2018

Vancomycin Dosing: Bayesian derived AUC/MIC vs. trough only monitoring

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Vancomycin Dosing: Bayesian Derived AUC/MIC vs. Trough Only Monitoring

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The speaker has no actual or potential conflicts of interest in relation to this presentation.

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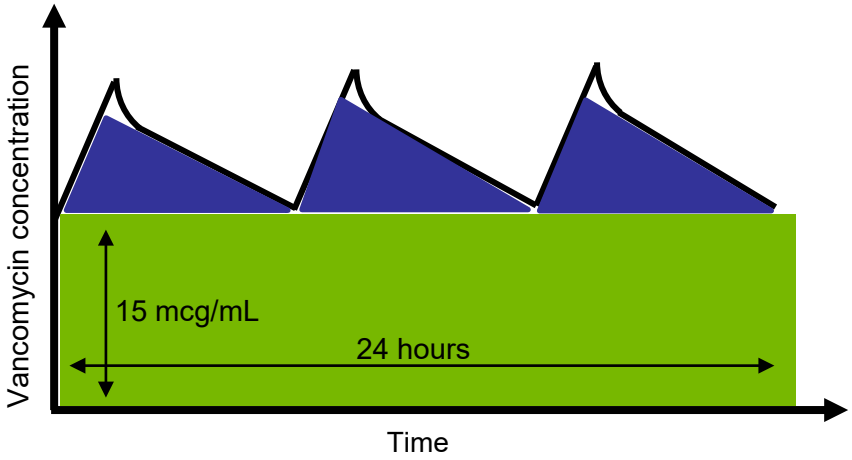
Background

- Area under the curve (AUC_{24})
  - Total concentration of drug in the body for a 24 hour duration
- Minimum inhibitory concentration (MIC)
  - Minimum concentration needed in the body to inhibit bacterial growth
- AUC/MIC ratio
  - Concentration of drug in the body for a 24 hour duration divided by the organisms MIC
- Trough
  - Lowest concentration of drug in the body
  - Surrogate marker for AUC



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Previous Studies

	van Hal et al (2013)	Finch et al (2017)	Zonozi et al (2019)
Study design	Meta-analysis (15 studies)	Retrospective cohort (n=1,280)	Retrospective cohort (n=21,285)
Primary endpoint	Incidence of nephrotoxicity	Incidence of nephrotoxicity	Frequency and risk factors for elevated vancomycin concentrations
Results	**Troughs ≥ 15 mcg/mL were associated with increased nephrotoxicity** compared to troughs < 15 mcg/mL (OR 2.67 [95% CI: 1.95-3.65])	**AUC-guided dosing was associated with less nephrotoxicity** compared to trough-guided dosing (OR 0.52 [95% CI: 0.34-0.80])	Patients with elevated concentrations had longer durations of vancomycin therapy (p<0.001) and **longer lengths of stay** (p=0.03)

van Hal SJ et al. 2013
Finch NA et al. 2017
Zonozi R et al. 2019

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Guidelines

Therapeutic Monitoring of Vancomycin: A Revised Consensus Guideline and Review

American Society of Health-System Pharmacists, Infectious Diseases Society of America, Pediatric Infectious Diseases Society, Society of Infectious Diseases Pharmacists (ASHP/IDSA/PIDS/SIDP)

A Bayesian-derived **AUC/MIC ratio of 400 to 600** should be advocated as the target to achieve clinical efficacy while improving patient safety.

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Rybak et al. 2019

Guidelines

The most accurate and optimal way to manage vancomycin dosing is through **AUC-guided dosing and monitoring.**

1. Utilize 1st order pharmacokinetic calculations to estimate AUC based on collection of two concentrations

2. Collect one or two concentrations to estimate AUC with the use of Bayesian software programs

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Rybak et al. 2019

Benefits of Bayesian Kinetics

- Compared to 2 point pharmacokinetics:
  - Reduced lab sticks to the patient
  - Less frequent monitoring
  - Fewer timing issues with lab draws

- Compared to the trough-based method:
  - Non-inferior efficacy with potentially improved safety
  - Equivalent or less lab costs
  - Shorter hospital length of stay, if reduced complications

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Assessment Question #1

New guidelines recommend targeting which of the following when dosing and monitoring vancomycin therapy?

A. Trough 15-20 mcg/mL
B. AUC 400-600
C. AUC < 400
D. Trough 20-25 mcg/mL

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Assessment Question #1

New guidelines recommend targeting which of the following when dosing and monitoring vancomycin therapy?

A. Trough 15-20 mcg/mL

B. AUC 400-600

C. AUC < 400

D. Trough 20-25 mcg/mL

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Assessment Question #2

Studies have found that utilizing AUC/MIC-based dosing for vancomycin can:

A. Reduce the risk of developing acute kidney injury (AKI)
B. Increase the total daily dose of vancomycin
C. Increase overall hospital use of vancomycin
D. Lead to higher trough concentrations

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Assessment Question #2

Studies have found that utilizing AUC/MIC-based dosing for vancomycin can:

A. Reduce the risk of developing acute kidney injury (AKI)

B. Increase the total daily dose of vancomycin

C. Increase overall hospital use of vancomycin

D. Lead to higher trough concentrations

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Purpose

To investigate whether Bayesian derived AUC/MIC dosing results in reduced incidence of acute kidney injury (AKI) compared to trough-based dosing in patients being treated with vancomycin at our hospital.

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Parkview Regional Medical Center (PRMC)

- Parkview Health
- Community hospital
- Level II trauma center
- 460 adult and pediatric inpatient beds
- 6 critical care units

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PRMC Current Policy

Vancomycin Pharmacy Dosing Protocol

Loading dose	Maintenance dose
25 mg/kg (max 2500 mg)	15 mg/kg (max 1500 mg)
Indications: endocarditis, meningitis, osteomyelitis, pneumonia, sepsis	Adjust frequency for renal function (Creatinine clearance)

Target trough:
10-15 mcg/mL (mild/moderate skin & soft tissue infections and urinary tract infections)
15-20 mcg/mL (all other indications)

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Study Design

- Single center
- October 2019 to March 2020
- Prospective enrollment with retrospective analysis
  - 8 study team members
  - Institutional Review Board approved
  - Informed consent not required (AUC dosing adopted per hospital policy)
- Grant was obtained to cover the cost of the temporary use of the pharmacokinetic software program

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Inclusion Criteria

- Pharmacy-to-dose consult for ongoing vancomycin therapy
- ≥ 18 years old
- Admitted to PRMC
- At least one vancomycin concentration obtained

Exclusion Criteria

- Pregnancy/breastfeeding
- Receiving vancomycin prior to admission
- Peri-operative vancomycin
- Renal replacement therapy

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Study Design

Given limited data for using trough concentrations alone to estimate AUC in certain populations…

- Guidelines recommend obtaining **two concentrations** for patients meeting the following criteria:
  - **Critically ill**
  - **Unstable renal function**
  - **BMI ≥ 40 kg/m²**

- Patients not meeting the above criteria had an AUC estimated based off the collection of **one concentration**

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Rybak et al. 2019

Study Design

Control group

Trough based
Managed by non-study team pharmacists per PRMC trough-based dosing protocol

AUC/MIC group

Bayesian, one level	Bayesian, two levels
Target AUC: 500	
Non-critically ill	Critically ill
Stable renal function	Unstable renal function
BMI < 40 kg/m²	BMI ≥ 40 kg/m²

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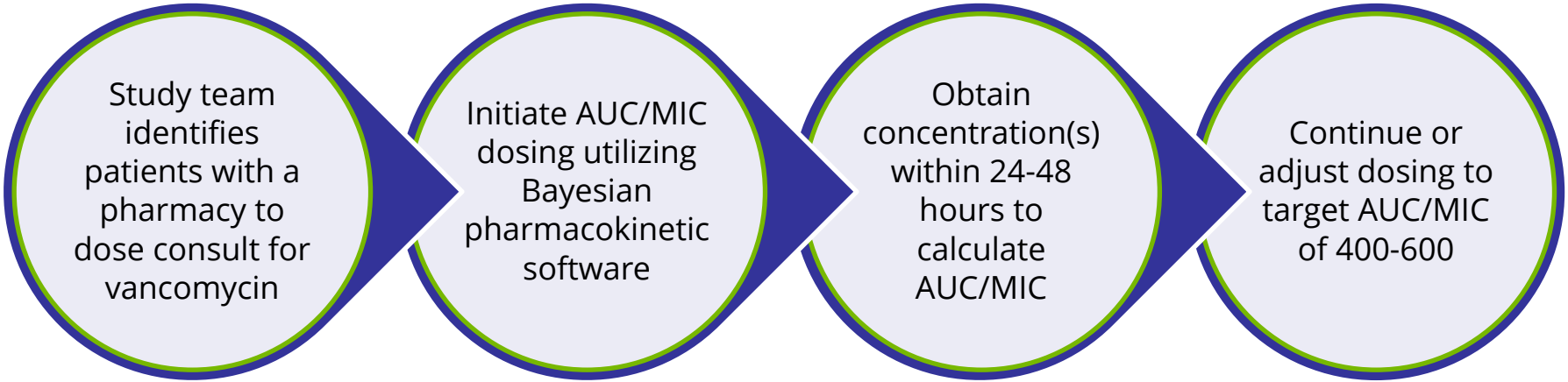
Study Workflow



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Endpoints

- Primary endpoint:
  - Incidence of AKI as defined by the Kidney Disease: Improving Global Outcomes (KDIGO) criteria
    - → Rise in serum creatinine by ≥ 0.3 mg/dL within 48 hours or ≥ 1.5 times baseline within 7 days

- Secondary endpoints:
  - Average total daily dose of vancomycin (mg/kg)
  - Intensive care unit (ICU) length of stay (LOS)
  - Total LOS
  - Receipt of at least one concomitant nephrotoxin
  - Total days receiving vancomycin

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KDIGO AKI Work Group. 2012.

Matching

AUC/MIC patients with a calculated AUC were matched to control patients in a **1:2** manner based on:

Age	Renal function (Cockcroft-Gault)	ICU vs non-ICU	BMI
< 40 years	< 44 mL/min	Any ICU stay < 24 hours during admission	< 30 kg/m²
≥ 40 years	45 – 64 mL/min	Any ICU stay ≥ 24 hours during admission	30 – 40 kg/m²
	65 – 100 mL/min		> 40 kg/m²
	> 100 mL/min		

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Statistical Analysis

- Primary endpoint
  - Categorical data was assessed with the Chi square test
- Secondary endpoints
  - Continuous data were assessed with the T-test
- Secondary analysis
  - Intention-to-treat
- Subgroup analysis in the AUC/MIC group comparing one vs two concentrations

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Baseline Characteristics

	AUC/MIC dosing (n = 101)	Trough dosing (n = 202)
Age (years), median (IQR)	63.0 (54.0 – 72.0)	62.5 (54.0 – 72.8)
Sex, female (%)	41.6%	36.6%
Race, white (%)	94.1%	91.6%
Weight (kg), median (IQR)	87.5 (69.7 – 104.3)	88.5 (69.3 – 104.3)
BMI (kg/m²), median (IQR)	29.4 (24.4 – 35.3)	29.7 (24.4 – 34.7)
Creatinine clearance (mL/min), median (IQR)	83.8 (54.3 – 109.4)	82.9 (54.2 – 112.9)

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Baseline Characteristics

	AUC/MIC, one level (n = 64)	AUC/MIC, two levels (n = 37)
Age (years), median (IQR)	64.5 (51.8 – 73.3)	62.0 (55.0 – 71.0)
Sex, female (%)	45.3%	35.1%
Race, white (%)	93.8%	94.6%
Weight (kg), median (IQR)	84.2 (67.4 – 94.5)	105.2 (85.0 – 136.5)
BMI (kg/m²), median (IQR)	28.0 (24.3 – 31.2)	35.3 (27.0 – 45.1)
Creatinine clearance (mL/min), median (IQR)	83.7 (56.4 – 105.4)	84.2 (48.4 – 123.4)
ICU admission >24 hours (%)	12.5%	35.1%

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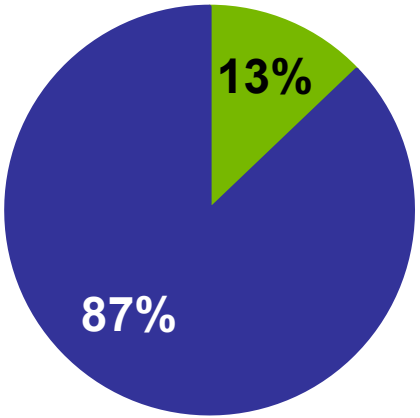
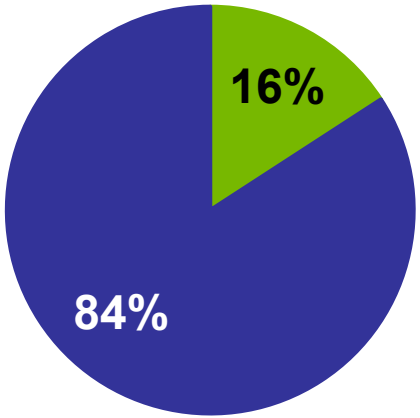
Primary Outcome (Per Protocol)

AUC/MIC Dosing
(n = 101)



Trough Dosing
(n = 202)



p = 0.49

AKI

No AKI

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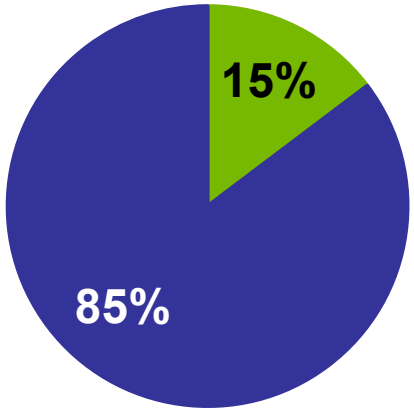
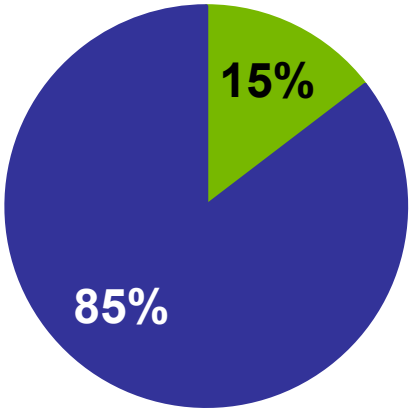
Primary Outcome (Intention-to-Treat)

AUC/MIC Dosing (n = 231)



Trough Dosing (n = 1378)



p = 0.97

AKI

No AKI

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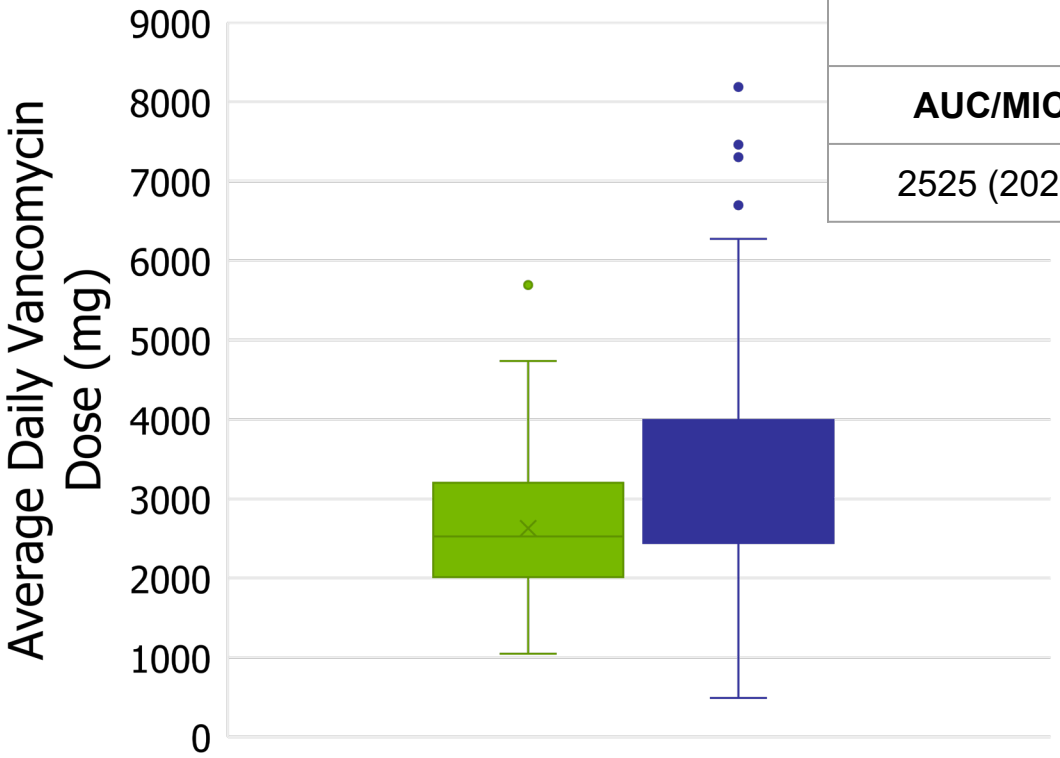
Average Daily Vancomycin Dose (Per Protocol)

Dose (mg), median (IQR)	
AUC/MIC dosing	**Trough dosing**
2525 (2020 – 3162)	3180 (2461 – 3991)



$p < 0.05$

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Secondary Outcomes

	AUC/MIC dosing (n = 101)	Trough dosing (n = 202)	P-value
ICU LOS (days), median (IQR)	4.8 (2.8 – 7.4)	5.6 (3.4 – 9.6)	0.24
Total LOS (days), median (IQR)	5.9 (3.3 – 8.9)	5.3 (3.3 – 8.6)	0.76
Total days on vancomycin, median (IQR)	2.1 (1.5 – 3.2)	1.8 (1.1 – 2.6)	0.04
Receipt of 1+ concomitant nephrotoxin(s)	86.1%	84.2%	0.65

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Secondary Outcomes

	AUC/MIC, one level (n=64)	AUC/MIC, two levels (n=37)	P-value
Average daily dose of vancomycin (mg/kg), median (IQR)	2527 (1916 – 3158)	3396 (2324 – 4351)	0.35
ICU LOS, median (IQR)	3.3 (3.0 – 6.8)	3.8 (2.3 – 6.6)	0.25
Total LOS, median (IQR)	5.7 (3.0 – 8.5)	5.0 (3.3 – 8.0)	0.45
Total days on vancomycin, median (IQR)	2.4 (1.5 – 3.4)	1.6 (1.0 – 2.6)	0.78
AUC, median (IQR)	421 (364 – 502)	423 (307 – 475)	

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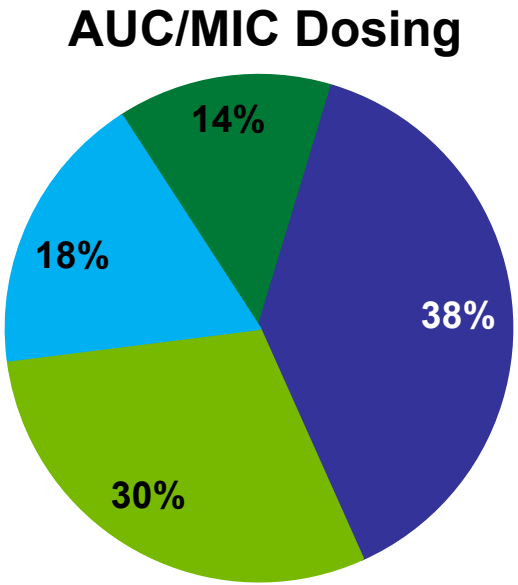
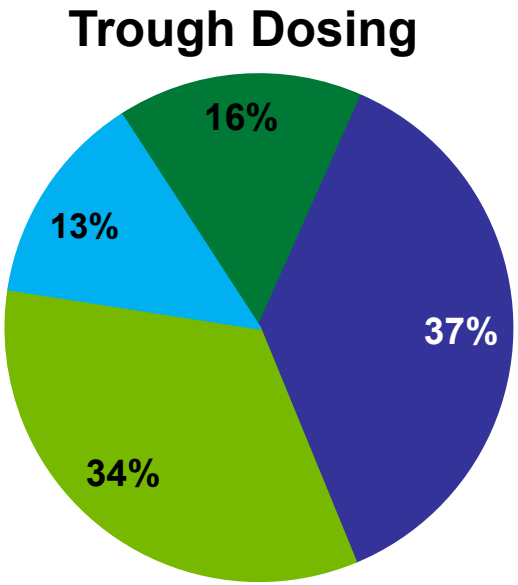
Concomitant Nephrotoxins





None
One
Two
Three or more

	AUC/MIC (n = 101)	Trough (n = 202)
Piperacillin/tazobactam	70 (69.3%)	127 (62.9%)
Furosemide	34 (33.7%)	66 (32.7%)
Lisinopril	12 (11.9%)	35 (17.3%)

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Conclusions

- There was no difference in AKI between the AUC-guided and trough-based dosing groups
  - All of the patients with AKI received at least one concomitant nephrotoxin
  - Combination of vancomycin and piperacillin/tazobactam can increase risk of AKI compared with other broad-spectrum regimens
- Clinically and statistically significant difference in average total daily dose of vancomycin
  - AUC/MIC patients received on average 650 mg less than trough patients
  - Potential cost savings
- No significant difference in LOS or ICU LOS
  - Overall low enrollment of ICU patients

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Mullins BP et al. 2018.

Limitations

- Single center, small sample size
- Limited enrollment with only project pharmacist(s) able to enroll patients in the AUC/MIC dosing group
- Retrospective data review (for the trough dosing patients)
- High rate of vancomycin discontinuation before concentrations could be obtained
- Low enrollment of ICU patients and patients with poor renal function

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Future Directions

- Expanded enrollment
  - ICU patients
  - Patients with poor renal function
- Explore other AUC dosing calculators

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Concomitant Nephrotoxins

- Acyclovir, ganciclovir, valacyclovir, valganciclovir
- Amphotericin B (liposomal and conventional)
- Amikacin, gentamicin, tobramycin
- Captopril, enalapril, enalaprilat, lisinopril
- Carboplatin, cisplatin
- Cefotaxime, ceftazidime, cefuroxime
- Cidofovir, foscarnet
- Colistimethate
- Cyclosporine, methotrexate, sulfasalazine
- Dapsone
- Furosemide, torsemide, bumetanide
- Gadopentetate dimeglumine, gadoextate disodium, iodixanol, iopamidol, ioversol, iohexol, gadobutrol
- Ibuprofen, ketorolac
- Ifosfamide
- Lithium
- Mesalamine
- Nafcillin, piperacillin/tazobactam
- Sirolimus, tacrolimus
- Topiramate
- Zonisamide

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Goldstein SL et al. 2016.