Strategies to Decrease Vancomycin-associated Nephrotoxicity

What is their worth?

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Disclosures

- I have no conflicts of interest in relation to the presentation
- Opinions expressed today are those of the presenter and do not represent the position or views of the Department of Veterans Affairs or the US Government

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Objectives

- Strategy 1: Examining risks of concurrent use of piperacillin/tazobactam and vancomycin
  - Alternatives to reduce nephrotoxicity
  - Empiricism in gram negative coverage
  - Strategies to mitigate nephrotoxicity risk
- Strategy 2: Dose Vancomycin targeting AUC vs trough therapeutic range
  - Discuss the limitations of trough guided vancomycin dosing.
  - Evaluate the potential benefits and limitations of AUC guided dosing on clinical outcomes, with focus on nephrotoxicity.
  - Evaluate the available Bayesian software programs and its potential role in vancomycin dosing in a real world setting.

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Risk factors of vancomycin induced nephrotoxicity

Modifiable

- Combination with other nephrotoxic drugs
- Dosages greater than 4 grams per day
- Elevated trough concentrations
- Duration of therapy
- Piperacillin/tazobactam
- Exposure- dependent (trough vs. AUC)

Non-Modifiable

- Severity of illness
- ICU
- Obesity

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Watkins RR, Deresinski S. Clin Infect Dis. 2017;65(12):2137-43.; Elyasi S, et al. Eur J Clin Pharmacol 2012; 68:1243–55.

Definitions of AKI

- An increase in serum creatinine level of 0.3 mg/dL - 0.5 mg/dL from baseline or >50% increase from baseline
- RIFLE Criteria:
  - **R**isk: 1.5-fold increase in SCr level or decrease in GFR by 25%
  - **I**njury: 2-fold increase in SCr or GFR decrease by 50%
  - **F**ailure: 3-fold increase in SCr or GFR decrease by 75%
  - **L**oss of kidney function: persistent acute renal failure for greater than 4 weeks
  - **E**nd stage kidney disease: failure for greater than 3 months

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Bellomo R, et al., Crit Care , 2004, vol. 8 pg. R204

What is the evidence for vancomycin and piperacillin/tazobactam increasing nephrotoxicity ?

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Evidence of vancomycin and piperacillin/tazobactam (VPT) nephrotoxicity

Author, Year	Study Design	Outcome	Notes
Davies, 2016	Retrospective unmatched cohort (n=530)	VPT did not increase the risk of AKI compared to vancomycin alone (RR, 1.1; 95% CI, 0.99-1.2)	PT discontinuation lead to a faster return of renal function
Fodero, 2016	Retrospective unmatched cohort (n=453)	VPT increased risk for AKI compared to vancomycin alone (OR 3.2; 95%CI 1.4-7.9)	Stewardship decreased risk for AKI
Hammond, 2017	Meta-analysis of 14 observational studies (n=3549)	VPT was associated w >3 fold increase in AKI compared with vancomycin	Adults and children
Rutter, 2017	Retrospective unmatched cohort (n=11,650)	VPT was associated with twice the odds of AKI development compared to vancomycin or piperacillin/tazobactam alone	Patients were excluded if they had a diagnosis of chronic kidney disease.

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Hammond DA, et al. Clin Infect Dis. 2017;64(5):666-74. Mousavi M, et al. Pharmacotherapy. 2017;37(3):379-85. Davies SW, et al. Surg Infect (Larchmt). 2016;17(1):38-47. Fodero KE et al. Clin Ther. 2016;38(3):494-502. Rutter et al. J Hosp Med. 2017; 12(2)

Proposed Mechanisms of Nephrotoxicity

- Piperacillin/tazobactam may cause a subclinical interstitial nephritis and when combined with the oxidative stress or acute tubular necrosis of vancomycin, induces AKI
- Piperacillin may impair tubular function as evidenced by its association with magnesium and potassium loss
- Piperacillin/tazobactam may reduce vancomycin clearance resulting in increased exposure of vancomycin to the kidney
  - No relationship between trough and nephrotoxicity was found in patients treated with VPT in a study by Navalkele et. al.

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Rutter WC, et al. J Hosp Med. 2017;12(2):77-82.; Gomes DM, et al. Pharmacotherapy. 2014;34(7):662-9.; Burgess LD, et al. Pharmacotherapy. 2014;34(7):670-6.; Polderman KH, et al. Intensive Care Med. 2002;28(4):520-2. Rutter W et al. Pharmacotherapy. 2017;37(5):593-9.

Breaking up with piperacillin/tazobactam

We are putting patients at too great of risk for nephrotoxicity

The alternatives…

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What are the alternatives to piperacillin/tazobactam?

- Cefepime
- Carbapenems
- Fluoroquinolones
- Aminoglycosides
- Ceftazidime/avibactam
- Ceftolozane/tazobactam
- Meropenem/vaborbactam

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Evidence of vancomycin and piperacillin/tazobactam (VPT) nephrotoxicity compared with vancomycin and cefepime (VC)

Author, Year	Study Design	Outcome	Notes
Gomes, 2014	Retrospective matched cohort (n=224)	AKI rate was higher in the VPT compared with VC (OR, 5.7 95% CI 1.7-19.3)	-More PK monitoring in the VPT group than the VC group -Data presented via matched propensity scores and unmatched
Hammond, 2016	Retrospective cohort (n=122)	AKI incidence was 32.7% in the VPT group compared with 28.8% in the VC group (p=0.6). After adjusting for propensity score, there was no association between beta-lactam choice and AKI (B=-0.004; p=0.96)	- ICU LOS, hospital LOS, AKI duration and need for renal replacement therapy did not differ between the groups
Navalkele, 2017	Matched cohort (n=558)	VPT was associated with >4-fold increase in AKI compared with VC	-Matched based on severity of sepsis, ICU status, duration of combination therapy, daily dose of vancomycin and number of concurrent nephrotoxic medications -Median LOS was 8 days vs. 6 days; p=0.01 -No difference in mortality.
Rutter, 2017	Retrospective matched cohort (n=4103; 1633 in the matched analysis)	VPT was 2.2 times more likely to cause AKI vs. VC	-Excluded patients with AKI in the first 48 hours (n=152) -Vancomycin doses between 3-4 g per day were also correlated with AKI -Median hospital LOS was 8 days in both groups; p=0.08 -In-hospital mortality: VPT 7.7%, VC 9%; p=0.3.

LOS: length of stay

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Navalkele B, et al Clin Infect Dis. 2017; Rutter WC, et al. Antimicrob Agents Chemother. 2017; Gomes D. et al Pharmacotherapy 2014; Hammond et al Pharmacotherapy 2016.

Evidence of VPT nephrotoxicity compared with vancomycin & meropenem (VM)

Author, Year	Study Design	Outcome	Notes
Al Yami, 2017	Retrospective cohort (n=183)	AKI occurred in 7.4% of VPT and 5.3% of VM group; p=0.4	Low overall rates of nephrotoxicity in this study Underpowered study; type II error
Rutter, 2018	Retrospective cohort (n=10,236)	AKI occurred in 27% of VPT and 15% of VM group; p<0.0001 Odds of AKI 2.5 95% CI; 1.8-3.5	Inpatient mortality, median days of hospitalization and AKI recovery did not differ between patients

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Rutter WC, Burgess DS. Antimicrob Agents Chemother. 2018;62(7). Al Yami MS. J Infect Public Health. 2017;10(6):770-3.

Defining levels of renal insufficiency

Study	ABX	Any AKI	Risk (I)	Injury (II)	Failure (III)	Loss/ESRD	NNH
Fodero, 2016	VPT V	12.8% 6.7%	4.9% 2.7%	2.2% 3.6%	2.4% 2.7%	2.7%/2.7% 0/0.09%	17
Rutter, 2017	VPT VC	21.4% 12.6%*	11.7% 7.5%*	6.8% 3.6%*	2.9% 1.5%		12
Navalkele, 2017*	VPT VC	29% 11.1%	14.3% 4.3%	7.5% 2.9%	7.2% 3.9%		6
Rutter, 2018	VPT VM	27.4% 15.4%*	15.3% 9.8%*	7.8% 3.5%*	4.2% 2.1%		9

* Statistically significant

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Rutter WC, et al. Antimicrob Agents Chemother. 2017;61(2); Navalkele B, et al. Clin Infect Dis. 2017;64(2):116-23; Rutter WC, et al. Antimicrob Agents Chemother. 2018;62(7). Fodero KE, et al. Clin Ther. 2016;38(3):494-502.

Audience Question

- What is your work-horse broad-spectrum antimicrobial?
  - A.) Piperacillin/tazobactam
  - B.) Cefepime
  - C.) Carbapenems
  - D.) No formulary restrictions

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Regretting the break-up with piperacillin/tazobactam

Lets examine the consequences of abandoning piperacillin/tazobactam

Consequences of abandoning piperacillin/tazobactam

- *C. difficile*
  - Those who experienced piperacillin/tazobactam shortages increased *C. difficile* rates by a relative risk of 1.3 (95% CI 1.03-1.64)
- Selection for resistant and fungal pathogens
  - Carbapenem vs. piperacillin/tazobactam monotherapy for ESBL bacteremia found that those who received empiric piperacillin/tazobactam had a lower 30-day acquisition of MDR and fungal infections (7.4% vs. 24.6%) p<0.01
- Efficacy
  - Surviving Sepsis: recommends empiric broad spectrum therapy with one or more antimicrobials to cover all likely pathogens
  - Inappropriate initial empirical antimicrobial therapy was an independent predictor of hospital mortality (adjusted OR 3.87, 95% CI 2.77 to 5.41)

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Gross AE, et al. Clin Infect Dis. 2017;65(4):613-8.; Ng TM, et al. PLoS One. 2016;11(4):e0153696, Zillberg et al. Critical Care 2014.

What is your best empirical agent for *Pseudomonas* ?

- A.) Piperacillin/tazobactam
- B.) Cefepime
- C.) Carbapenems
- D.) A mix

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Efficacy: susceptibility trends

Organism	**Sader:** 2012-2014 **INFORM**	**Sutherland:** 2013-2014	**Hachem:** 2010-2014	**Gales:** 2006-2009 **SENTRY**
Proteus mirabilis - Cefepime - Piperacillin/tazobactam - Meropenem	(n=493) 99.8% 100%			
Enterobacter cloacae - Cefepime - Piperacillin/tazobactam - Meropenem	(n=356) 83.1% 98.6%		(n=42) 95% 71% 98%	
Pseudomonas aeruginosa - Cefepime - Piperacillin/tazobactam - Meropenem	(n=442) 87.1% 83% 80.9%	(n=1,257) 77% 72% 76%	(n=70) 89% 86% 91%	(n=9,130) 75% 81% 74%
E. coli - Cefepime - Piperacillin/tazobactam - Meropenem	(n=2,876) 96.9% 99.7%	(n=1,306) 87% 91% 99%	ESBL-100 / ESBL+50 87% / 14% 82% / 64% 95% / 90%	(n=17,035) 89% 92.5% 99.7%
Klebsiella sp. - Cefepime - Piperacillin/tazobactam - Meropenem	(n=1,484) 89.6% 94.9%	(n=1,205) 85% 85% 93%	ESBL-33 / ESBL+34 91% / 35% 88% / 35% 97% / 97%	(n=9,774) 81.5% 69.5% 95.9%

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Sader et al. AAC, 2016. Sutherland et al. Clinical Therapeutics 2015. Hachem et al. AAC, 2017. Gales et al. JAC 2011.

Maybe a compromise

- At least 2 million people become infected with an MDR organism and 23,000 die each year due to resistance
  - MDR was strongly associated with the receipt of initially inappropriate therapy (adjusted OR 13.05, 95% CI 7.00 to 24.31).
- If piperacillin/tazobactam is your best empirical antibiotic for gram negative- lets explore some ways to minimize the risk of nephrotoxicity

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Centers for Disease Control and Prevention. Antibiotic Resistance Threats in the United States: CDC; 2013; Zilberg et al. Critical Care 2014

Going Steady with Piperacillin/tazobactam

ways to mitigate risk…

a case for stewardship

Risk factors for AKI

- Knowledge of risk factors for nephrotoxicity in patients receiving VPT is an important tool for stewardship teams seeking to prevent or mitigate AKI

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Karino S, et al. Antimicrob Agents Chemother. 2016;60(6):3743-50.

Risk factors for AKI

Covariate	Adjusted Odds Ratio	Confidence Interval
Vancomycin dose 3-4 grams	1.6	1.1-2.3
Vancomycin duration >/=7 days	1.5	1.1-1.9
Acyclovir	2.2	1.2-4.1
Amphotericin B	2.3	1.1-4.1
Loop diuretic	2.8	2.2-3.5
Dehydration exposure	1.8	1.2-2.7
Loading dose of vancomycin	2.3	1.1-4.9
Gram positive infection	2.1	1.2-3.8
Receipt of any nephrotoxin	2.3	1.3-4.0

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Rutter WC et al. Antimicrob Agents Chemother. 2017;61(2). Karino S, et al. Antimicrob Agents Chemother. 2016;60(6):3743-50.

Extended vs. conventional infusion of piperacillin/tazobactam:

- No difference between nephrotoxicity rates in patients who received vancomycin and piperacillin/tazobactam with the piperacillin/tazobactam being administered via extended infusion or conventional infusion

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Fodero KE, et al. Clin Ther. 2016;38(3):494-502. Karino S. et al. Antimicrob Agents Chemother. 2016;60(6):3743-50. Mousavi M et al. Phamacotherapy. 2017

When does nephrotoxicity occur?

- Karino et al.: a spike in nephrotoxicity rates was seen at day 4-5 of combination therapy (~40% of nephrotoxicity cases). Day 4-10.7% and Day 5-19.3% of at risk patients developed AKI
- Navalkele et al.: median duration of combination therapy prior to the development of AKI was 5 (IQR: 3-7) days in the VC group and 3 days (IQR: 2-5) in the VPT group; $p<0.0001$
- Rutter et al.: median time to AKI was 8 (IQR: 3-9) days in VPT and 8 days (IQR: 4-16.8) in VC
- Stewardship opportunity: most cultures return on day 3 of therapy, thus Stewardship teams could deescalate therapy before the largest risk timeframe.

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Karino S, et al. Antimicrob Agents Chemother. 2016; Navalkele B, et al. Clin Infect Dis. 2017;64(2):116-23. Rutter WC, et al. Antimicrob Agents Chemother. 2017;61(2).

Does limiting the duration of VPT impact incidence of nephrotoxicity?

- Retrospective cohort of 3299 ICU patients
- All patients received an antipseudomonal beta-lactam and vancomycin for 24-72 hours
- Overall incidence of stage 2 or 3 AKI was 9%
- After adjusting for confounders- VPT did not pose a greater risk of stage 2 or 3 AKI compared with VC or VM
- No significant differences at 60-days were found with regard to persistent kidney dysfunction, new dialysis dependence or death
- Clinical Pharmacists were responsible for dosing and monitoring vancomycin and beta-lactams

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Schreier, et al. CID ahead of print, 2018

Is stewardship the answer?

- Stewardship decreased the rate of nephrotoxicity – OR 2.1 (95%CI 1.02-4.3)
- Stewardship was highly individualized

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Fodero KE, et al. Clin Ther. 2016;38(3):494-502.

Stewardship

- Encourage cultures for rapid streamlining
- Individualization of patient care – severity of illness, hospital antibiogram, prior antimicrobial use, antibiotic allergies, nephrotoxicity risk factors
- In the absence of cultures, utilizing MRSA nares surveillance swabs may be beneficial
  - Meta-analysis – MRSA nares screening had a high specificity and negative predictive value for ruling out MRSA pneumonia in CAP/HCAP

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Parente DM, et al. Clin Infect Dis. 2018;67(1):1-7.

What is your plan for gram negative coverage?

- A.) Continue to use piperacillin/tazobactam and incorporate stewardship tactics
- B.) Increase use of cefepime when patients are receiving vancomycin
- C.) Increase use of meropenem when patients are receiving vancomycin
- D.) Other

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Take home points

- The combination of vancomycin and piperacillin/tazobactam increases the risk of nephrotoxicity
- Defining acceptable risk of nephrotoxicity while providing the best empirical coverage in patients with a high severity of illness
  - requires individualization of treatment
- Stewardship teams should be proactive with regards to concurrent risk factors of nephrotoxicity
- Nephrotoxicity occurs between day 3-8 of therapy allowing for de-escalation if proper cultures are obtained

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Strategy Two

AUC vs. trough guided monitoring to reduce the risk of vancomycin induced nephrotoxicity

Audience Question

What is your current institutional protocol for vancomycin dosing and monitoring?

A) Trough concentration based monitoring
B) AUC based monitoring using 2 levels + calculation
C) AUC based monitoring using Bayesian software
D) No concentration monitoring

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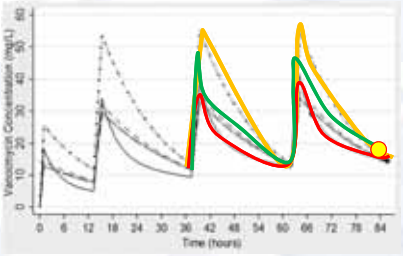
Breaking up with troughs

- 2009 IDSA Vancomycin TDM Guidelines recommended measurement of troughs as the most accurate and practical method for monitoring effectiveness
- Achievement of troughs 15-20mg/L would likely achieve $AUC_{24}/MIC \geq 400$
- However, do trough concentrations tell us enough?
  - Using trough values alone significantly underestimates "true" AUC by 25%
  - 60% of patients with true AUC ≥ 400, did not have trough >15 mg/L
  - Large variability (up to 3-5x) of AUC_{24} found in neonatal, adult, and elderly population for a given C_{min}



Pai M et al. AAC 2017.

Rybak M et al. Am J Health-Syst Pharm 2009.
Neely MN et al. AAC 2014
Bel Kamel et al. Ther Drug Monit 2017

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Trough Concentrations and Clinical Outcomes

- Data on correlation of ↑ trough with ↑ clinical efficacy is limited and mixed[1]
- First trough concentrations > 15mg/L had ↑ risk to nephrotoxicity (OR 3.12; 95% CI 1.81-5.37)[2, 3]
- When comparing AUC, C_{max}, and C_{min}, AUC and C_{max} better correlated with AKI outcome[4]
- Current dosing in adults to achieve trough goals > 10mg/L or >15mg/L is likely sufficiently achieving $AUC_{24} \geq 400$mg x h/L[5]
- *Thus, ↑ doses to achieve troughs >15 could needlessly ↑ risk for AKI*
- **Shifting paradigm**: move away from trough monitoring for efficacy and toxicity → AUC monitoring

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[1] Pai 2014. [2] van Hal SJ 2013.
[3] Wong-Beringer 2011. [4] Rhodes 2016. [5] Neely 2014.

What AUC/MIC is enough for efficacy?

Study	N	Population	MIC Method	AUC Method	AUC/MIC and Efficacy Outcomes
Moise-Broder 2004	108	MRSA pneumonia	BMD	Formula	≥ 345
Holmes 2013	182	*S. aureus* Blood Stream Infxn (BSI)	BMD	Formula	> 373
Kullar 2011	320	MRSA BSI	BMD	Formula	> 421
Ghosh 2014	127	MRSA BSI	Etest BMD	Formula	≥ 270 (Etest) ≥ 398 (BMD)
Caspao 2015	139	MRSA Infective Endocarditis (IE)	BMD	Bayesian	> 600 (Day 1)
Brown 2012	50	Complicated MRSA BSI and IE	Etest	Bayesian	> 211
Gawronski 2013	59	Complicated MRSA BSI and osteo	Etest	Bayesian	> 293
Jung 2014	76	MRSA BSI	Etest BMD	Bayesian	> 430 (Etest) > ~400 (BMD)
Lodise 2014	123	MRSA BSI	Etest BMD	Bayesian	≥ 303 (Etest-Day 1) ≥ 320 (Etest-Day 2) ≥ 521 (BMD-Day 1) ≥ 650 (BMD-Day 2)
Jumah 2018	57	Enterococcus BSI	Etest	Bayesian	≥ 389

What AUC is too high leading to Nephrotoxicity?

Study	N	Population studied	Time point AUC evaluated	Bayesian Software used	AUC_{24} threshold for AKI
Lodise 2009	166	Adult patients	Steady state	ADAPT V	>1300
Suzuki 2012	31	Adult, MRSA pneumonia	Steady state	NONMEM	>700
Chavada 2017	127	Adult, MRSA BSI	Steady state	DoseMeRx	>563
Mogle 2018	44	Adult, MRSA BSI	Steady state	Non-Bayesian method (2 lvls)	>710
Zasowski 2017	323	Adult, BSI or pneumonia	Day 1 Day 2	ADAPT V	≥ 677 (Day 1) ≥ 683 (Day 2)
Le 2014	680	Peds (3m–21yo)	Steady state	NONMEM	≥1000

Friday, Oct 5	Poster 1391	Aljefri D et al.	Vancomycin Area under the Curve (AUC) to Predict Nephrotoxicity: A systematic Review and Meta-analysis of observational studies

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All studies defined AKI: ↑ Scr by 0.5mg/dL or 50% from baseline

AUC and nephrotoxicity threshold

- Early target attainment important for efficacy outcome in MRSA blood stream infections
  - Largest study to date in adult patients used first 24-48h AUC to determine nephrotoxic threshold
  - Almost 4x increased risk for AKI when AUC_{24} > ~700 mg x h/L
- Nephrotoxic threshold may vary depending on severity of illness, body weight, diagnosis, concomitant nephrotoxins, duration of therapy
  - Risk likely occurs along a continuum

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Lodise TP et al. CID 2009; Lodise TP et al. CID 2014
Zasowski E et al. AAC 2017

Clinical studies evaluating AUC guided dosing on AKI

Is prospective AUC guided dosing feasible?

Does AUC guided dosing lead to better patient care?

Methods of Vancomycin AUC estimation:

Non-Bayesian approach	2 steady state levels (peak + trough) + first-order PK equations[1]	Finch et al. AAC 2017 Stoessel et al. J Pharm Pract 2018 Shahrami B et al. Crit Care Res Pract 2016. Troung J et al. J Clin Pharm 2018
Bayesian approach	Limited sampling (1 level) + Bayesian software	Neely et al. AAC 2017

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[1] Pai M et al. Advanced Drug Delivery Review 2014.

Non-Bayesian Method Decreased Risk for Nephrotoxicity

Multicenter (4 hospitals within same health system) quasi-experimental study

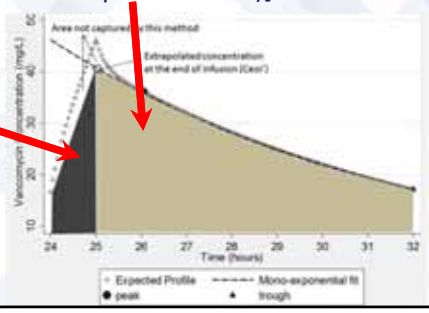
Included: Adult patients treated with vancomycin; excluded patients with concomitant piperacillin-tazobactam

AUC estimated by minimum of two vancomycin samples drawn during the same dosing interval within 96h of initiation of vanco.

Total 24h AUC = [AUC_{inf} (trapezoidal rule) + $AUC_{elim\ phase}$ (logarithmic trapezoidal rule)] x # of daily doses

Target AUC_{24} steady state range: 400-600 mg x h/L

Definition of AKI – by AKIN, RIFLE, and ↑ Scr by 0.5 or 50%



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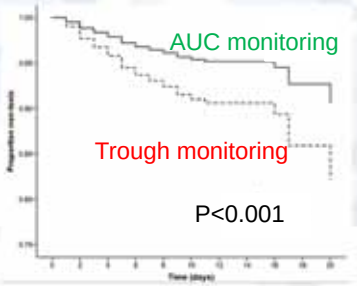
Graphic: Pai M 2014.
Study: Finch N 2017.

Lower doses needed to achieve therapeutic goal

Variable	Trough guided (n=150)	AUC guided (n=150)	P value
Cumulative dose first 24h	3250mg (2438-4250)	3000mg (2000-3750)	<0.001
Cumulative dose first 48h	5250mg (4000-7500)	5000mg (3750-6500)	<0.001
$Cmin_{24}$	12.7 (8.9-16.6)	10 (5.7-13.4)	<0.001
$Cmin_{48}$	14.2 (10.3-19.5)	12.5 (8.3-16.7)	0.003
AUC_{0-24h}	705 (540-883)	474 (360-611)	<0.001
AUC_{24-48h}	663 (538-857)	532 (406-667)	<0.001

Multivariable logistic regression for nephrotoxicity (Scr ↑ 0.5mg/dL)

Variable	Adjusted OR	95% CI	P value
AUC monitoring	0.514	0.332-0.794	0.003
Concomitant furosemide	1.771	1.127-2.784	0.013
Elixhauser comorbidity index	1.149	1.060-1.245	0.001
Duration of therapy	1.093	1.044-1.145	<0.001
APACHE II score	1.070	1.045-1.097	<0.001



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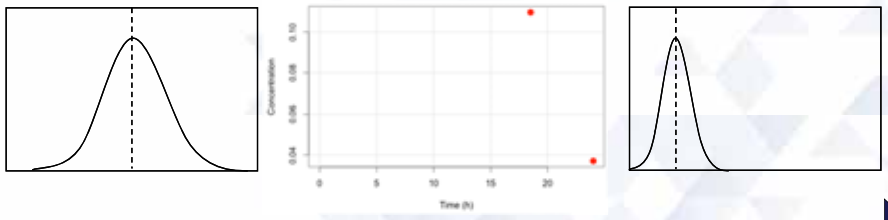
Finch N 2017

Integrating Bayesian feedback into Clinical Practice

Bayesian Control



Population CL → Data → Individual CL

Bayesian Prior → Bayesian Posterior

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Slide courtesy of M Neely

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CLINICAL THERAPEUTICS

Prospective Trial on the Use of Trough Concentration versus Area under the Curve To Determine Therapeutic Vancomycin Dosing

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Inclusion: Adult patients treated with vancomycin

Target AUC range: 400-800 mgxh/L (300 allowed if clinically responding)

Bayesian software used: BestDose

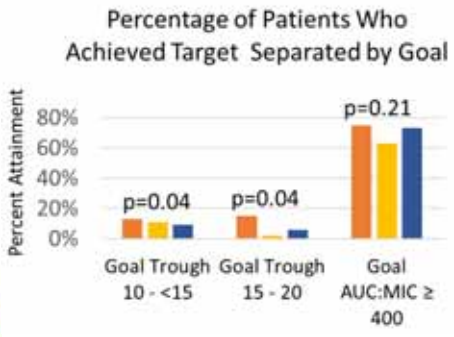
Year 1 Trough guided dosing

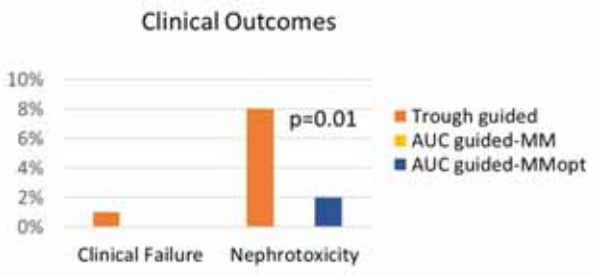
Year 2 Multiple Model (MM) Bayesian adaptive Control algorithm

Year 3 Similar to year 2. Additionally used MM optimal sampling

Main Findings

	Trough guided	AUC guided- MM	AUC guided-MMopt	P-value
Avg daily dose (mg)	1818 (275-2760)	1750 (700-3360)	1577 (750-4300)	0.46
Avg daily dose (mg/kg)	24 (7.4-52.6)	22 (9.5-67.2)	22.6 (8.8-85.7)	0.30
# of samples/patient	3.6 (1-15)	2.1 (1-8)	2.4 (1-12)	0.007
Trough concentrations (mg/L)	N=84 14.4 (3.8-27.2)	N=87 9.7 (4.5-39.6)	N=43 10.9 (3.5-25.8)	0.005
Daily AUC (mgxh/L)	510 (160-1050)	459 (154-975)	459 (194-890)	0.29





Neely 2017

Benefits of AUC monitoring

Overall benefits
1. Targeting PD target that correlates closely with efficacy 2. Tighter control of vanco exposure 3. Lower risk for nephrotoxicity
Additional Benefits by Using Bayesian Software
1. Limited sampling required (1 vs 2 levels) 2. Flexibility of sampling times 3. Can account for changes in patient's renal function that can influence PK over time 4. Do not have to wait for steady state to make clinical decision 5. More accurate predictions in patients with quickly changing parameters 6. Potentially less time consuming for clinical pharmacists

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Stewardship Implementation of AUC monitoring

Development of institution specific protocol

- Testing method: Etest vs BMD
- MIC_{90} for *S. aureus* (and other GPC) isolates
- PD target: Data on therapeutic window can be used to guide target attainment, although clinical factors may warrant deviations, or utilization of vancomycin alternatives
- Bayesian vs non-Bayesian method?
  - If non-Bayesian approach: if sampling timed correctly, median error of AUC estimation ≤2%
- AKI definition: when to consider change to vancomycin alternative due to rising Scr

Education, Education, Education: Pharmacists, nurses (appropriate timing and documentation), lab, physicians ….. Audit and feedback

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Pai M et al. Advanced Drug Delivery Review 2014. Minejima E et al. AAC 2011.

Implementation of non-Bayesian AUC monitoring

Variables	Factors to Consider
Timing of serum conc monitoring	Steady State Emerging data on sampling after 1st dose
Optimal Timing of Peak	C_{peak} 1.75h – 3h after end of infusion minimized error in AUC calculation
Optimal Timing of Trough/2nd level	Ideally from same dosing interval as 1st level
Estimation of AUC	Sawchuk-Zaske method: determine k_e from 2 levels → determine true peak and trough→ estimate AUC 1. Modified trapezoidal rule =$AUC_{infusion}$ + $AUC_{elimination\ phase}$ 2. Extrapolate C_{max} to start of infusion → $AUC_{elimination\ phase}$
Continued monitoring	Once achieve target, further monitoring done with 1 or 2 level monitoring?
Limitations	Provides only a snapshot of AUC for sampling period; sampling time important

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Pai M 2014; Troung 2018

Implementation of Bayesian AUC monitoring

Variables	Factors to Consider
Timing of serum conc monitoring	After 1st dose vs waiting until steady state
Optimal Timing of Lvl	Timing not as important as non-Bayesian method Individualize per patient or standardize practice?
# of serum conc	1 vs ≥1. Start with 2 to determine precision for your population? Special pops (obesity): 2 lvls more appropriate
Fit/ Error	Do you want your pharmacists to determine the fit to guide decisions?
Limitations	Best *a priori* model for specific patient populations, including obese and dialysis may limit limited sampling method initially Cost of software

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Pai 2014. Neely 2017. Carreno 2017.

Functions to consider of Bayesian software

Essential	Extra Perks
• COST 🤑🤑🤑🤑	• Graphical User interface
• Population model used	• Availability for smartphone
• 1 vs 2 compartmental model	• Reports – sending to MD with recommendations
• Interface with EMR and lab information management system	• Additional clinical decision support tools
• Storage of patient specific details and regimens	• Data mining or data reporting (audit and feedback)
• Availability of technical and clinical manuals/support	• Ability to add in own drug models
• Can handle drugs administered continuous infusion, non-steady state (with one level vs multiple levels) and irregular regimens	• Can handle drug-drug or drug-disease interactions
	• Other non-antibiotic drug models

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Fuchs A et al. Clin Pharmacokinet 2013.

Available Bayesian Software

Software	CrCl estimation	Para- vs non-parametric statistics	1 vs 2 Comprtmt model	EMR integration	Optimal Sampling Time	Cost	Data analysis function/ storage
InsightRx	Cockroft &Gault	Parametric	2	EPIC, Cerner, Allscripts	No	$70,000/yr	Analytics tools
DoseMeRx	Cockroft &Gault	Parametric	1	EPIC, Cerner, Allscripts	No	$12,000/yr	DoseMe Crunch
Precise PK (formerly known as TDMS2000)	Cockroft &Gault/ Shwartz-peds	Parametric	2	No	No	$1200/yr	No
BestDose	Jelliffe	Non-Parametric	2	No	Yes	Donation, $595	No

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Adapted from Fuchs A et al. Clin Pharmacokinet 2013.

Future Areas of Interest

- *Does AUC-guided vancomycin dosing improve survival in prospective trials?*
  - PROVIDE study- prospective study in MRSA BSI targeting $AUC_{DAY2}/MIC_{Etest} \geq 320$ or $AUC_{DAY2}/MIC_{BMD} \geq 650$
- *Is AUC-guided vancomycin dosing providing cost-effective care?*
  - Mean cost of treating AKI episode - $11,234
  - Trough guided dose adjustments – cost of preventing 1 vanco AKI episode $5,564 if receiving concomitant nephrotoxins or $8,363 ICU patients
  - Bayesian guided dosing significantly reduced costs for Aminoglycosides: $33,810 / 100 patient courses

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Lodise TP et al. ID Week 2017 abstract
Darko W et al. Pharmacotherapy 2003.
Van Lent-Evers, N et al. Ther Drug Monitor 1999.

Summary

- Nephrotoxicity leads to ↑ length of stays, ↑ mortality, and ↑ healthcare costs
- Stewardship can positively affect outcomes with active surveillance of modifiable risk factors for AKI: 1) duration of combination use, 2) ↓ unnecessarily high exposures
- AUC-guided vancomycin dosing is effective and decreased risk for nephrotoxicity
  - Both Bayesian and non-Bayesian methods described in literature
  - More precise dosing lead to tighter control and decreased total daily doses
  - Overall decrease in number for sampling
- Certain populations likely to benefit from AUC guided and additionally Bayesian approach more than others

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