW LIPOPHILICITY

more polar

short acting

TETRACYCLINE CHELATION: All TCs- **See Drug interactions**

Chelation

M^{++}

dipole

anionic dipole

in gut, chelates are insoluble → no drug absorption

Same as FQs (and some HIV drugs)

chelate multivalent ions

separate doses from dairy

PHOTOTOXICITY: All TCs

like FQs

generate radicals in light

mainly happens w/ halogenated ones

CHLORTETRACYCLINE R=CH_3

DEMECLOCYCLINE R=H

distribute into skin & teeth

get rxns!

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

Use M & D not T

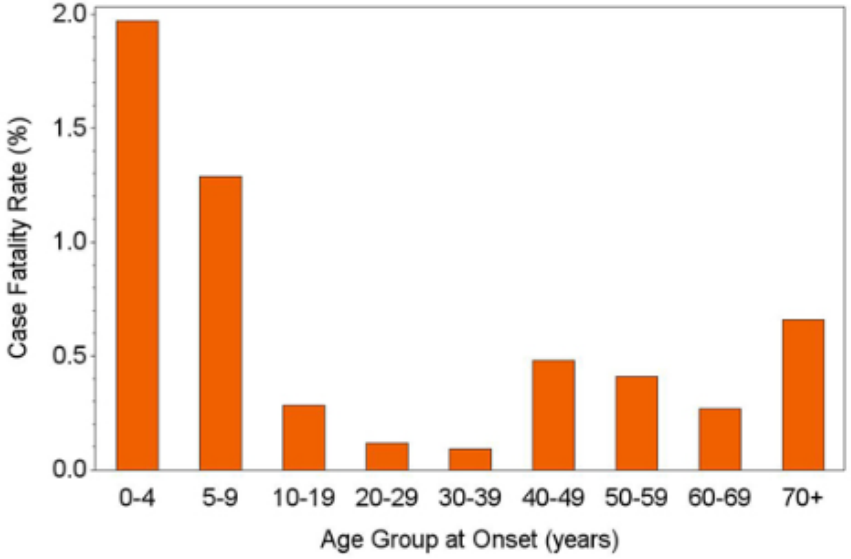
1. no 6' OH
   less polar, more stable
2. no D ring halogens
3. optimally lipophilic

3

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.

CDC.gov: Research on doxycycline and tooth staining

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

Fact: I direct you to a beautiful review on this topic in OFID

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MAJOR ARTICLE

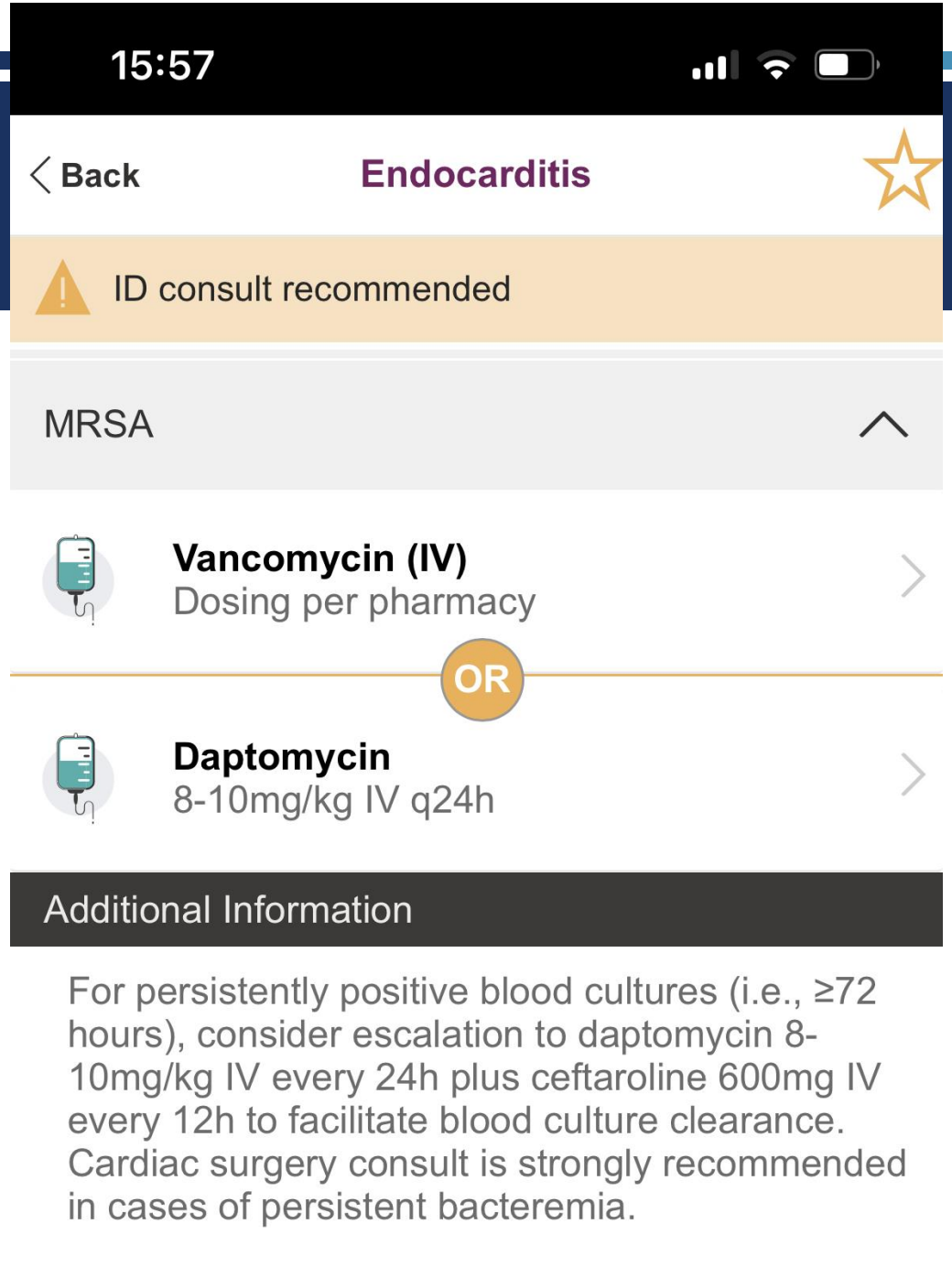
IDSA Infectious Diseases Society of America

hivma hiv medicine association

OXFORD

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

Jonathan H. Ryder,[1,©] Steven Y. C. Tong,[2,3] Jason C. Gallagher,[4] Emily G. McDonald,[5] Irani Thevarajan,[2,3] Todd C. Lee,[5,a] and Nicolás W. Cortés-Penfield[1,a]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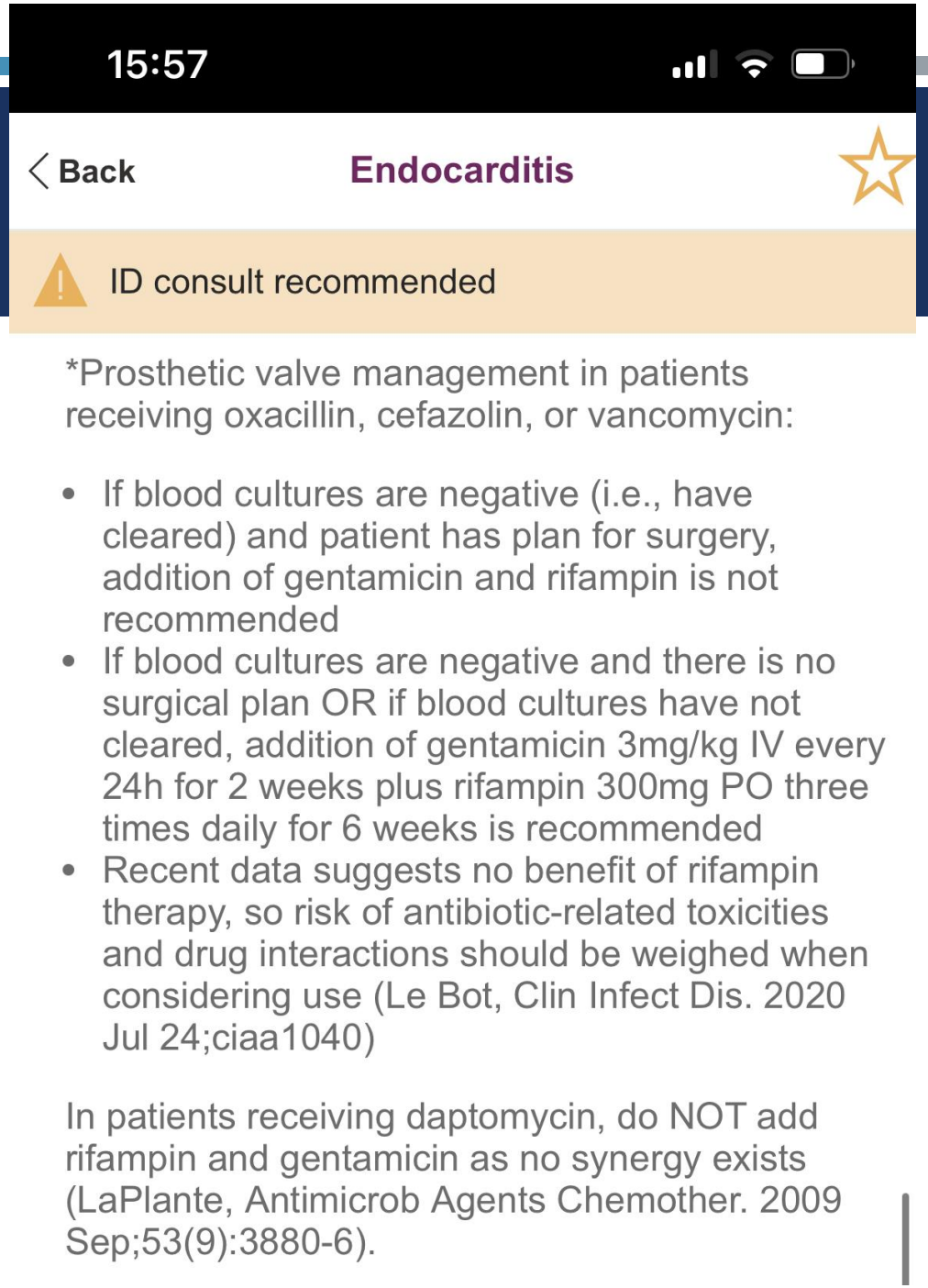
Endocarditis
ID consult recommended
MRSA
Vancomycin (IV)
Dosing per pharmacy
OR
Daptomycin
8-10mg/kg IV q24h
Additional Information
For persistently positive blood cultures (i.e., ≥72 hours), consider escalation to daptomycin 8-10mg/kg IV every 24h plus ceftaroline 600mg IV every 12h to facilitate blood culture clearance. Cardiac surgery consult is strongly recommended in cases of persistent bacteremia.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Endocarditis
ID consult recommended
*Prosthetic valve management in patients receiving oxacillin, cefazolin, or vancomycin:
• If blood cultures are negative (i.e., have cleared) and patient has plan for surgery, addition of gentamicin and rifampin is not recommended
• If blood cultures are negative and there is no surgical plan OR if blood cultures have not cleared, addition of gentamicin 3mg/kg IV every 24h for 2 weeks plus rifampin 300mg PO three times daily for 6 weeks is recommended
• Recent data suggests no benefit of rifampin therapy, so risk of antibiotic-related toxicities and drug interactions should be weighed when considering use (Le Bot, Clin Infect Dis. 2020 Jul 24;ciaa1040)
In patients receiving daptomycin, do NOT add rifampin and gentamicin as no synergy exists (LaPlante, Antimicrob Agents Chemother. 2009 Sep;53(9):3880-6).

DEBUNKING ANTIBIOTIC MYTHS FOR THE INFECTIOUS DISEASES CLINICIAN

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