ID Pharmacy Initiatives

Matt Davis, PharmD
Christine Pham, PharmD BCIDP
Meganne Kanatani, PharmD
Ross Pineda, PharmD

Outline

- Beta-Lactam Dose Optimization - Active
- Vancomycin AUC-Based Monitoring - Pending

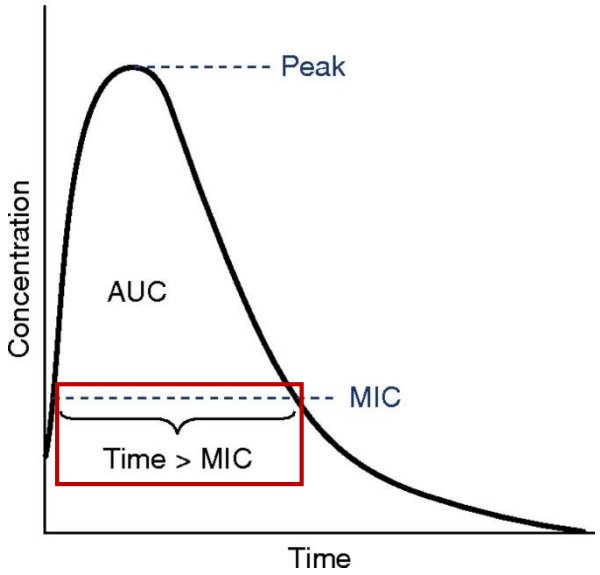
Beta-Lactam Dose Optimization

Strategies to improve pharmacodynamics effects of beta-lactams and clinical outcomes

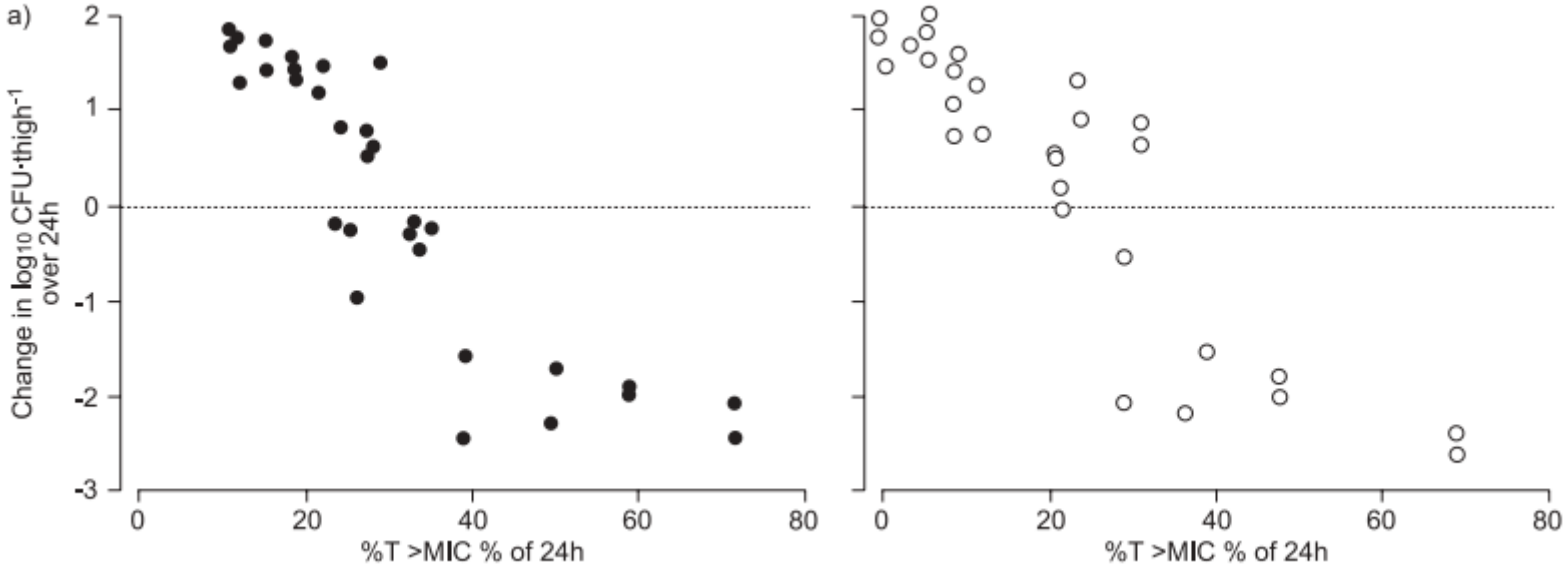
Background – Pharmacokinetics

Antibiotics fall into three major pharmacokinetic categories:

- Peak-dependent (aminoglycosides)
- **Time-dependent (beta-lactams)**
- AUC-dependent (vancomycin)



E. coli ***Pseudomonas aeruginosa***



https://cjasn.asnjournals.org/content/14/7/1080/tab-figures-data
https://doi.org/10.1183/09059180.00010304

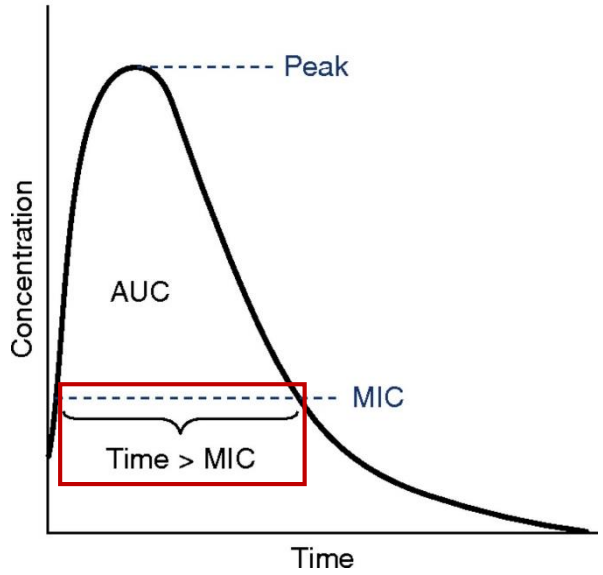
*Data shown for piperacillin-tazobactam

Beta-Lactam Extended Infusion Evidence

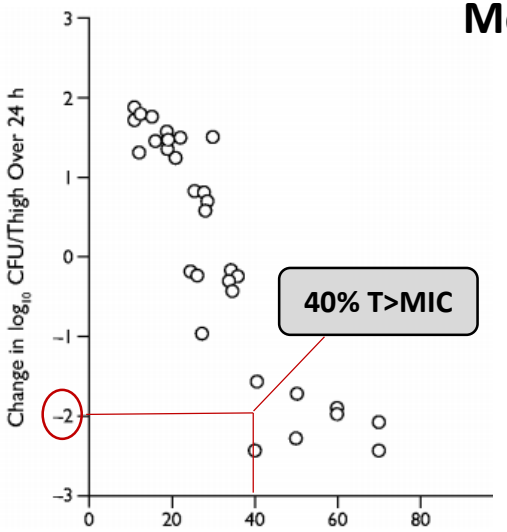
Pharmacodynamics

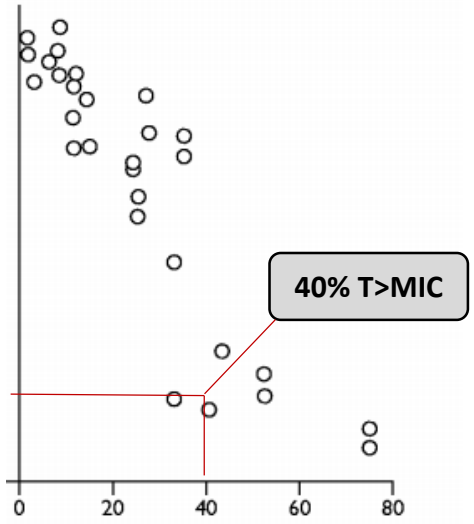
Antibiotics fall into three major categories:

- Peak-dependent (aminoglycosides)
- **Time-dependent (beta-lactams)**
- AUC-dependent (vancomycin)



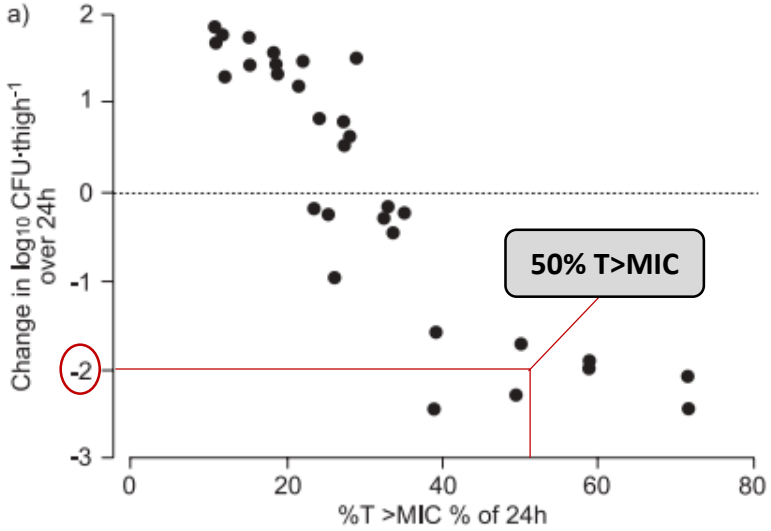
Meropenem

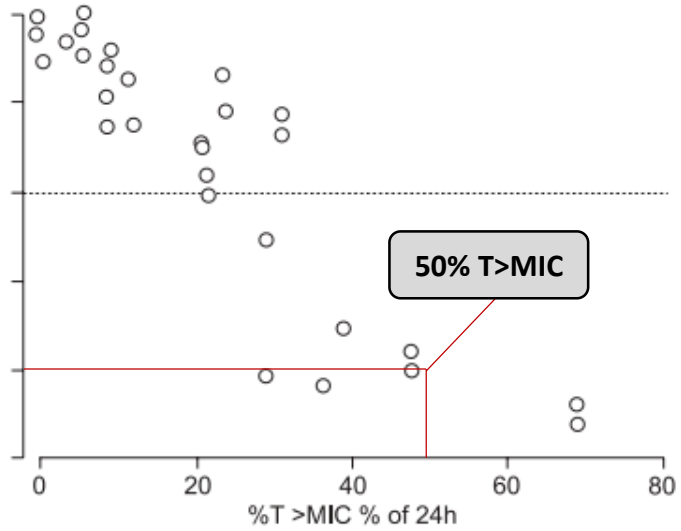




E. coli ***Pseudomonas aeruginosa***

Piperacillin-tazobactam



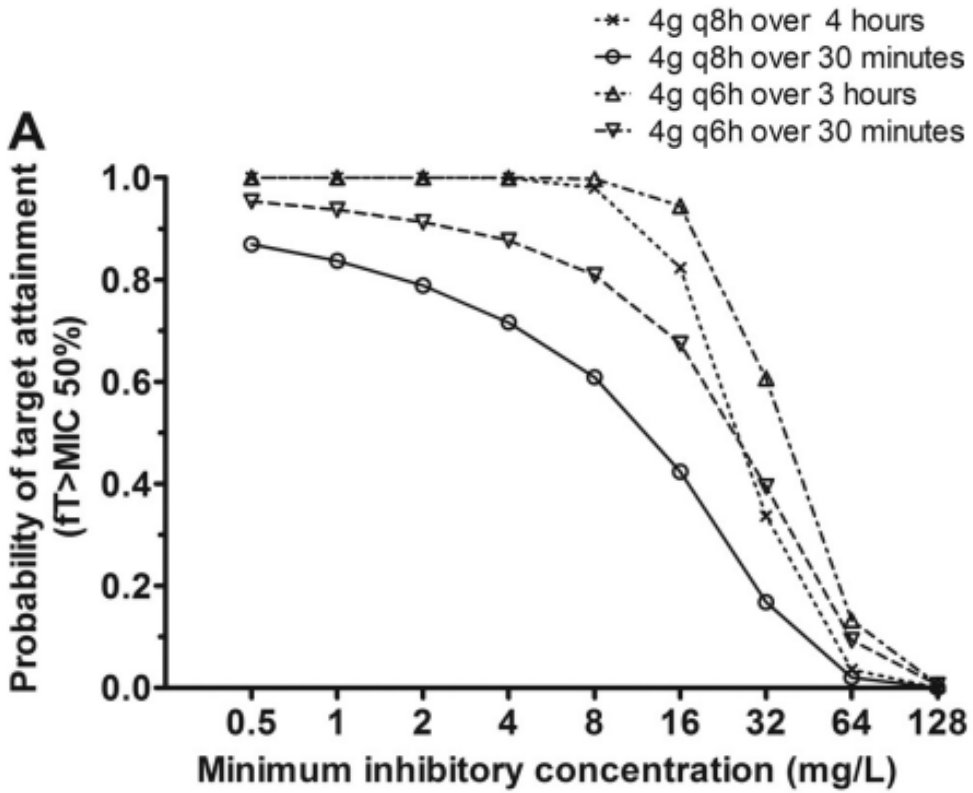


Increased %T > MIC = Increased killing

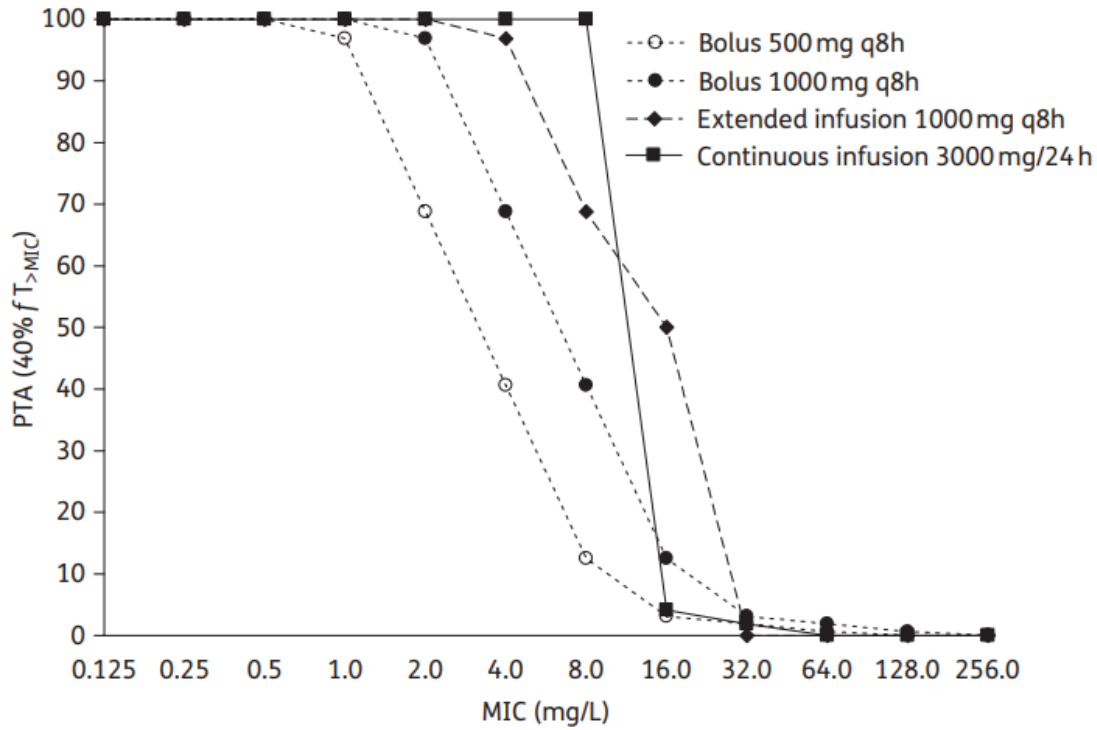
https://www.sciencedirect.com/science/article/pii/S0149291804800018?via%3Dihub
https://cjasn.asnjournals.org/content/14/7/1080/tab-figures-data
https://doi.org/10.1183/09059180.00010304

Pharmacokinetics – Monte Carlo Population Data

Piperacillin-tazobactam



Meropenem



https://doi.org/10.1093/jac/dkq449
https://doi.org/10.1128/AAC.00521-12

Clinical Outcomes Data

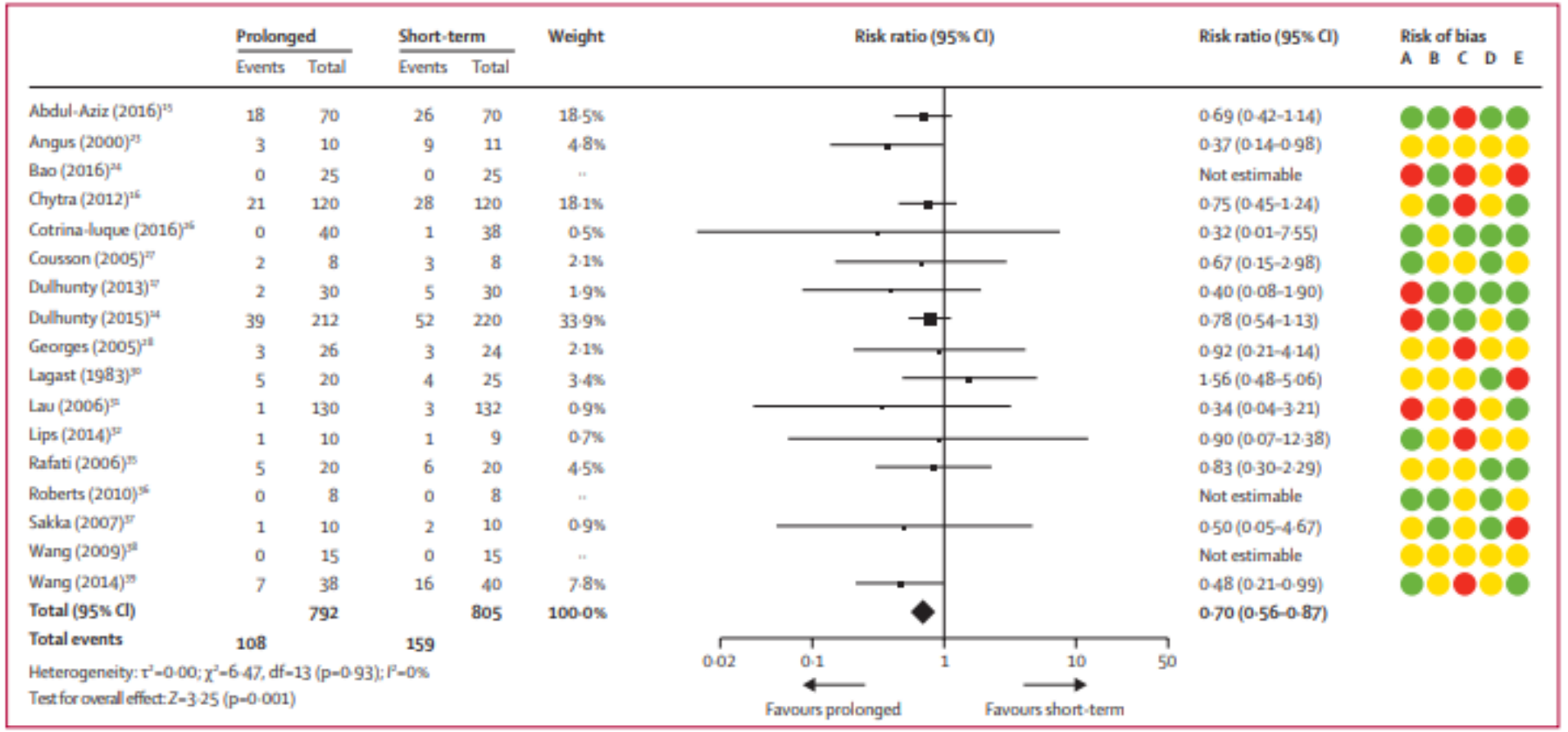
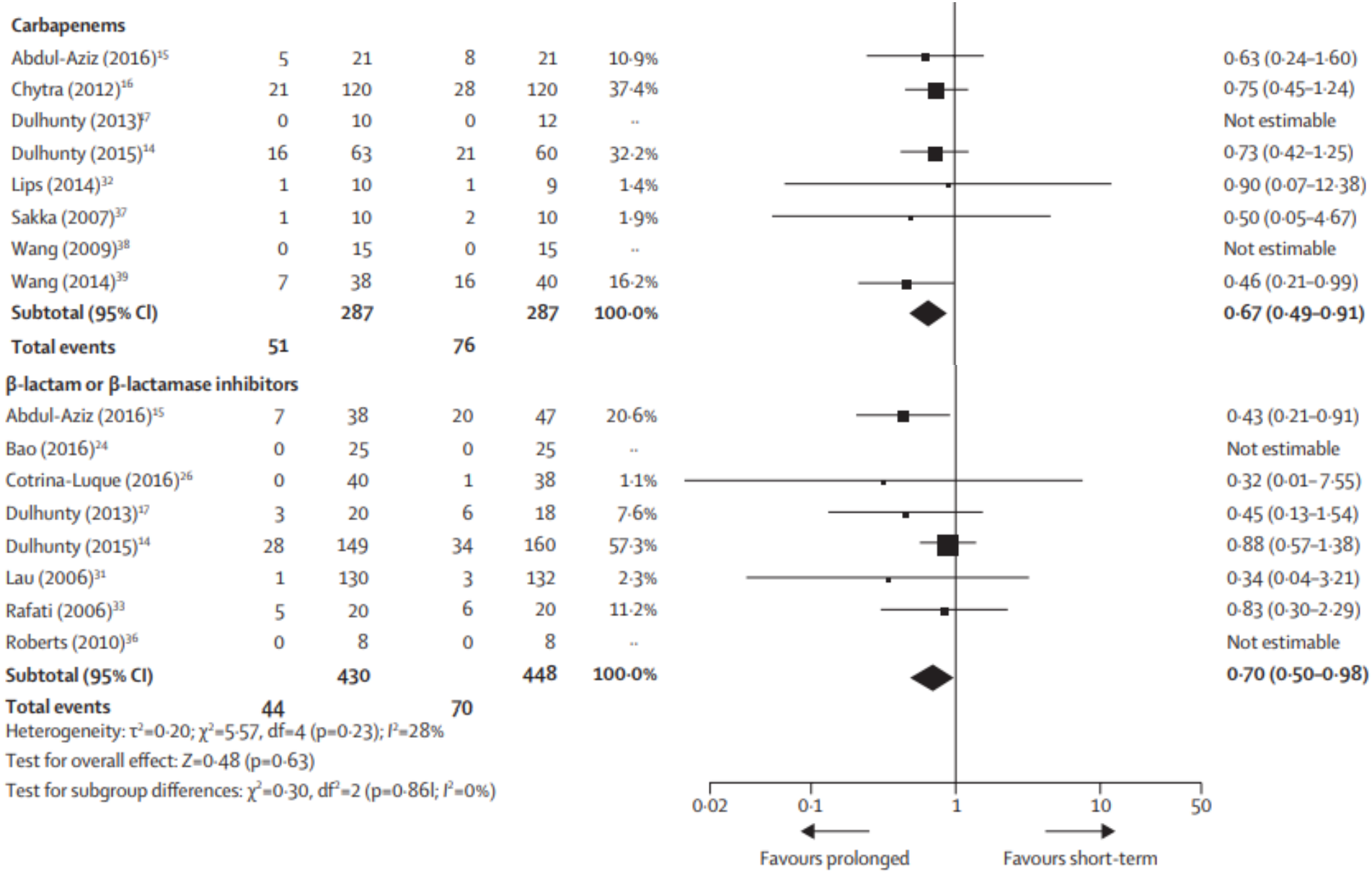


Figure 2: **Forest plot of mortality among patients treated with prolonged versus short-term infusion of antipseudomonal antibiotics**
The areas of squares are proportional to the weight given to each study. Risk ratios are the centres of each square. df=degrees of freedom.

Meta-analysis of 14 RCTs (n= 1,597); Anti-pseudomonal beta-lactams in patients with sepsis

"Prolonged infusion was associated with lower all-cause mortality than short-term infusion **(RR 0·70, 95% CI 0·56–0·87)**."

https://doi.org/10.1016/S1473-3099(17)30615-1



- Significant effect maintained in subgroup studies with carbapenems and BLBLIs
- Cure was higher in one RCT in prolonged group for *A. baumannii* and *P. aeruginosa* (high MICs) (52% vs 25%, p=0·05)
- In accordance with previous analyses, patients with more severe infections seemed to benefit more from prolonged infusion.

Piperacillin-tazobactam – In Spectrum

Indication	Old Dose	New Dose	Reference
CF	LD, 4.5g IV Q6 over 3h OR 18g continuous infusion	No change	https://doi.org/10.1093/jac/dkt300
Obesity	LD, 4.5 IV Q8 over 4h	No change	https://doi.org/10.1002/phar.1324
Neutropenic fever, critically ill/ICU, *PSEUDOMONAS*	LD, 3.375g IV Q8 over 4h	**LD, 4.5g IV Q8 over 4h**	https://doi.org/10.3390/antibiotics4040643 https://doi.org/10.1177/0897190016684453
Non-severe infections	LD, 3.375 IV Q8 over 4h	No change	https://doi.org/10.1086/510590
Renal Impairment			
CrCl ≤20	LD, 3.375 IV Q12 over 4h	LD, 3.375-4.5g* IV Q12 over 4h	https://doi.org/10.1177/0897190016684453
IHD	LD, 3.375 IV Q12 over 4h	LD, 3.375-4.5g* IV Q12 over 4h	https://doi.org/10.1177/0897190016684453
CVVHD	LD, 3.375 IV Q8 over 4h	Flow Rate 1-4 L/hr: LD, 4.5g IV Q8 over 4h Flow Rate>4L/hr: Call ID Pharmacy; TDM Suggested	https://doi.org/10.2215/CJN.10260915 Uptodate

*Higher dose is recommended for obesity, severe infections (critically ill or neutropenic fever), or MIC > 8
LD = loading dose

Meropenem – In Spectrum

Indication	Old Dose	New Dose	Reference
CNS, Cystic Fibrosis, MIC ≥ 2	2g IV Q8	LD 2g over 30min, then 2g IV Q8 **infused over 4h**	https://doi.org/10.1016/j.jcf.2016.04.002 https://doi.org/10.1016/S1473-3099(17)30615-1
All other indications	1g IV Q8	LD 1g over 30min, then 1g IV Q8 **infused over 4h**	https://doi.org/10.1186/s40560-020-00442-7 https://doi.org/10.3390/antibiotics4040643 https://doi.org/10.1128/aac.49.1.461-463.2005
		Renal Impairment	
>25 CrCl ≤50 ml/min	1-2g IV Q8	LD 1-2g* over 30min, then 1-2g* IV Q12 **infused over 4h**	https://doi.org/10.10mrdav16/S1473-3099(17)30615-1
10 ≤CrCl ≤ 25 mL/min	0.5-1g IV Q12	LD 0.5-1g* over 30min, then 0.5-1g* IV Q12 **infused over 4h**	https://doi.org/10.1016/S1473-3099(17)30615-1
CrCl <10 ml/min	0.5-1g IV Q24	LD 0.5-1g* over 30min, then 0.5-1g* IV Q24 **infused over 4h**	https://doi.org/10.1016/S1473-3099(17)30615-1
IHD	0.5g IV Q24	LD 0.5-1g* over 30min, then 0.5-1g* IV Q24 **infused over 4h**	UptoDate https://doi.org/10.1016/S1473-3099(17)30615-1
CVVHD	1-2g IV Q8-12 (Q8 is recommended for rates exceeding 2L/H)	Flow Rate ≤ 2L/H: LD 1-2g* over 30min, then 1-2g* IV Q12 **over 4h** Flow Rate 2-4L/H: LD 1-2g* over 30min, then 1-2g* IV Q8h **over 4h** Flow Rate >4L/H: Call ID Pharmacy; TDM Suggested	

*Higher dose is recommended for CNS, cystic fibrosis, and MIC 2 or greater
LD = Loading dose

Cefepime – In Spectrum

Indication	Old Dose	New Dose	Reference
CNS, critically ill, neutropenic fever, *Pseudomonas, Enterobacterales* MIC > 2,	2g IV Q8	LD 2g over 30min, then 2g IV Q8 **infused over 4h**	https://doi.org/10.1016/S1473-3099(17)30615-1 https://doi.org/10.1093/cid/cis916
All other indications	1g IV Q8	LD 1g over 30min, then 1g IV Q8 **infused over 4h**++	https://doi.org/10.1016/S1473-3099(17)30615-1
Renal Impairment			
>30 CrCl ≤, 60 ml/min	1-2g IV Q8	LD 1-2g* over 30min, then 1-2g* IV Q12 **infused over 4h**	UptoDate https://doi.org/10.1016/S1473-3099(17)30615-1
11 ≤CrCl ≤ 29 mL/min	1-2g IV Q12-Q24	LD 0.5-1g* over 30min, then 0.5-1g* IV Q12 **infused over 4h**	
CrCl <11 ml/min	0.5-1g IV Q24	LD 0.5-1g* over 30min, then 0.5-1g* IV Q24 **infused over 4h**	
IHD	1g IV Q24	LD 0.5-1g* over 30min, then 0.5-1g* IV Q24 **infused over 4h**	UptoDate https://doi.org/10.1016/S1473-3099(17)30615-1
CVVHD	1-2g IV Q8-12 (Q8 is recommended for rates exceeding 2L/H)	Flow Rate ≤ 2L/H: LD 2g over 30min, then 2g IV Q12 **over 4h** Flow Rate 2-4L/H: LD 2g over 30min, then 2g IV Q8h **over 4h** Flow Rate >4L/H: Call ID Pharmacy; TDM Suggested	

*Higher dosing for CNS, Enterobacterales MIC > 2, critically ill, neutropenia *Pseudomonas*
++Can consider 2g Q12h for dosing convenience
LD = Loading dose

Prolonged Infusion Summary

- Lower all-cause mortality in sepsis has been observed with extended infusion beta-lactams
  - Biologically plausible (pharmacodynamics)
  - 4-hr infusion will be preferred at UCLA (**note: not mandatory**)
- Can be ordered via order panels (similar to piperacillin-tazobactam)
- Consider
  - Line access of patient and concomitant medications
  - Ask a pharmacist!

Panels are Live:
4/19/2021 meropenem
5/3/2021 pip-tazo, cefepime

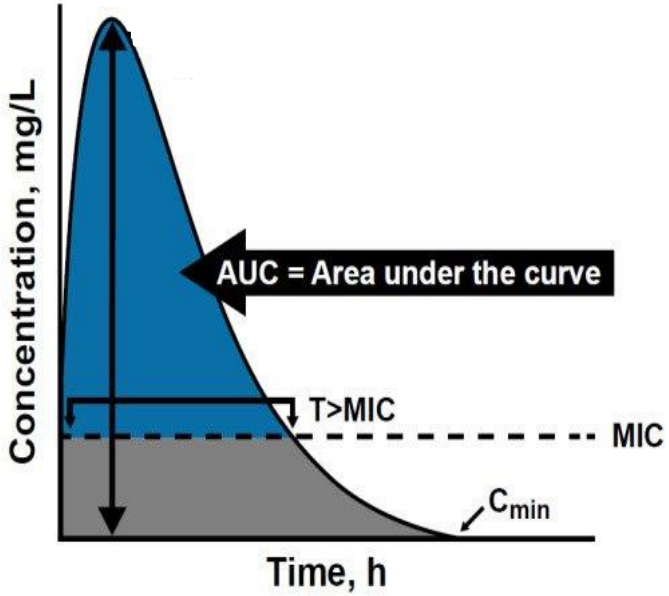
Vancomycin AUC Monitoring

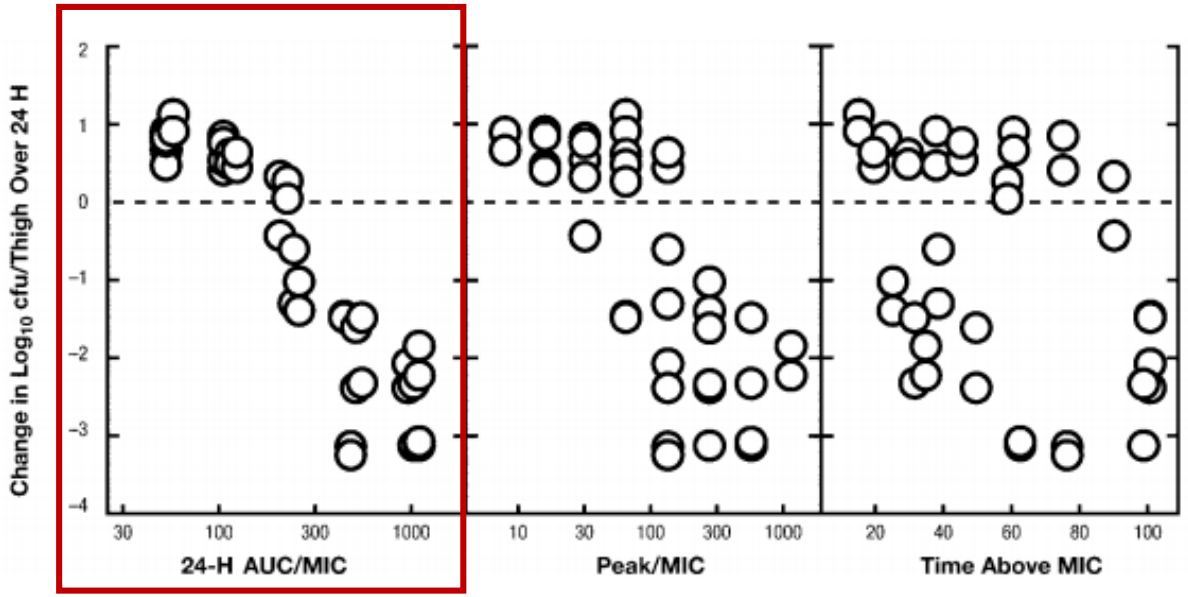
New proposed monitoring system to reduce toxicity while maintaining efficacy

Background - Pharmacokinetics

Antibiotics fall into three major pharmacokinetic categories:

- Peak-dependent (aminoglycosides)
- Time-dependent (beta-lactams)
- **AUC-dependent (vancomycin)**

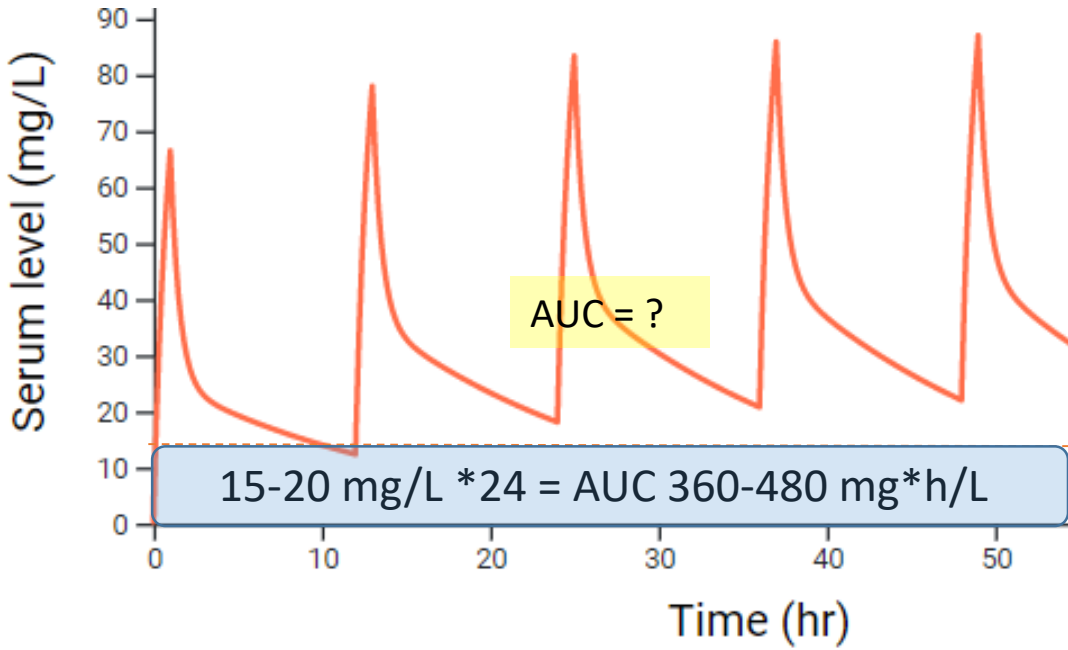




https://www.medscape.org/viewarticle/767071
https://doi.org/10.1086/491712

What's in a Trough? Rationale for Old Targets

- Previous data with improved clinical outcomes for AUC > 400
- Old guidelines recommended trough 15-20 mg/L for severe infections because:
  - Trough serum vancomycin concentrations [of 15-20 mg/L] should achieve an AUC/MIC of 400 but only accounts for drug concentrations at its lowest point (i.e. trough).
  - Often overshoots AUC toxicity threshold if totality of drug exposure is accounted for (i.e. peaks)



- Bottom Line: Trough of 15-20 mg/L **was never the real target** but a surrogate for true target of AUC > 400 mg*hr/L

1. https://doi.org.10.2165/00003088-200443130-00005
2. https://doi.org.10.1093/cid/ciaa1743

New IDSA Vancomycin TDM Guidelines

Published March 19, 2020

ASHP REPORT

Therapeutic monitoring of vancomycin for serious methicillin-resistant *Staphylococcus aureus* infections: A revised consensus guideline and review by the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, the Pediatric Infectious Diseases Society, and the Society of Infectious Diseases Pharmacists

AJHP VOICES An audio interview that supplements the information in this article is available on AJHP's website at www.ajhpvoices.org.

Am J Health-Syst Pharm. 2020;77:835-864

Michael J. Rybak, PharmD, MPH, PhD, FCCP, FIDP, FIDSA, Anti-Infective Research Laboratory, Department of Pharmacy Practice, Eugene Applebaum College of Pharmacy & Health Sciences, Wayne State University, Detroit, MI, School of Medicine, Wayne State University, Detroit, MI, and Detroit Receiving Hospital, Detroit, MI

Jennifer Le, PharmD, MAS, FIDSA, FCCP, FCSHP, BCPS-AQ ID, Skaggs School of Pharmacy and Pharmaceutical Sciences, University of California San Diego, La Jolla, CA

Thomas P. Lodise, PharmD, PhD, Albany College of Pharmacy and Health Sciences, Albany, NY, and Stratton VA Medical Center, Albany, NY

Donald P. Levine, MD, FACP, FIDSA, School of Medicine, Wayne State University, Detroit, MI, and Detroit Receiving Hospital, Detroit, MI

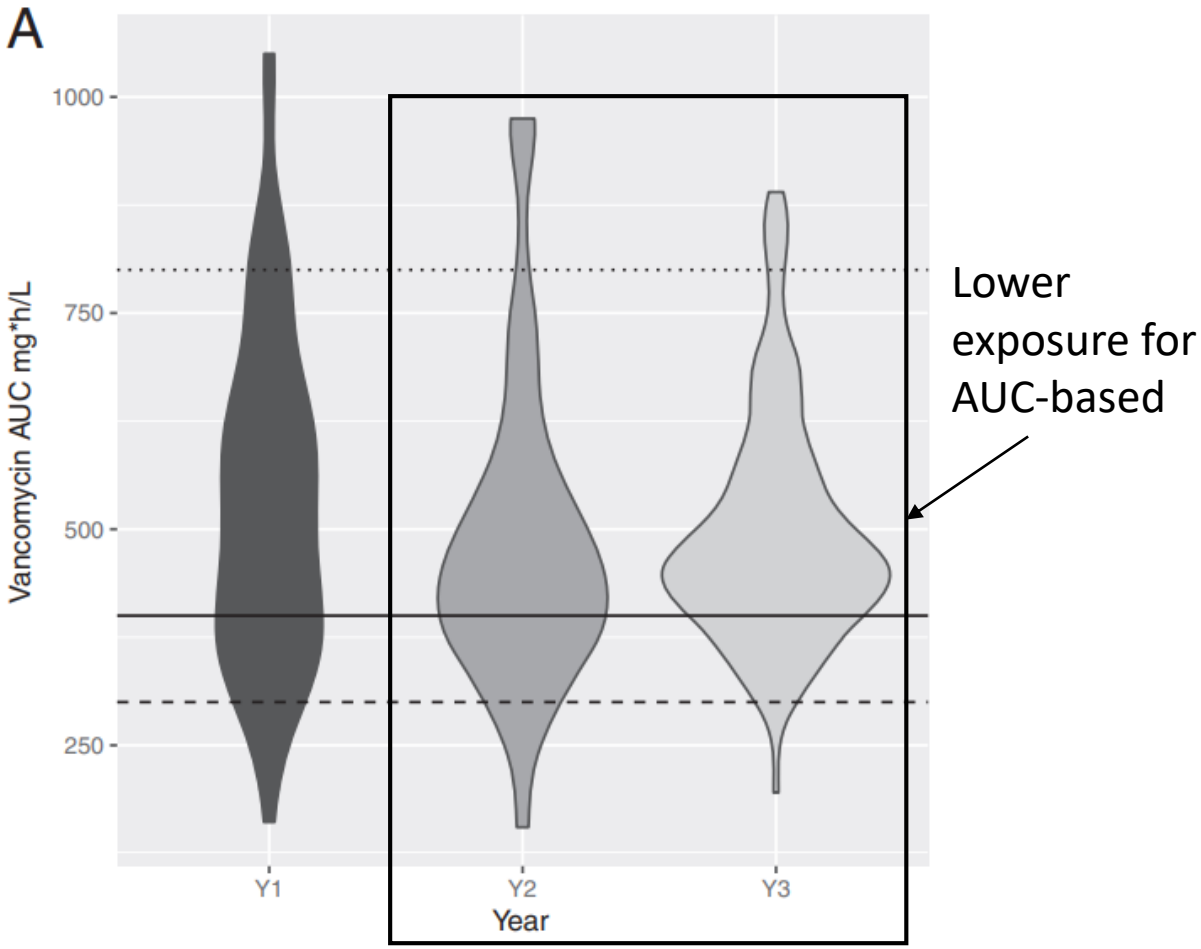
The first consensus guideline for therapeutic monitoring of vancomycin in adult patients was published in 2009. A committee representing 3 organizations (the American Society for Health-System Pharmacists [ASHP], Infectious Diseases Society of America [IDSA], and Society for Infectious Diseases Pharmacists [SIDP]) searched and reviewed all relevant peer-reviewed data on vancomycin as it related to in vitro and in vivo pharmacokinetic and pharmacodynamic (PK/PD) characteristics, including information on clinical efficacy, toxicity, and vancomycin resistance in relation to serum drug concentration and monitoring. The data were summar- *Staphylococcus aureus* (MRSA) infections. It should be noted, however, that when the recommendations were originally published, there were important issues not addressed and gaps in knowledge that could not be covered adequately because of insufficient data. In fact, adequate data were not available to make recommendations in the original guideline for specific dosing and monitoring for pediatric patients outside of the neonatal age group; specific recommendations for vancomycin dosage adjustment and monitoring in the morbidly obese patient population and patients with renal failure, including specific dialysis dosage ad-

2020 IDSA Recommendations

- *"In patients with suspected or definitive serious MRSA infections, an individualized target of the* ***AUC/MIC ratio of 400 to 600*** *should be advocated"* ***(A-II)***
- ***"Trough-only monitoring,*** *with a target of 15 to 20 mg/L,* ***is no longer recommended" (A-II).***
- *"Given the narrow vancomycin AUC range for therapeutic effect and minimal AKI risk, the most accurate and optimal way to manage vancomycin dosing should be through* ***AUC-guided dosing and monitoring" (A-II).***
- "The preferred approach to monitor AUC involves **Bayesian software programs**, to optimize the delivery of vancomycin based on the collection of **1 or 2 vancomycin concentrations, with at least 1 trough.**"

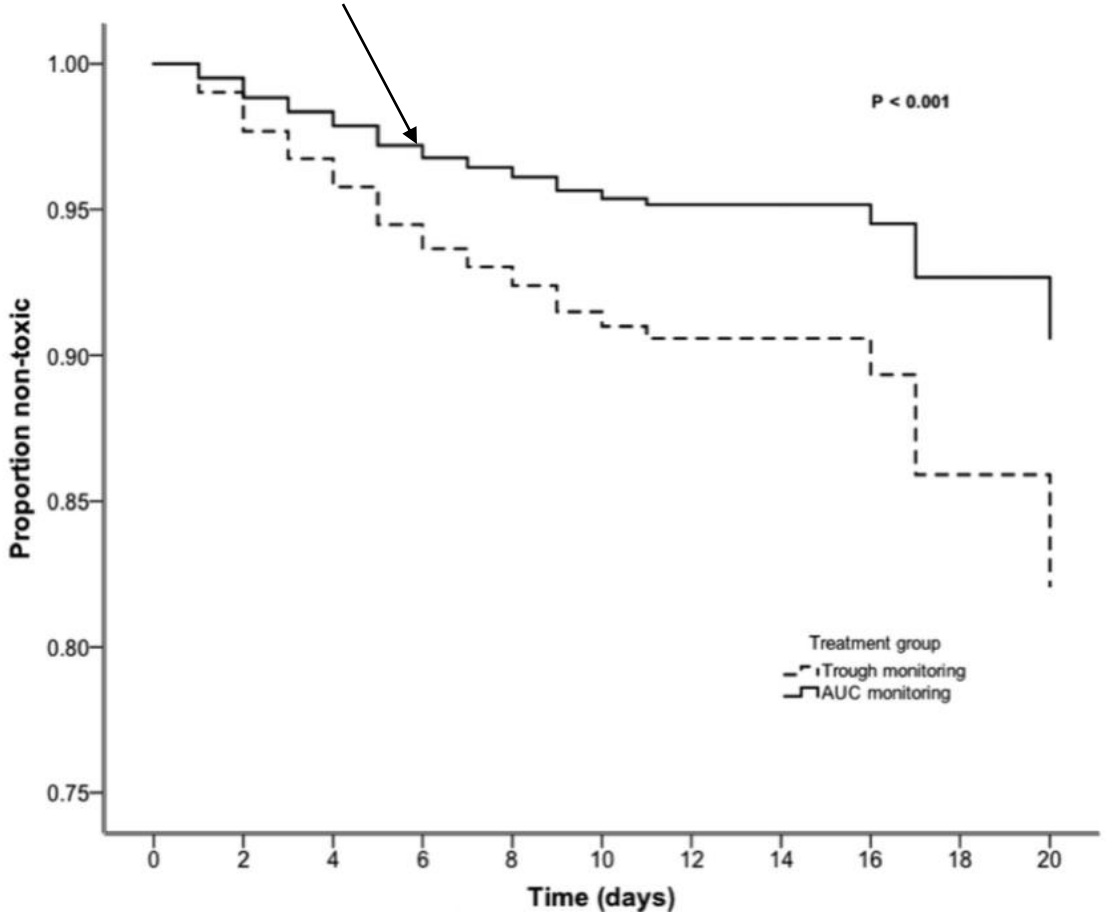
https://doi.org/10.1093/ajhp/zxaa036

Trough vs. AUC



Lower exposure for AUC-based

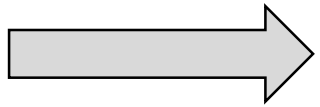
Lower toxicity For AUC-based



https://doi.org/10.1128/AAC.02042-17
https://doi.org/10.1128/AAC.01293-17

New Targets

VANCOMYCIN GOAL TROUGH LEVELS	
Goal Trough 10-15 mg/L	**Goal Trough 15-20 mg/L**
• Skin and soft tissue infections • Urinary tract infections • Febrile neutropenia (empiric) • Coagulase-negative staphylococci (e.g. *S.epidermidis, S. hominis, etc.*) ◦ Excluding sites with limited drug penetration (CNS, osteomyelitis, endocarditis)	**Serious** infections caused by ***S. aureus*** **(MRSA)** • Central nervous system (CNS) • Bloodstream infection • Endovascular (endocarditis) • Pneumonia (health-care associated) • Osteomyelitis • Septic joint (+prosthetic joints)



VANCOMYCIN GOAL LEVELS	
Goal AUC 400-600	
• Skin and soft tissue infections • Urinary tract infections • Febrile neutropenia (empiric) • Coagulase-negative staphylococci (e.g. *S.epidermidis, S. hominis, etc.*) ◦ Excluding sites with limited drug penetration (CNS, osteomyelitis, endocarditis)	**Serious** infections caused by ***S. aureus*** **(MRSA)** • Central nervous system (CNS) • Bloodstream infection • Endovascular (endocarditis) • Pneumonia (health-care associated) • Osteomyelitis • Septic joint (+prosthetic joints)

Exceptions to AUC-based monitoring:

- Unstable renal function
- Hemodialysis

Logistical Considerations

- Inpatient monitoring will be AUC-based, but home health companies/SNFs might not universally have access to AUC-based dosing
  - **Patient-specific trough targets** (which correlate to target AUCs) can be generated via Bayesian calculator **prior to discharge for instruction to home health**
  - ID pharmacy/rounding pharmacy can help facilitate this if contacted prior to discharge
- Vancomycin levels do not need to be at steady state and do not need to be precisely timed
- Vancomycin trough levels may be lower than we are used to seeing
- Vancomycin daily doses may be lower than we are used to seeing

Vancomycin AUC Summary

- Transition to AUC-based monitoring via Bayesian software will:
  - Provide lower vancomycin exposure → lower toxicity risk
  - Maintain therapeutic targets (AUC/MIC 400-600 mg*h/L)
  - Decrease time to effective monitoring/dose-adjustment

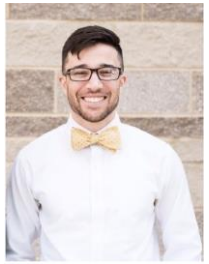
Go-Live:

Anticipated Q3 2021

Currently performing on a case-by-case basis

When to Call ID Pharmacy

- **<u>Dosing</u>**
- Antibiotic allergies (cross-reactivity, alternatives)
- Microbiology (new bugs, odd resistance)
- Renal (dys)function/AKI, CVVHD, IHD
- Antimicrobial toxicity concerns
- Nerd out about antibiotics



RRMC - Adults
Extension: x71423
Pager: p99917
CC Chat: Matthew Davis
Hours: M-F 0730-1600

SMH – Adults
Extension: x77567
Pager: p61029
CC Chat: Christine Pham
Hours: M-F

RRMC – Adults/Peds
Extension: x78510
Pager: p92528
CC Chat: Meganne Kanatani
Hours: MWF 9-1730, TTh 10-1830