Updates in Infectious Diseases

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Disclosures

- I have no disclosures or financial relationships relevant to the content of this activity.

Learning Objectives

- At the completion of this activity, **pharmacists** will be able to:
  - Utilize dose-optimization techniques for vancomycin
  - Advocate for pharmacy-driven beta-lactam allergy services in all healthcare settings
  - Justify shorter durations of therapy for common infections
- At the completion of this activity, **pharmacy technicians** will be able to:
  - Explain the role of non-ID trained healthcare team members in antimicrobial stewardship
  - Identify rapid diagnostic technologies and their role in antimicrobial stewardship
  - List newly approved antimicrobial agents

Outline

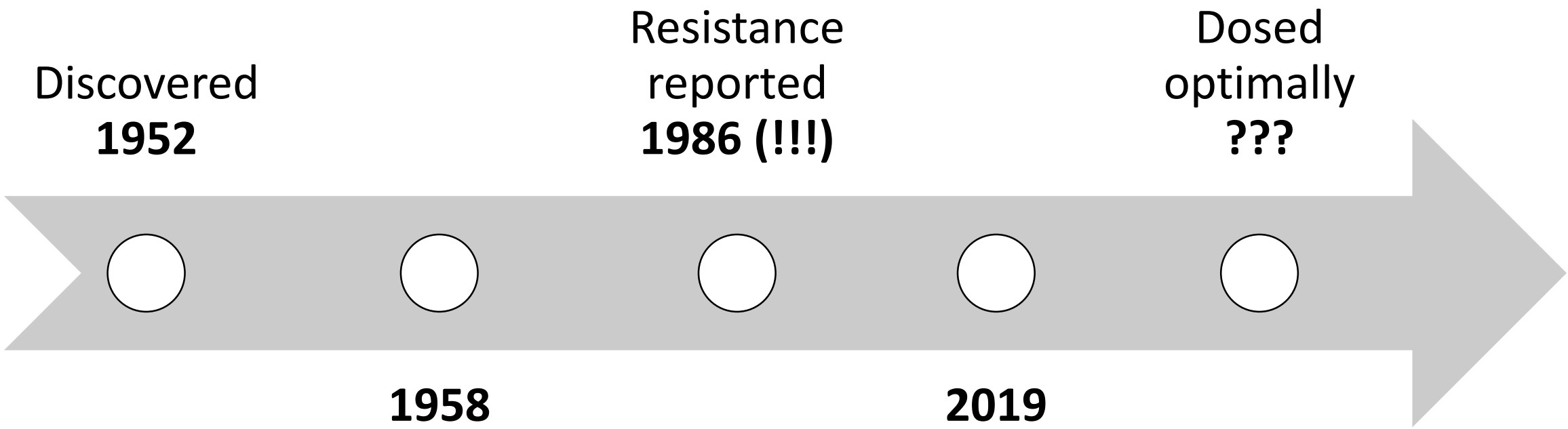
- Vancomycin AUC-based dosing
- Dose-optimization of other antimicrobials
- Beta-lactam allergies
- Stewardship resources and personnel
- Optimal treatment of ESBL infections
- Rapid diagnostic technologies
- Durations of therapy for common infections
- New guidelines with a focus on asymptomatic bacteriuria
- Formulary considerations for novel antimicrobials
- Social factors in antibiotic stewardship

Disclaimer

- If I am missing your favorite article or ID-related topic, I am sorry
- ID is the best subject ever
- Every single patient will have an ID consideration (at some point)
- There are a LOT of compelling data published almost daily (yay!)
- I can’t possibly cover it all (☹)
- But I will do my best ☺

ID = Infectious Diseases

A brief history of vancomycin



Levine, DP. Clin Infect Dis. 2006;42:S5–12.

AUC/MIC isn't new

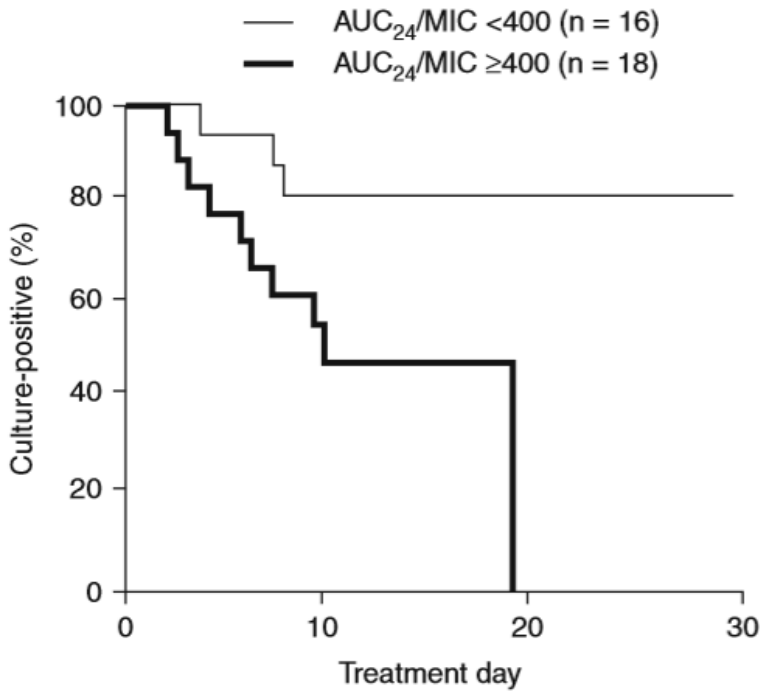
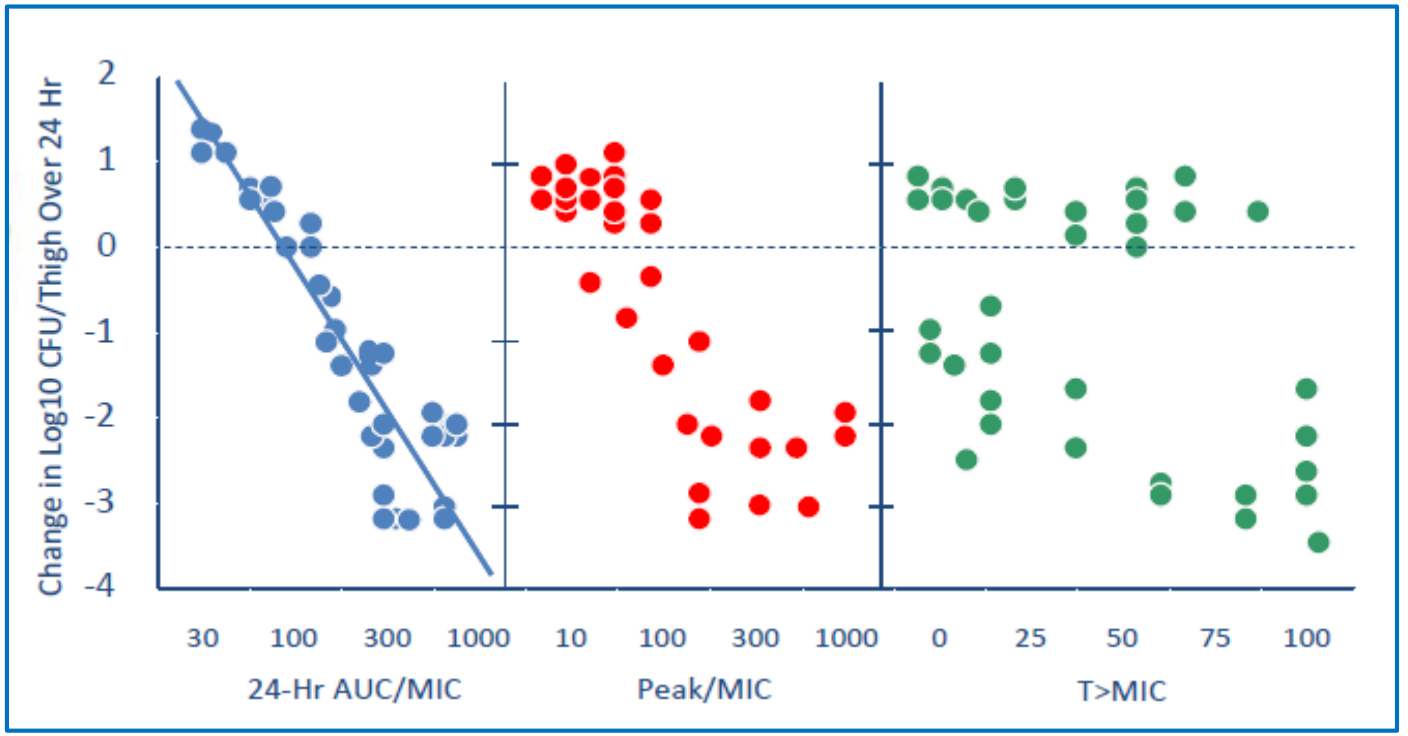


Fig. 4. Time (days of therapy) to bacterial eradication vs vancomycin AUC_{24}/MIC <400 and AUC_{24}/MIC ≥400 illustrated by a Kaplan-Meier survival plot of day of therapy vs the percentage of patients remaining culture-positive on that day. The two AUC_{24}/MIC groups differed significantly (p = 0.0402). **AUC_{24}/MIC** = steady-state 24-hour area under the concentration-time curve divided by the minimum inhibitory concentration.

Moise-Broder PA, et al. Clin Pharmacokinet. **2004**;43(13):925-42.



Ebert S. In vitro cidal activity and pharmacokinetic parameters for vancomycin against methicillin-susceptible and resistant S. aureus. [abstract 439]. In: Program and abstracts of the 27th Interscience Conference on Antimicrobial Agents and Chemotherapy**. 1987**.

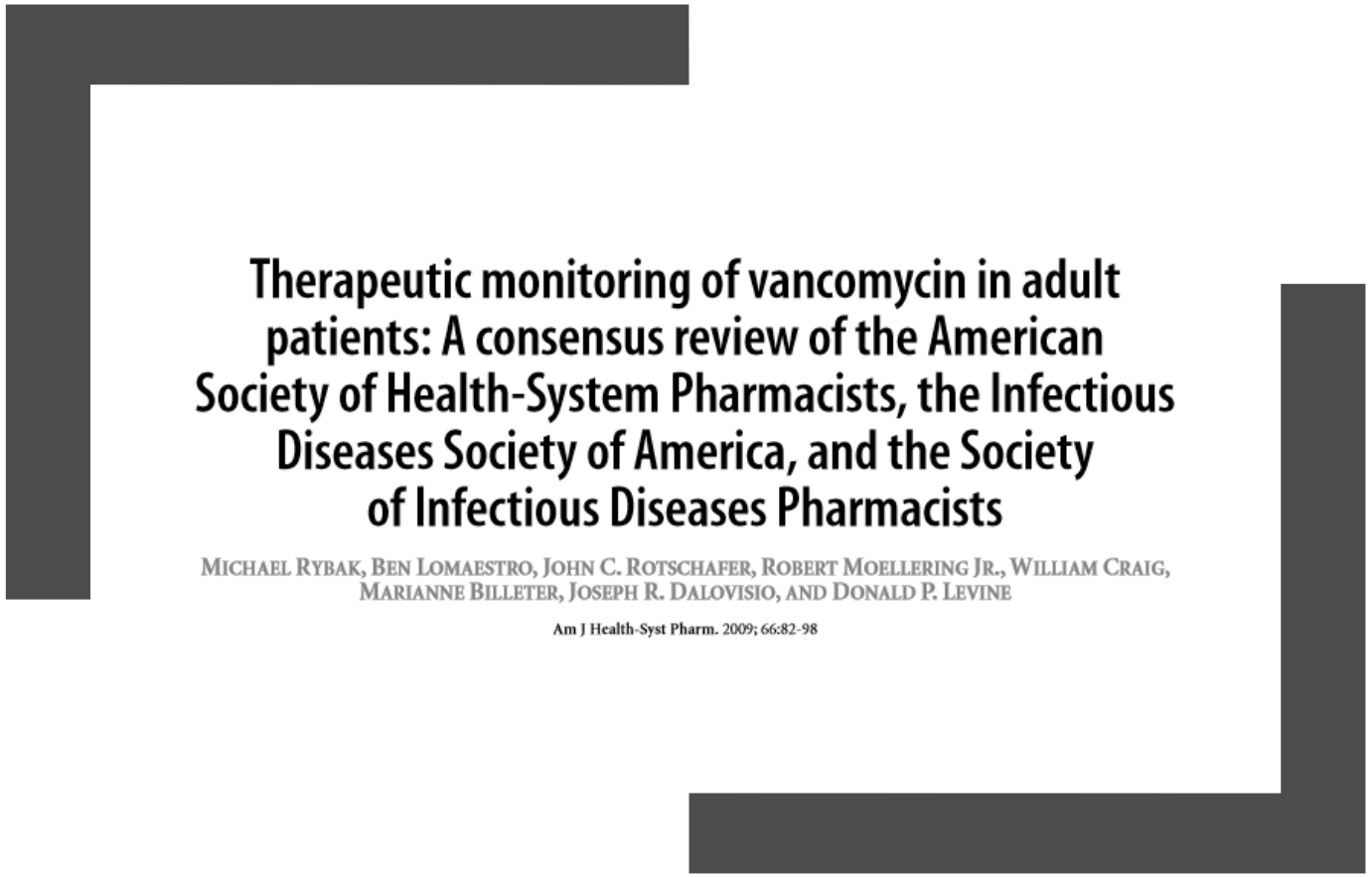
Table IV. Odds ratios for clinical success

Characteristic	Odds ratio	95% CI	p-Value
Vancomycin AUC_{24}/MIC value ≥350	7.19	1.91, 27.3	0.0036

Moise-Broder PA, et al. Clin Pharmacokinet. **2004**;43(13):925-42.

The guidelines said this, too.

Rybak MJ, et al. Am J Health Syst Pharm. 2009;66(1):82-98.



Therapeutic monitoring of vancomycin in adult patients: A consensus review of the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, and the Society of Infectious Diseases Pharmacists

MICHAEL RYBAK, BEN LOMAESTRO, JOHN C. ROTSCHAFER, ROBERT MOELLERING JR., WILLIAM CRAIG, MARIANNE BILLETER, JOSEPH R. DALOVISIO, AND DONALD P. LEVINE

Am J Health-Syst Pharm. 2009; 66:82-98

"An **AUC/MIC ratio of ≥400** has been advocated as a target to achieve clinical effectiveness with vancomycin. Animal studies and limited human data appear to demonstrate that vancomycin is not concentration dependent and that the **AUC/MIC is a predictive pharmacokinetic parameter for vancomycin**."

But logistically…

- "However, because **it can be difficult** in the clinical setting to obtain multiple serum vancomycin concentrations to determine the AUC and subsequently calculate the AUC/MIC, **trough serum concentration monitoring**, which can be used as a **surrogate** marker for AUC, is recommended as the most accurate and practical method to monitor vancomycin."

Rybak M, et al. Am J Health Syst Pharm. 2009;66(1):82-98.

And so we landed on 15-20

- "Based on the potential to improve penetration, increase the probability of optimal target serum vancomycin concentrations, and improve clinical outcomes for complicated infections such as bacteremia, endocarditis, osteomyelitis, meningitis, and hospital-acquired pneumonia caused by *S. aureus*, **total trough serum vancomycin concentrations of 15–20 mg/L are recommended**. Trough serum vancomycin concentrations in that range ***should*** achieve an AUC/MIC of ≥400 in most patients if the MIC is ≤1 mg/L."
- Level of evidence = III, grade of recommendation = B

Rybak M, et al. Am J Health Syst Pharm. 2009;66(1):82-98.

Oops…

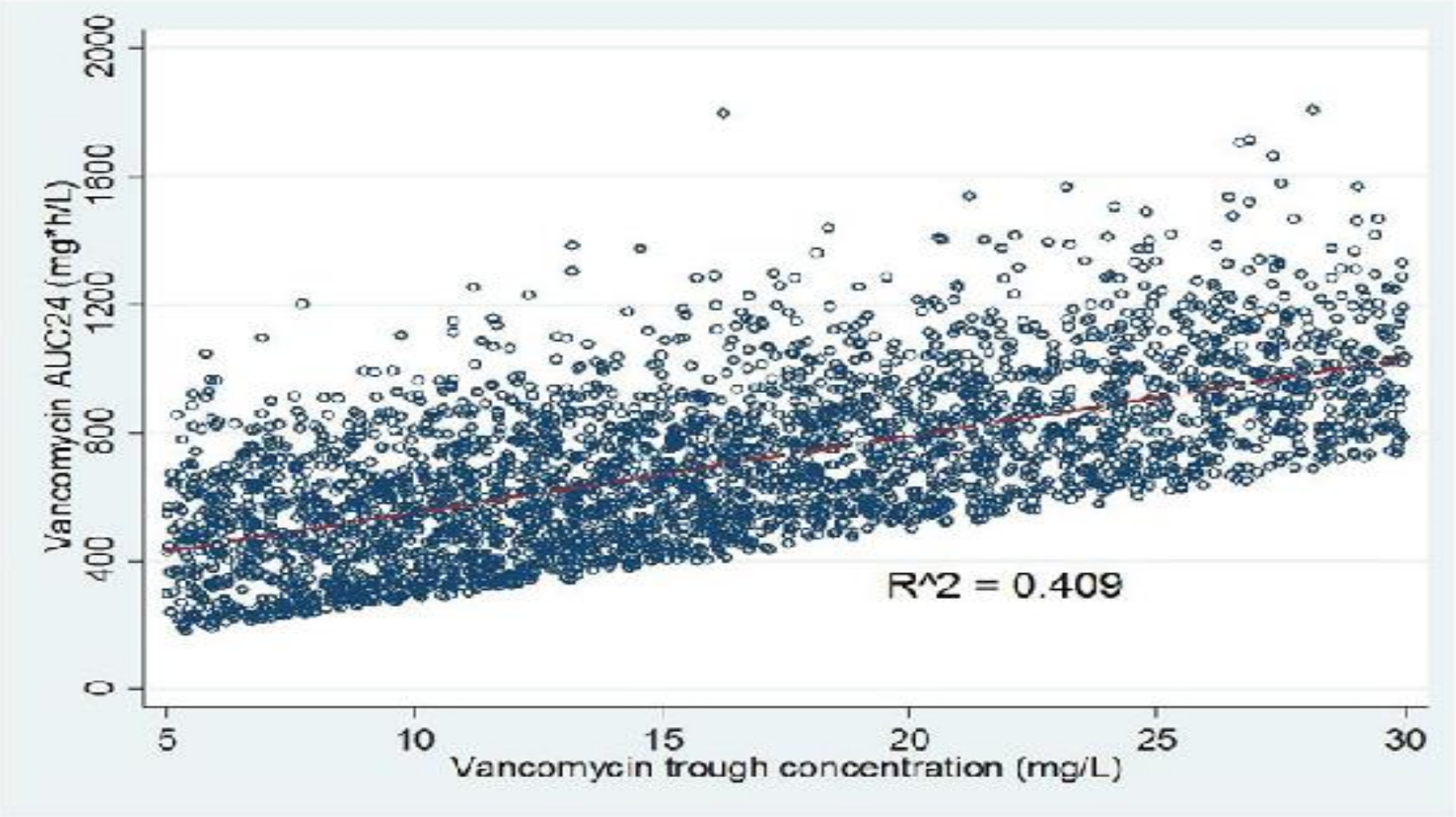


Fig. 2. Scatter and linear fit plot of vancomycin area under the curve over 24 h (AUC24) versus trough vancomycin concentration from 5000 subject Monte Carlo simulation.

Pai MP Adv Drug Deliv Rev. 2014

Double oops

Study or Subgroup	High troughs ≥15mg/L Events	Total	Low trough <15mg/L Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Bosso et al. (21)	42	142	13	146	9.8%	4.30 [2.19, 8.43]
Cano et al. (22)	22	89	7	99	7.2%	4.32 [1.74, 10.69]
Chung et al. (23)	12	25	16	48	6.5%	1.85 [0.69, 4.96]
Hermsen et al. (30)	5	16	4	39	3.6%	3.98 [0.91, 17.46]
Hidayat et al. (13)	11	63	0	32	1.1%	14.24 [0.81, 249.87]
Jeffres et al. (15)	27	49	13	45	7.7%	3.02 [1.28, 7.11]
Kralovicova et al. (31)	21	60	29	138	9.8%	2.02 [1.04, 3.96]
Kullar et al. (32)	8	116	1	84	2.0%	6.15 [0.75, 50.13]
Kullar et al. (8)	27	139	23	141	10.6%	1.24 [0.67, 2.28]
Lodise et al. (36)	7	27	14	139	6.2%	3.13 [1.12, 8.69]
McKamy et al. (38)	16	57	8	110	7.0%	4.98 [1.98, 12.52]
Minejima et al. (39)	17	72	25	155	9.6%	1.61 [0.80, 3.21]
Prabaker et al. (43)	7	54	24	294	7.3%	1.68 [0.68, 4.11]
Wunderink et al. (50)	26	118	24	215	10.7%	2.25 [1.22, 4.13]
Zimmermann et al. (51)	8	12	0	33	1.0%	126.56 [6.19, 2585.90]
Total (95% CI)		**1039**		**1718**	**100.0%**	**2.67 [1.95, 3.65]**
Total events	256		201			

Heterogeneity: $Tau^2 = 0.14$; $Chi^2 = 23.89$, df = 14 (P = 0.05); $I^2 = 41\%$

Test for overall effect: Z = 6.13 (P < 0.00001)

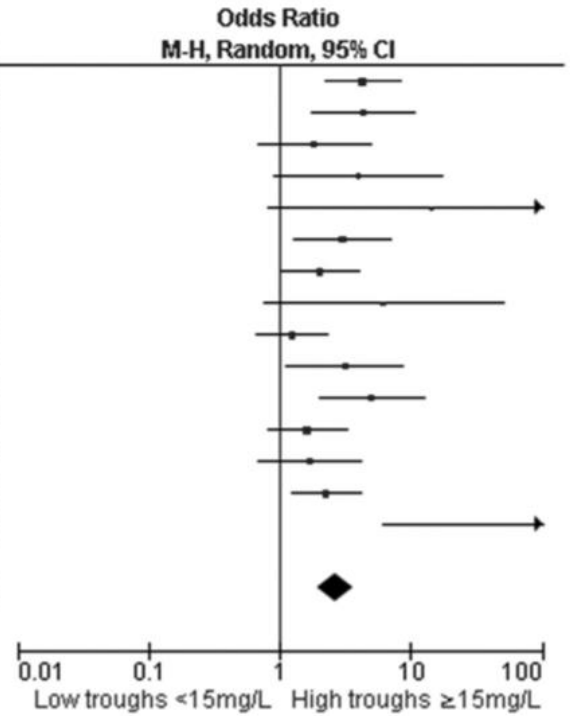


FIG 1 Forest plot (using Mantel-Haenszel [M-H] analysis) of events denoting nephrotoxicity associated with vancomycin, comparing rates for trough levels of ≥15 mg/dl and <15 mg/dl. Squares indicate point estimates, and the size of the square indicates the weight of each study.

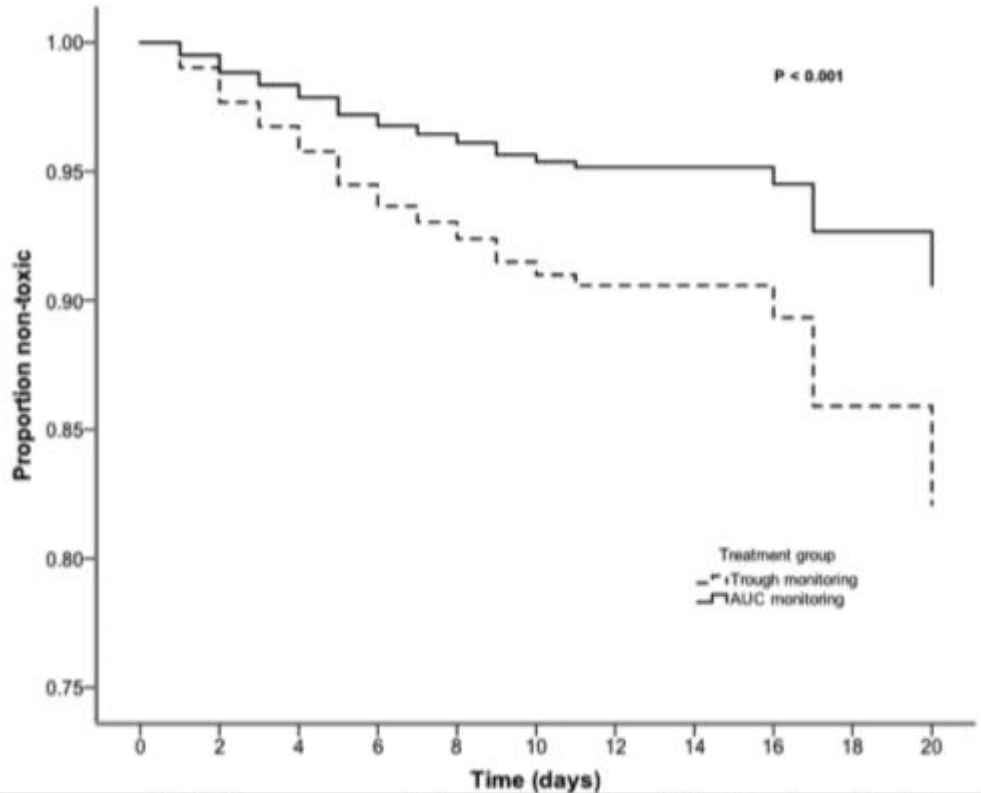
Van Hal SJ, et al. Antimicrob Agents Chemother. 2013;57(2):734-44.

But hey, that AUC/MIC thing looks pretty good

TABLE 3 Bayesian estimated vancomycin exposure profile subgroup analysis

Variable	Values for the following groups[a]: Trough concn-guided dosing group (n = 150)	AUC-guided dosing group (n = 150)	P value
C_{min24} (mg/liter)	12.7 (8.9–16.6)	10.0 (5.7–13.4)	<0.001
C_{min48} (mg/liter)	14.2 (10.3–19.5)	12.5 (8.3–16.7)	0.003
AUC_{0-24} (mg · h/liter)	705 (540–883)	474 (360–611)	<0.001
AUC_{24-48} (mg · h/liter)	663 (538–857)	532 (406–667)	<0.001

[a]Data represent the median (IQR).



Variable	Hazard Ratio	95% CI	P value
AUC-TD	0.501	0.336 – 0.748	0.001
Concomitant furosemide	1.636	1.072 – 2.496	0.022
Elixhauser Comorbidity Index	1.123	1.044 – 1.208	0.002
APACHE II score	1.066	1.042 – 1.091	<0.001
Concomitant IV contrast	1.508	0.972 – 2.339	0.067
Concomitant tobramycin [a]	-	-	-
Duration of therapy, days [a]	-	-	-

[a] Not retained in final model

FIG 1 Time to nephrotoxicity by Cox proportional hazards regression. AUC-TD, AUC- and trough concentration-guided dosing.

Finch NA, et al. Antimicrob Agents Chemother. 2017;61(12). pii: e01293-17.

Caution: there is a tox threshold with AUC

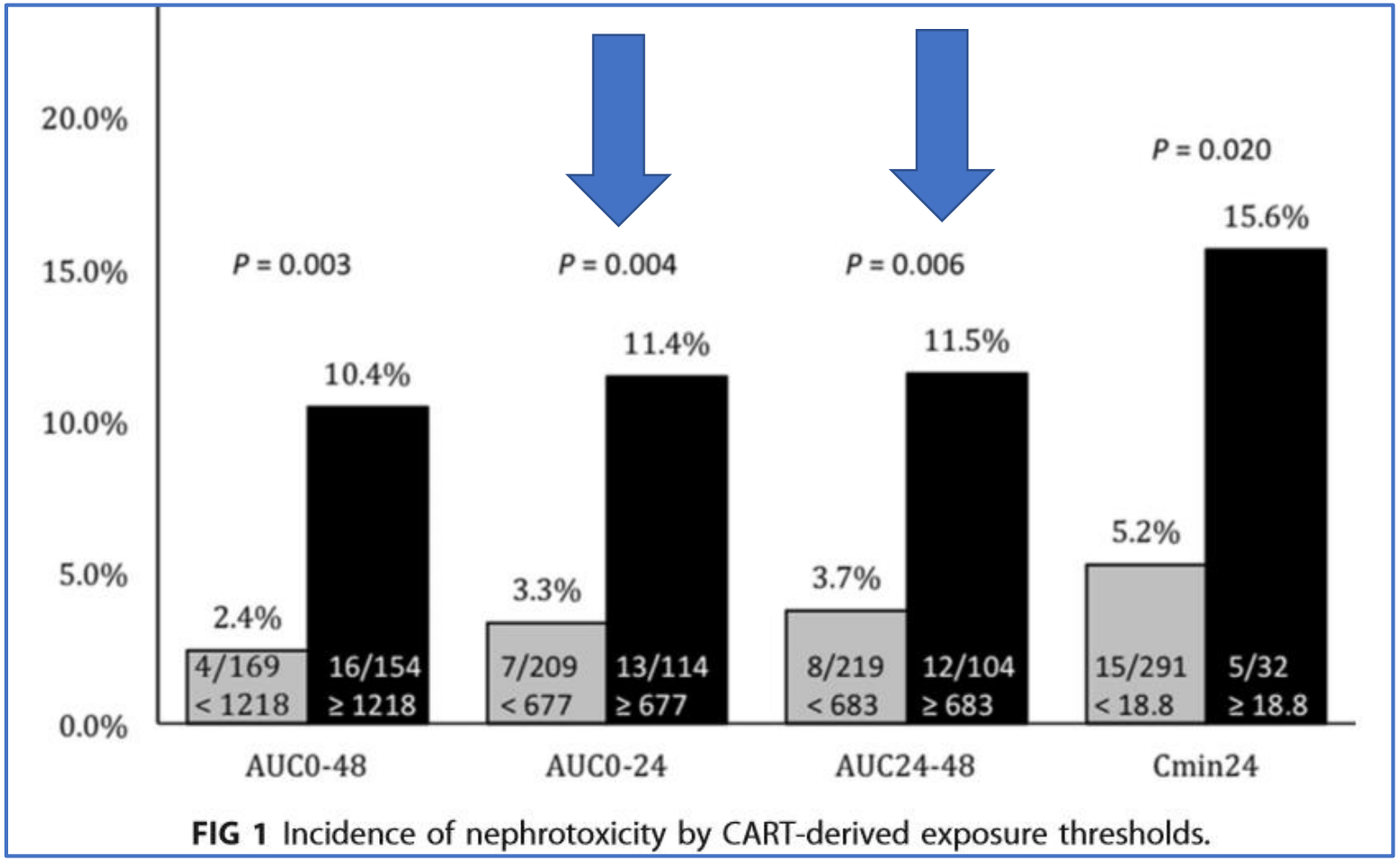


FIG 1 Incidence of nephrotoxicity by CART-derived exposure thresholds.

Zasowski EJ, et al. Antimicrob Agents Chemother. 2017;62(1). pii: e01684-17.

Alright…here's where we're at with this:

- AUC/MIC ~400 or greater is associated with ↑ efficacy
  - A trough ≥ 15 mg/L will hit this AUC:MIC target if MIC ≤ 1 mg/L
- Higher exposures = more nephrotoxicity
  - In fact, a trough ≥ 15 mg/L ↑ toxicity
  - AUC ~650 or greater ↑ toxicity
  - Yikes…
- Trough is an extremely poor surrogate of AUC
- You can hit an AUC ≥ 400 with troughs < 15 mg/L
- Consider maintaining trough above 10 mg/L to prevent emergence of resistance
- We have data to demonstrate AUC dosing increases **safety**
  - Importantly, we do NOT have data to demonstrate that it increases efficacy compared to troughs ≥ 15 mg/L

2019 Revised Vancomycin Consensus Guidelines

NOTE: These recommendations were posted for public comment and are not final.

- A Bayesian-derived **AUC/MIC$_{BMD}$ ratio of 400-600 should be advocated as the target** to achieve clinical efficacy while improving patient safety (IA+)
  - Assuming a vancomycin MIC$_{BMD90}$ of 1 mg/L
- The most accurate and optimal way to manage vancomycin dosing is through AUC-guided dosing and monitoring. This can be accomplished two ways:
  - Use Bayesian software programs (preferred)
    - Preferred to obtain two samples, especially if lacking "richly sampled" prior data for the model
  - Collect two concentrations during same interval
    - Estimate AUC via first-order PK equations

2019 Revised Vancomycin Consensus Guidelines

NOTE: These recommendations were posted for public comment and are not final.

- **Trough only monitoring, with target between 15-20 mg/L, is no longer recommended for patients with serious infections due to MRSA** (IIB-)
- Monitoring should be performed in patients:
  - Receiving aggressive dosing for MRSA infections to achieve sustained targeted AUC
  - At risk of nephrotoxicity
  - With unstable renal function
  - Receiving prolonged courses of therapy
- **We can assume the MIC is 1 mg/L**
  - MIC testing methods lack precision and have substantial variability
- Continuous infusions are “reasonable” alternatives
  - Steady state concentration 20-25 mg/L
  - Makes your AUC calculation easy!

Making the change to area under the curve–based vancomycin dosing

Am J Health-Syst Pharm. 2018; 75:e828-37

- Define included populations
- Pick a calculator and where that will live
  - Equations
  - Spreadsheet v. incorporate into EHR v. Bayesian modeling software
- Write a guideline
- Provide EXTENSIVE education
  - Pharmacists, nurses, physicians, laboratory staff
  - Presentations, practice cases, discussion groups, audit and feedback
- Track and report your outcomes!

Heil EL, et al. Am J Health Syst Pharm. 2018;75(24):1986-1995.
Turner RB, et al. Pharmacotherapy. 2018;38(12):1174–1183.
Kisgen J, Seddon M. Staying Ahead of the Curve: Implementing AUC-Guided Vancomycin Dosing. www.contagionlive.com. Accessed March 2019.

What do pharmacists think?

Post AUC-implementation survey

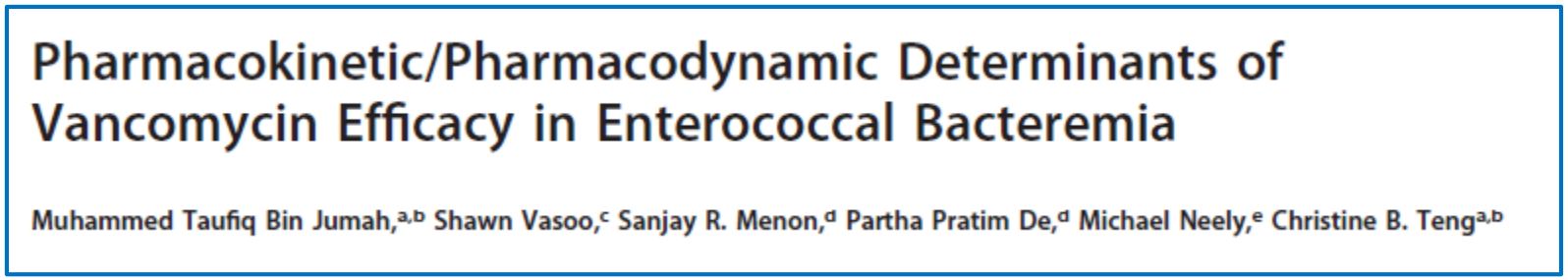
- Initial dosing
  - ↑use of population PK initial dose calculations (37% v 88%)
  - ↓ 15 mg/kg dosing
  - ↑ time to calculate dose (8 v 15 mins)
- ↑ proportion of respondents felt
  - Vanco dosing should be responsibility of clinical pharmacy specialists (14% v 22%)
  - AUC/MIC was the ideal PK/PD index of efficacy (42.% v 93.9%)
- Major concerns = ↑ time commitment, lack of competency
- A pharmacist-to-dose policy associated with
  - Working to the top of degree
  - Increased confidence in antimicrobial stewardship team training
- Pharmacy administrative support essential

Claeys KC, et al. Pharmacists' perceptions of implementing a pharmacist-managed area under the concentration time curve-guided vancomycin dosing program at a large academic medical center. J. American College of Clnical Pharmacy. 2019.

Don’t forget!

NOTE: These recommendations were posted for public comment and are not final.

- “Extrapolation of these recommendations to methicillin-susceptible strains, coagulase-negative staphylococci, and other pathogens should be viewed with **extreme caution**”
  - Although…


Pharmacokinetic/Pharmacodynamic Determinants of Vancomycin Efficacy in Enterococcal Bacteremia

Muhammed Taufiq Bin Jumah,[a,b] Shawn Vasoo,[c] Sanjay R. Menon,[d] Partha Pratim De,[d] Michael Neely,[e] Christine B. Teng[a,b]

Antimicrob Agents Chemother. 2018;62(3). pii: e01602-17.

- MRSA can be really tough to treat
  - “Combination therapy and multiple medical interventions beyond antibiotic therapy may be necessary to improve patient outcomes”

Combo therapy, huh?

- β-lactam + vancomycin or daptomycin is promising
  - "Seesaw" effect
  - PBP1 blockade most strongly associated
    - Cefazolin, nafcillin, meropenem, etc.
  - ↑ PBP2, ↓PBP4 expression
  - Inactivation of *mecA* gene
  - ↑ host immune response
- Daptomycin + ceftaroline is in vogue
  - Ceftaroline
    - In vitro activity against MRSA
    - Displays stronger PBP2 binding as vanco & dapto MICs ↑
    - Enhances dapto-induced cell membrane depolarization
  - Recent *(published online 3/11/19!)* RCT terminated early
    - Mortality: 0% (0/17) combo vs. 26% (6/23) standard monotherapy (😯)
- … but is it necessary?
  - CAMERA-2 trial: vanco or dapto + flucloxacillin/cloxacillin/cefazolin in **first 7 days**
  - Also terminated early….

Geriak M, et al. Antimicrob Agents Chemother. 2019 Mar 11. pii: AAC.02483-18.
Tong SY, et al. Trials. 2016;17:170.

And we're not just rethinking how we dose vanco

Klebsiella pneumoniae		
Antimicrobial	**Interpretation**	**Result**
Amikacin	≤ 16	S
Ciprofloxacin	≤ 1	S
Ceftriaxone	>32	R
Cefepime	4	SDD
Meropenem	≤ 1	S
Gentamicin	≤ 1	S
Pip Tazobactam	8	S
Sulfa-Trimeth	>16/8	R
Tobramycin	≤ 1	S

Maybe breakpoints aren't black and white

Intermediate	Susceptible-Dose Dependent
• "Usually attainable" blood and tissue levels • Implies clinical efficacy in body sites where drugs are physiologically concentrated or when a higher-than-normal dose can be used • Response rates may be lower than for susceptible isolates	• The susceptibility of an isolate depends on the dosing regimen used • Must use higher doses, more frequent doses, or both to achieve higher drug exposure than we can achieve with the dose that was used to establish the susceptible breakpoint

Why the switch?

- Intermediate is overlooked or not understood by clinicians – they assume intermediate = resistant or ineffective
- SDD meant to "highlight" dose-optimization as an option for clinicians
- Due to increasing antimicrobial resistance, there is a serious need to refine susceptibility reporting to maximize clinicians use of available drugs
- SDD is assigned when higher doses are supported by the literature, widely used clinically, and/or approved

CLSI M100. 29th Edition. 2019.

Antimicrobial	MIC (µg/mL)	Dose
Cefepime		
Enterobacteriaceae	S: ≤ 2	1g q12h over 30 min
	SDD: 4	1g q8h or 2g q12h over 30 min
	SDD: 8	2g q8h over 30 min
Pseudomonas	S: ≤ 8	1g q8h or 2g q12h over 30 min
	I: 16	
Ceftaroline		
S. aureus	S: ≤ 1	600mg q12h over 1 hour
	SDD: 2-4	600mg q8h over 2 hours
Daptomycin		
Enterococcus spp.	S: ≤ 1	6 mg/kg/day TBW
	SDD: 2-4	8-12 mg/kg/day TBW
Fluconazole		
C. albicans, parapsilosis, tropicalis	S: ≤ 2	
	SDD: 4	In GENERAL, Dose/MIC ~50-100
C. glabrata	SDD: ≤ 32	In GENERAL, Dose/MIC ~50-100

Challenges we will face when trying to take care of our patients:

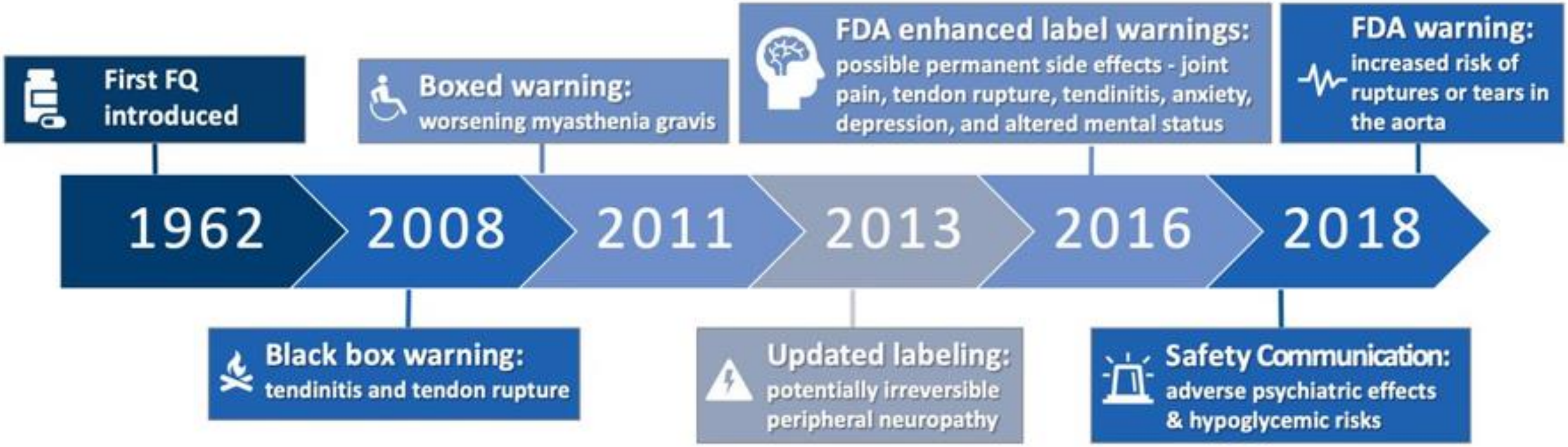
- Automated panel updates lag behind these recommendations
- Clinician fear of higher dosing
- Difficult to grasp, even for ID specialists
- System barriers to dose optimization strategies

CLSI M100. 29th Edition. 2019.
CLSI M60. 1st Edition. 2017.

Other “new” doses or breakpoints to be aware of in your practice

Antimicrobial	MIC (µg/mL)	Dose
Meropenem		
Enterobacteriaceae	S: ≤ 1	1g q8h over 30 mins
	I: 2	
Pseudomonas	S: ≤ 2	1g q8h over 30 mins
	I: 4	
Meropenem-vaborbactam		
Enterobacteriaceae	S: ≤ 4/8	4g q8h over 3 hours (2g meropenem, 2g vaborbactam)
	I: 8/8	
Ceftolozane/tazboactam		
Enterobacteriaceae	S: ≤ 2/4	1.5g q8h over 1 hour
	I: 4/4	
Pseudomonas	S: ≤ 4/4	1.5g q8h over 1 hour
	I: 8/4	
Ciprofloxacin		
Enterobacteriaceae	S: ≤ 0.25	400mg IV q12h or 500mg PO q12h
Pseudomonas	S: ≤ 0.5	400mg IV q8h
Levofloxacin		
Enterobacteriaceae	S: ≤ 0.5	750mg IV or PO q24h
Pseudomonas	S: ≤ 1	750mg IV or PO q24h

Another year, another FQ black box warning



Jones, Travis (@tmjones6). https://twitter.com/tmjones6/status/1076120535258542081. Dec 2018.

The truth about penicillin allergies

- **They are bad**
  - More FQ, clindamycin, vancomycin, aztreonam use
  - More *C. difficile,* MRSA, VRE infection and colonization
  - More surgical site infections
- **They are… questionable**
  - >95% of patients with reported allergies have negative skin tests
  - Rates of true anaphylaxis
    - 1/207,191 (0.00048%) → oral penicillin exposure
    - 1/95,298 (0.00105%) → parental penicillin exposure
    - No fatalities in over 100,000,000 oral amoxicillin courses
- **They are not forever**
- **Med chem matters….**

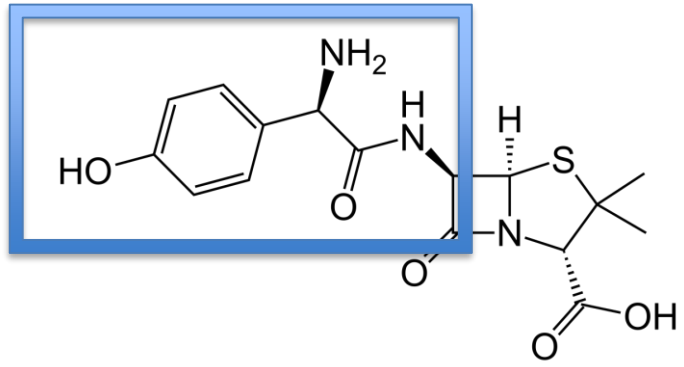
Heil EL, et al. Open Forum Infect Dis. 2016;23:3.
Macy E, Chen LH. J Allergy Clin Immunol. 2017;139 (2 Suppl):AB3.
Lee P, Shanson D. J Antimicrobial Chemotherapy. 2007;60:1172-9.
Blumenthal KG, et al. Clin Infect Dis. 2018;66(3):329-36.
Sakoulas G, et al. Clin Infect Dis. 2018.

5.1. Cefazolin does not share a common side chain with any other beta-lactams

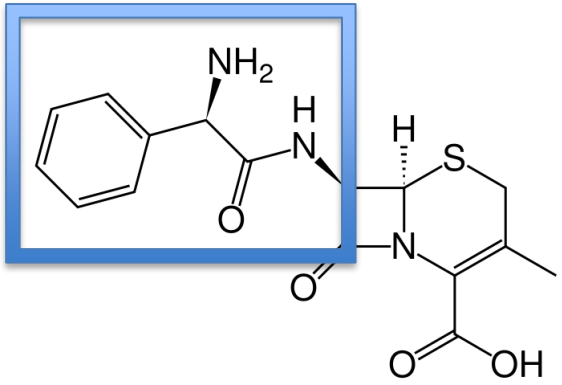
Table 1. FDA-approved Beta-lactam Antibiotics with Similar Side Chains[a]

Agent	Agents with Similar Side Chains				
Amoxicillin	Ampicillin	Cefaclor	Cefadroxil[c]	Cefprozil[c]	Cephalexin
Ampicillin	Amoxicillin	Cefaclor[c]	Cefadroxil	Cefprozil	Cephalexin[c]
Aztreonam[b]	Ceftazidime[c]	Ceftolozane			
Cefaclor	Amoxicillin	Ampicillin[c]	Cefadroxil	Cefprozil	Cephalexin[c]
Cefadroxil	Amoxicillin[c]	Ampicillin	Cefaclor	Cefprozil[c]	Cephalexin
Cefdinir	Cefixime[d]				
Cefditoren	Cefepime[c]	Cefotaxime[c]	Cefpodoxime[c]	Ceftriaxone[c]	
Cefepime	Cefditoren[c]	Cefotaxime[c]	Cefpodoxime[c]	Ceftriaxone[c]	Ceftaroline
Cefixime	Cefdinir[d]				
Cefotaxime	Cefditoren[c]	Cefepime[c]	Cefpodoxime[c]	Ceftriaxone[c]	Ceftaroline
Cefoxitin	Cefuroxime[d]	Penicillin G			
Cefpodoxime	Cefditoren[c]	Cefepime[c]	Cefotaxime[c]	Ceftriaxone[c]	Ceftaroline
Cefprozil	Amoxicillin[c]	Ampicillin	Cefaclor	Cefadroxil[c]	Cephalexin
Ceftaroline	Cefepime	Cefotaxime	Cefpodoxime	Ceftriaxone	Ceftazidime
Ceftazidime	Aztreonam[c]	Ceftolozane			
Ceftolozane	Aztreonam	Ceftazidime			
Ceftriaxone	Cefditoren[c]	Cefepime[c]	Cefotaxime[c]	Cefpodoxime[c]	Ceftaroline
Cefuroxime	Cefoxitin[d]				
Cephalexin	Amoxicillin	Ampicillin[c]	Cefaclor[c]	Cefadroxil	Cefprozil
Penicillin G	Cefoxitin				

[a]Agents not listed are either not approved for use in the United States (ceftizoxime, ceftibiprole) or do not share common side chains (e.g. piperacillin, ticarcillin, nafcillin, dicloxacillin)
[b]Aztreonam cross-reacts with ceftazidime and ceftolozane, with which it shares an identical side-chain
[c]Identical R1 side chain
[d]Identical R2 side chain



amoxicillin



cephalexin

University of Wisconsin Health. 2016.

A good history takes care of the majority of “allergies”

- **What** age reaction occurred
- **What** reaction looked like *(prompt “hives”)*
- **Where** reaction occurred *(e.g., localized v. whole body)*
- **When** reaction occurred in relation to taking the antibiotic
- **How** long did reaction last
- **How** reaction was treated *(did they need to seek urgent medical care?)*
- Was the medication was ever **re-challenged?**
- Have they have tried **similar antibiotics?**
  - E.g. Augmentin, Amoxicillin, Keflex/Cephalexin
- **Educate the patient** why your questions are important
- **DOCUMENT your findings** – the more detailed, the better

Research Report

Pharmacy-Led β-Lactam Allergy Interview (BLAI) Reduces Duration of Fluoroquinolones Within a Community Hospital

Elizabeth W. Covington, PharmD[1], Beth Jobson Baldwin, Pharr and Emily Warren, PharmD[2]

Annals of Pharmacotherapy
1–8

← Pharmacist extenders can do this!

J Antimicrob Chemother
doi:10.1093/jac/dkz082

Journal of Antimicrobial Chemotherapy

Evaluation of a pharmacist-led penicillin allergy de-labelling ward round: a novel antimicrobial stewardship intervention

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J Antimicrob Chemother 2017; 72: 2657–2660
doi:10.1093/jac/dkx171 Advance Access publication 10 June 2017

Antimicrobial Chemotherapy

AJHP RESIDENTS EDITION AZTREONAM

Initiative to reduce aztreonam use in patients with self-reported penicillin allergy: Effects on clinical outcomes and antibiotic prescribing patterns

Am J Health-Syst Pharm. 2018; 75(suppl 3):S58-62

Anthony Phan, Pharm.D., Department of Pharmacy, St. Vincent's HealthCare, Jacksonville, FL.
Bryan Allen, Pharm.D., BCPS.

Purpose. Evaluation of the clinical impact of a pl... allergy assessment initiative to enhance antibiotic s...

Optimizing preoperative prophylaxis in patients with reported β-lactam allergy: a novel extension of antimicrobial stewardship

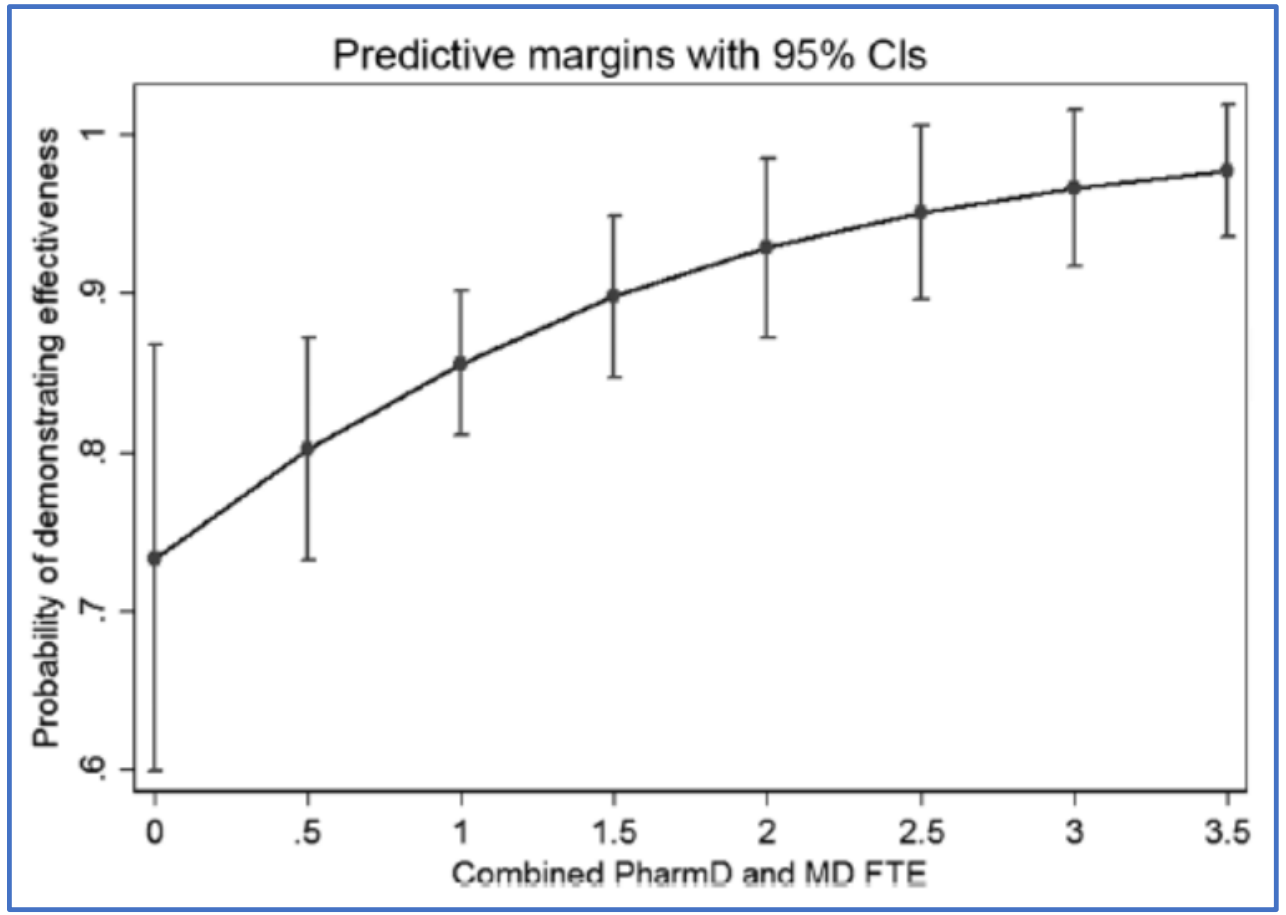
Alon Vaisman[1]*, Janine McCready[2], Sandy Hicks[3] and Jeff Powis[2]

Essential Resources and Strategies for Antibiotic Stewardship Programs in the Acute Care Setting

Sarah B. Doernberg,[1] Lilian M. Abbo,[2] Steven D. Burdette,[3] Neil O. Fishman,[4] Edward L. Goodman,[5] Gary R. Kravitz,[6] James E. Leggett,[7] Rebekah W. Moehring,[8] Jason G. Newland,[9] Philip A. Robinson,[10] Emily S. Spivak,[11] Pranita D. Tamma,[12] and Henry F. Chambers[1]

- Each 0.50 increase in combined FTE availability resulted in a 1.48-fold increase in the odds of demonstrating effectiveness (95% confidence interval, 1.06–2.07)

- Even programs with positive outcomes perceive understaffing



Clin Infect Dis. 2018;67(8):1168-74.

You’re gonna need more people to review all those carbapenems…

- Piperacillin-tazobactam vs. meropenem for bloodstream infections caused by ceftriaxone-resistant *E. coli* or *K. pneumoniae*
  - Min = 4, max = 14 days treatment
- 30-day mortality
  - Pip/tazo: 23/187 (12.3%)
  - Meropenem: 7/191 (3.7%)
- Conclusion: Pip/tazo is not noninferior
- So that settles it, right?

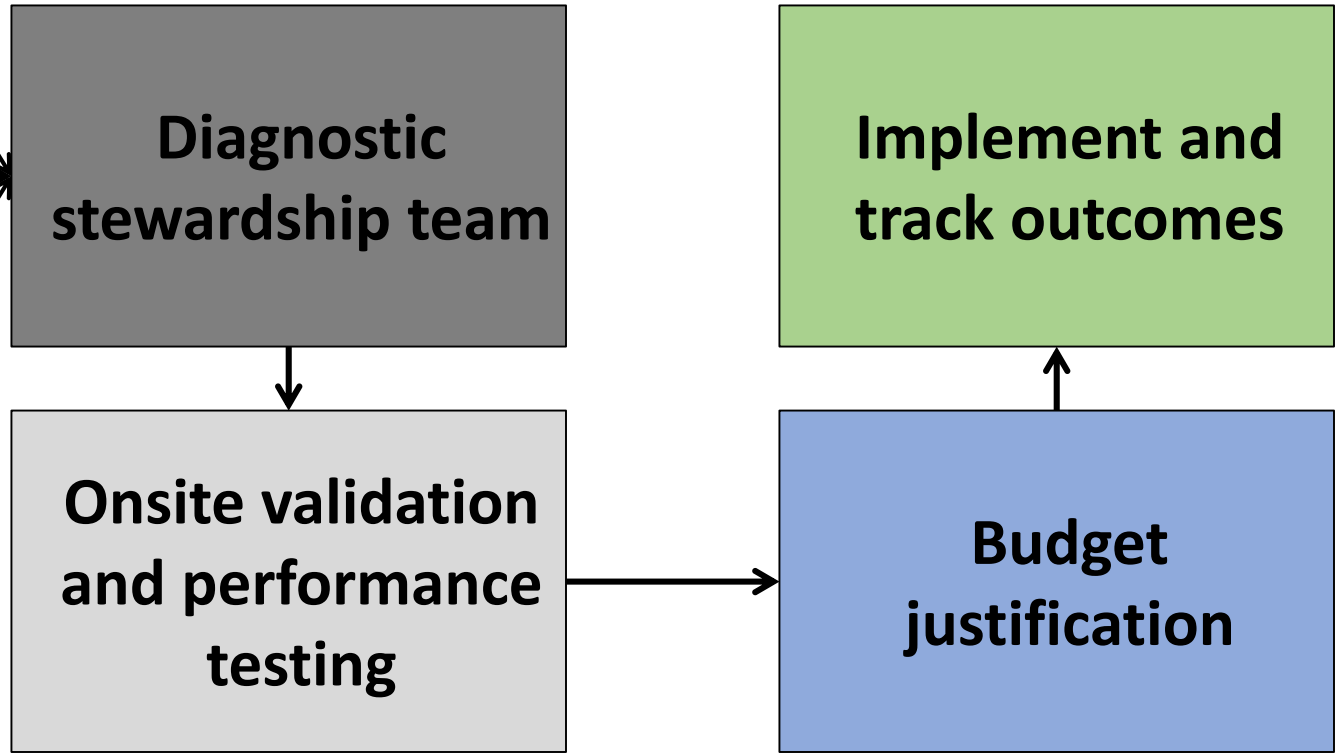
Harris PNA, et al. JAMA. 2018;320(10):984-994.

Antimicrobial stewardship teams implementing and optimizing rapid diagnostics technologies will be the new normal

Microbiology S.O.C.
- Turn around times
- Available technology
- Staffing

Local epidemiology
- Bloodstream pathogens
- Resistance patterns
- Adequacy of empiric therapy

Stewardship capabilities
- ASP model/approach
- Staffing/availability
- Well-defined algorithms



Slide adopted from Ryan K. Shields, PharmD, MS

Rapid diagnostic budget justification

"Improving patient care" doesn't cut it anymore

Antibiotic consumption

- Discontinuation of empiric vancomycin
- Escalation to active therapy earlier
- ↓ combination agents
- De-escalation to narrow spectrum antibiotics
- ↓ total antibiotic days

Decreased LOS

- De-escalation for patients with uncomplicated BSI
- Escalation for patients with BSI due to MDRO
- Shorter durations of antibiotics for BSI

Collateral benefits

- Decreased adverse events
- Fewer cases of *C. difficile*
- Less hands-on time for microbiology
- ↓ readmissions
- ↑ collaboration with and confidence in stewie program

Slide adopted from Ryan K. Shields, PharmD, MS

2018: The Year of the MRSA PCR

- Pooled prevalence of MRSA pneumonia: 10%

Type of Pneumonia	No. Studies	Sensitivity, % (95% CI)	Specificity, % (95% CI)	PPV, %	NPV, %
All	22	70.9 (58.8-80.6)	90.3 (86.1-93.3)	44.8	**96.5**
CAP/HCAP	4	85 (59.7-95.6)	92.1 (81.5-96.9)	56.8	**98.1**
VAP	5	40.3 (17.4-68.4)	93.7 (77.1-98.4)	35.7	**94.8**

The Clinical Utility of Methicillin-Resistant *Staphylococcus aureus* (MRSA) Nasal Screening to Rule Out MRSA Pneumonia: A Diagnostic Meta-analysis With Antimicrobial Stewardship Implications

Diane M. Parente,[1] Cheston B. Cunha,[2,3] Eleftherios Mylonakis,[2,3] and Tristan T. Timbrook[4]

Parente DM, et al. Clin Infect Dis. 2018;67(1):1-7.
Slide adopted from Louise-Marie Oleksiuk, PharmD, BCPS

A “nudge” works too

Specimen:

Sputum Culture	Moderate Growth of Normal Oral Flora
	Negative For Methicillin Resistant Staphylococcus aureus.
	Negative for Staphylococcus aureus.
	Negative for Pseudomonas aeruginosa.
Gram Stain	Few WBC Seen
	Few Epithelial Cells Seen
	Rare Gram Negative Rods
	Moderate Gram Positive Cocci
	Rare Gram Positive Rods
	Specimen Optimum for Culture

Musgrove MA, et al. Open Forum Infect Dis. 2018;5(7):ofy162.

How low can we go?

You must understand the patient populations of these studies and how they relate to your patient and your patient's infection. This is not black and white.

Disease	Short Duration	Long Duration
Community acquired pneumonia	3-5	7-10
Asymptomatic bacteriuria, bronchitis	0	Anything else
Hospital-acquired, ventilator-associated pneumonia	7-8	10-15
Pyelonephritis	7	10-14
Intraabdominal infections	3-4	10
Acute exacerbation of chronic bronchitis	≤ 5	7-10
Acute bacterial sinusitis	5	10
Uncomplicated gram-negative bacteremia (Enterobacteriaceae)	7	14
Uncomplicated gram-negative bacteremia (Pseudomonas)	8-10	14-17
Cellulitis	5-6	10
Neutropenic fever	Afebrile x 72h	ANC > 500
Osteomyelitis	42	84

Llewelyn MJ, et al. BMJ. 2017 ;358:j3418.
Spellberg B. JAMA Intern Med. 2016;176(9):1254-5.
Hanretty AM, Gallagher JC. Pharmacotherapy. 2018;38(6):674-687.
BALANCE Trial: Clinical Trials NCT03005145

New guidelines

- IDSA
  - Outpatient Parenteral Antimicrobial Therapy
  - Diagnosis, Treatment, Chemoprophylaxis, and Institutional Outbreak Management of Seasonal Influenza
  - Clostridium difficile Infection in Adults and Children 
  - Antimicrobial Prophylaxis for Adult Patients With Cancer-Related Immunosuppression
  - Fever and Neutropenia in Adults with Cancer
  - Guidelines for the Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents
  - Laboratory Diagnosis of Infectious Diseases
- International Consensus Guidelines for the Optimal Use of the Polymyxins
- The Third International Consensus Guidelines on the Management of Cytomegalovirus in Solid-organ Transplantation
- Hepatitis C
- And more!

Clinical Practice Guideline for the Management of Asymptomatic Bacteriuria: 2019 Update by the Infectious Diseases Society of America[a]

Lindsay E. Nicolle,[1] Kalpana Gupta,[2] Suzanne F. Bradley,[3] Richard Colgan,[4] Gregory P. DeMuri,[5] Dimitri Drekonja,[6] Linda O. Eckert,[7] Suzanne E. Geerlings,[8] Béla Köves,[9] Thomas M. Hooton,[10] Manisha Juthani-Mehta,[11] Shandra L. Knight,[12] Sanjay Saint,[13] Anthony J. Schaeffer,[14] Barbara Trautner,[15] Bjorn Wullt,[16] and Reed Siemieniuk[17]

- In older patients with bacteriuria and no local symptoms or other systemic signs of infection, **assess for other causes and observe carefully rather than treat!**
  - Functional and/or cognitive impairment
  - Delirium
  - Acute mental status change
  - Confusion
  - Experience a fall

  For real, these are all included!
  #watchandwait #saveabx
- Do not screen and treat ASB in anyone EXCEPT:
  - Pregnant women
  - Renal transplant recipients within 1 month of surgery
  - Pre-op endoscopic urologic procedures associated with mucosal trauma (1-2 doses!)
- No recommendation for high-risk neutropenia (lack of data)

Clin Infect Dis. 2019.

I saved the best for last

Drug	Approved	Indications	What you need to know
Ceftolozane/ tazobactam	**2014**	**IAI** **cUTI**	More effective and less toxic than polymyxins or aminoglycosides for *Pseudomonas* Effective for ESBLs (useful with mixed infections) Phase 3 trial using 3g dose in HABP/VABP completed
Ceftazidime/ avibactam	**2015**	**IAI** **cUTI** **HABP/VABP**	Only beta-lactamase inhibitor for Class D (OXA-48-like) Superior to historical agents for CRE, watch resistance development, approved in peds! Can be useful for non-fermenters
Meropenem/ vaborbactam	**2017**	**cUTI**	Potent KPC inhibitor paired with dose-optimized meropenem; role for caz/avi-resistant CRE No role for carbapenem-resistant *Pseudomonas* Superior to best available therapy for CRE
Plazomicin	**2018**	**cUTI**	Stable to all aminoglycoside-modifying enzymes Dosed on AUC in Phase III bloodstream infection trial
Eravacycline	**2018**	**cIAI**	Similar to tigecycline (maybe slightly more potent) for CRE, *Acinetobacter*, ESBLs Failed UTI trial with oral formulation, only available PO

Table from: Tamma PD, Hsu AJ. J Pediatric Infect Dis Soc. 2019 Feb 22. pii: piz002.

Agent	KPC-producer	NDM-producer	OXA-48-like-producer	Carbapenem-resistant *Pseudomonas aeruginosa*	Carbapenem-resistant *Acinetobacter baumannii*	*Stenotrophomonas maltophilia*
Aztreonam-avibactam						
Cefiderocol						
Ceftazidime-avibactam						
Ceftolozane-tazobactam						
Eravacycline						
Fosfomycin (intravenous)						
Imipenem-relebactam						
Meropenem-vaborbactam						
Plazomicin						
Polymyxin B or Colistin						
Tigecycline						

Susceptibility anticipated > 80%

Susceptibility anticipated 30-80%

Susceptibility anticipated < 30%

Bugs don’t care how the drugs get there!

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Partial Oral versus Intravenous Antibiotic Treatment of Endocarditis

Kasper Iversen, M.D., D.M.Sc., Nikolaj Ihlemann, M.D., Ph.D., Sabine U. Gill, M.D., Ph.D., Trine Madsen, M.D., Ph.D., Hanne Elming, M.D., Ph.D., Kaare T. Jensen, M.D., Ph.D., Niels E. Bruun, M.D., D.M.Sc., Dan E. Høfsten, M.D., Ph.D., Kurt Fursted, M.D., D.M.Sc., Jens J. Christensen, M.D., D.M.Sc., Martin Schultz, M.D., Christine F. Klein, M.D., Emil L. Fosbøll, M.D., Ph.D., Flemming Rosenvinge, M.D., Henrik C. Schønheyder, M.D., D.M.Sc., Lars Køber, M.D., D.M.Sc., Christian Torp-Pedersen, M.D., D.M.Sc., Jannik Helweg-Larsen, M.D., D.M.Sc., Niels Tønder, M.D., and Hennin

Clinical Infectious Diseases

MAJOR ARTICLE

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Oral versus Intravenous Antibiotics for Bone and Joint Infection

H.-K. Li, I. Rombach, R. Zambellas, A.S. Walker, M.A. McNally, B.L. Atkins, B.A. Lipsky, H.C. Hughes, D. Bose, M. Kümin, C. Scarborough, P.C. Matthews, A.J. Brent, J. Lomas, R. Gundle, M. Rogers, A. Taylor, B. Angus, I. Byren, A.R. Berendt, S. Warren, F.E. Fitzgerald, D.J.F. Mack, S. Hopkins, J. Folb, H.E. Reynolds, E. Moore, J. Marshall, N. Jenkins, C.E. Moran, A.F. Woodhouse, S. Stafford, R.A. Seaton, C. Vallance, C.J. Hemsley, K. Bisnauthsing, J.A.T. Sandoe, I. Aggarwal, S.C. Ellis, D.J. Bunn, R.K. Sutherland, G. Barlow, C. Cooper, C. Geue, zas, T. Wangrangsimakul, Bostock, J. Paul, G. Cooke, e OVIVA Trial Collaborators*

IDSA Infectious Diseases Society of America

hivma hiv medicine association

OXFORD

Early Oral Switch to Linezolid for Low-risk Patients With *Staphylococcus aureus* Bloodstream Infections: A Propensity-matched Cohort Study

Rein Willekens,[1,2] Mireia Puig-Asensio,[1,2] Isabel Ruiz-Camps,[1,2] Maria N. Larrosa,[3] Juan J. González-López,[3] Dolors Rodríguez-Pardo,[1,2] Nuria Fernández-Hidalgo,[1,2] Carles Pigrau,[1,2] and Benito Almirante[1,2]

[1]Department of Infectious Diseases, Hospital Universitari Vall d'Hebron, [2]Department of Medicine, Universitat Autònoma de Barcelona, and [3]Department of Microbiology, Hospital Universitari Vall d'Hebron, Barcelona, Spain

Clinical Infectious Diseases

EDITORIAL COMMENTARY

IDSA
Infectious Diseases Society of America

Clin Infect Dis. 2018 Nov 15.

Are Surgeons Different? The Case for Bespoke Antimicrobial Stewardship

Julia E. Szymczak[1,2]

"There is a need for stewardship interventions specifically tailored to the **social norms, professional identities,** and **motivations of physicians** in different medical specialties in order to change the culture surrounding antimicrobials on a broad scale."

The science is important, but we must appreciate beliefs and behaviors to truly change practice

This didn't fit in 45 minutes

Stewardship and common infections

- 5-day nitrofurantoin vs. single-dose fosfomycin for uUTI in woman: PMID 29710295
- Prophylactic antimicrobial therapy for acute aspiration pneumonitis: PMID 29438467
- ARREST trial: PMID 29249276
- Increasing duration of surgical prophylaxis does not decrease infection but increases ADRs (IDWeek 2018)
- OPAT among PWID may be safe and effective: PMID 30211247
- "Jumping the gun" with renal dosing: PMID 30219824

Global infections

- Antifungal combinations for cryptococcal meningitis in Africa: PMID 29539274
- Four months of rifampin or nine months of isoniazid for latent tuberculosis: PMID 30067931
- Continued experience with 8 weeks of treatment with glecaprevir and pibrentasvir (Mavyret) approved for all HCV genotypes
- Ceftriaxone-resistant Neisseria gonorrhoeae: PMID 29131780, 29553335

HIV

- MONCAY trial: PMID 30601976
- SWORD-1 and SWORD-2 trials: PMID 29310899
- Another patient was "cured" of HIV (N=2); and there might be a third!
- TAF/FTC noninferior to TDF/FTC for PrEP
- ATLAS and FLAIR trials of monthly, long-acting injectable cabotegravir and rilpivirine
- INSTIs associated with weight gain?
- CASCADE trial: PMID 29509839
- GEMINI-1 and GEMINI-2 trials: PMID 30420123
- U=U: PMID 30025681
- Primary prophylaxis against disseminated MAC disease no longer recommended for adults and adolescents with HIV who immediately initiate ART

Immunocompromised patients

- ANTIBIOSTOP: Early discontinuation of empirical antibacterial therapy in febrile neutropenia: PMID 29451055
- ACTIVE: Isavuconazole versus caspofungin in the treatment of candidemia: PMID 30289478
- Oral versus aerosolized ribavirin for RSV infections in HCT recipients: PMID 30202920
- Extended infusions associated with superior outcomes in patients with febrile neutropenia: PMID 29608680
- High-dose influenza vaccine for solid-organ transplant recipients: PMID 29253089
- Preemptive therapy preferred to universal prophylaxis for D+/R- liver transplant recipients (IDWeek 2018)

Everyone can (and should) be a steward

- **SIDP Antimicrobial Stewardship Certificate**
  - Acute care: https://www.sidp.org/StewardshipCertificate
  - Long-term care: https://www.sidp.org/LTCStewardship/
- **CDC Antibiotic Stewardship Training Series**
  - 9 modules: https://www.train.org/cdctrain/training_plan/3697
- **MAD-ID**
  - Basic Training Program: https://mad-id.org/antimicrobial-stewardship-programs/antimicrobial-stewardship-programs-basic-program/
  - Advanced Training Program: https://mad-id.org/antimicrobial-stewardship-programs/advanced-program/
- **IDStewardship.com**
  - Collection of resources: https://www.idstewardship.com/resources/

Updates in Infectious Diseases

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