Comparison of initial vancomycin costs between trough- and area under the time-concentration curve-guided dosing

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Abstract

Background: Vancomycin is the drug-of-choice for treatment of most invasive infections due to methicillin-resistant *Staphylococcus aureus* (MRSA). Though trough-guided vancomycin dosing is the current standard, dosing based on area under the 24-hour concentration-time curve (AUC_{24}) to minimum inhibitory concentration (MIC) ratio best predicts clinical efficacy while often reducing trough concentrations associated with increased risk of nephrotoxicity. However, several barriers exist in widespread adoption of AUC_{24}-guided dosing, including the potential impact of drug costs. The purpose of our study was to determine the relative cost of vancomycin therapy when initial dosing is guided by AUC_{24} compared to current practices. We also sought to describe the current dosing practice relative to attainment of targeted vancomycin exposures.

Methods: A retrospective, single-center study was performed on adults hospitalized at Duke University Hospital (DUH) in calendar year 2017 with suspected or confirmed invasive MRSA infection and stable renal function. For the primary outcome measure, a cost-minimization analysis was performed on 200 randomly-selected patients utilizing DUH wholesale vancomycin acquisition cost within the first 48 hours of therapy determined from actual (trough-, control) and AUC_{24}-guided dosing utilizing a Bayesian computer model. Secondary analyses described dosing practices and attainment of goal trough or AUC vancomycin exposures.

Results: In the 200 enrolled subjects, the median cost ($IQR_{25,75}$) difference between AUC_{24}- and trough-guided (reference) was $0.00 (-15.02, 15.02). Serum vancomycin troughs were timed and labeled correctly in only 54% of samples, while 20.7% exceeded two hours of the next scheduled dose. Mean loading doses among trough- and AUC_{24}-guided cohorts were 21.0 mg/kg and 24.8 mg/kg, respectively. Initial dosing was predicted to achieve an AUC_{24} within 400-600 mg*hr/L in 66.5% and 100%, respectively. Initial measured serum vancomycin troughs of 15-20 mcg/mL were observed in only 22% of subjects. Predicted troughs ≥ 15 mg/dL (a known risk factor for nephrotoxicity) would be avoided in 27.1% of patients if executed by AUC_{24}-guided dosing.

Conclusion: Vancomycin acquisition cost was comparable between dosing methods. Opportunities identified include dosing and monitoring modifications to improve target attainment.

Introduction

- Trough-guided vancomycin dosing continues to be common practice despite the potential for improved efficacy and safety of AUC_{24}-guided dosing.[1-4]
- Several logistic barriers exist to widespread implementation of AUC_{24}-guided dosing, including cost.

Objectives

Primary

- To compare the initial (48hr) acquisition cost of vancomycin using either trough- or AUC_{24}-guided dosing in hospitalized patients with suspected or confirmed invasive MRSA infection and stable renal function

Secondary

- To describe the number of measured or calculated steady-state serum vancomycin trough concentrations ≥ 15 mg/L between dosing cohorts
- To describe the practice of trough-guided dosing at DUH in terms of the following: loading doses; timing, labeling and attainment of targeted steady-state serum concentrations

Methods

- Study design: retrospective, single center, parallel design

Inclusion	Exclusion

• ≥ 18 years of age admitted to DUH 1/1/17 to 12/31/17
• Total body weight < 110 kg
• Inpatient initiation and receipt of IV vancomycin for suspected or confirmed invasive MRSA for ≥ 96 hours
• Absence of unstable renal function as evidenced by:
  • baseline SCr < 2 mg/dL or CrCl ≥50 mL/min (utilizing modified Cockcroft-Gault equation-see Table 1)
  • change of SCr ≤ 0.3 mg/dL or ≤ 50% from baseline within 24 hrs of vancomycin initiation up to 96 hrs
	• History of any renal replacement therapy or use within 96 hours of vancomycin initiation
	• Incomplete medical records

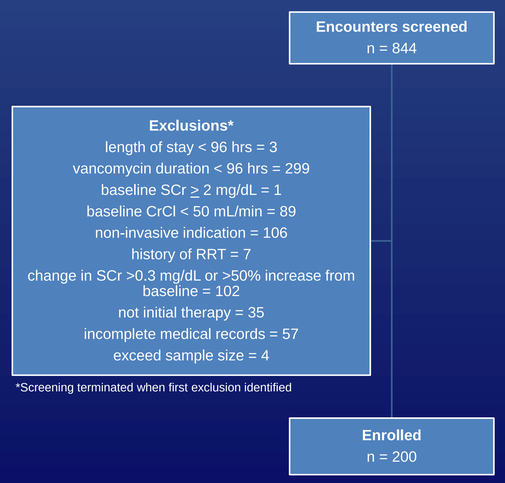
Primary Analysis	Secondary Analyses

• Endpoint
  – DUH acquisition cost of vancomycin within the first 48 hours of therapy
• Analysis
  – Cost-minimization from the hospital perspective inclusive of dosing at hours 00:00 and 48:00
	• Endpoints
	  – Results of calculated or measured steady-state serum vancomycin trough concentrations
	  – Loading doses (mg/kg)
	• Descriptive statistics among dosing cohorts and for endpoints describing dosing practices

- DUH acquisition costs determined for each dosing method
- AUC_{24}-guided initial dosing of vancomycin determined for each patient utilizing BestDose™ (V1.126; University of Southern California):
  - goal AUC $_{24}$ 400-600 mg*hr/L
  - loading doses capped at 3 g; maintenance doses capped at 2 g
  - CrCl estimated utilizing modified Cockcroft-Gault formula (see footnote Table 1)
  - preference to regimens with least frequent administration

Results

Figure 1. Patient Screening and Enrollment*



*Screening terminated when first exclusion identified

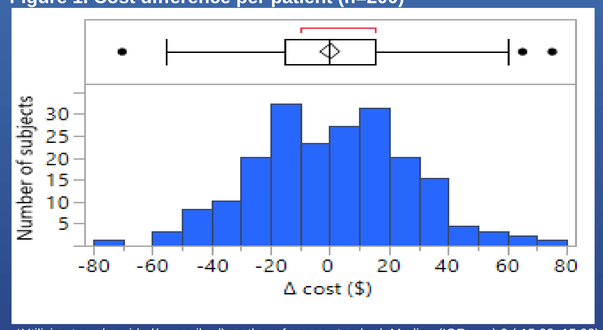
Results

Table 1. Patient demographics and clinical characteristics (n=200)

Age at arrival, yrs, median (range)	57 (18-87)
Gender, male, n (%)	124 (62)
Race, n (%)	
Caucasian/white	140 (70)
African American/black	50 (25)
Other	10 (5)
Baseline CrCl, mL/min, median (IQR)*	90.6 (67.3-121.4)
Vancomycin indication, n (%)	
Bacteremia	23 (11.5)
Bone and Joint	32 (16.0)
CNS	13 (6.5)
Endocarditis	2 (1.0)
Intra-abdominal	9 (4.5)
Pneumonia	63 (31.5)
Sepsis	29 (14.5)
Skin and Skin Structure	29 (14.5)
Serum concentrations/pt thru 96 hrs, n (%)	
0	16 (8)
1	148 (74)
2	32 (16)
3	4 (2)

Serum creatinine (SCr), creatinine clearance (CrCl), interquartile range (IQR)
* CrCl estimated utilizing modified Cockcroft-Gault formula (removing weight and 72 from numerator and denominator, respectively). Patients >70 years old, a SCr below 1 mg/dL rounded to 1 mg/dL

Figure 1. Cost difference per patient (n=200)*



*Utilizing trough-guided(prescribed) as the reference standard. Median ($IQR_{25,75}$) 0 (-15.02, 15.02)

Table 2. Initial dosing according to method (n=200)

	Trough-guided Dosing (Prescribed)	AUC_{24}-guided Dosing (Simulated)
Loading dose, mg/kg, mean (SD)	21.0 (3.2)	24.8 (1.0)
Dosing regimens within 96hrs, n (%)		
1	36 (18)	n/a
2	146 (73)	n/a
3	16 (8)	n/a
4	2 (1)	n/a

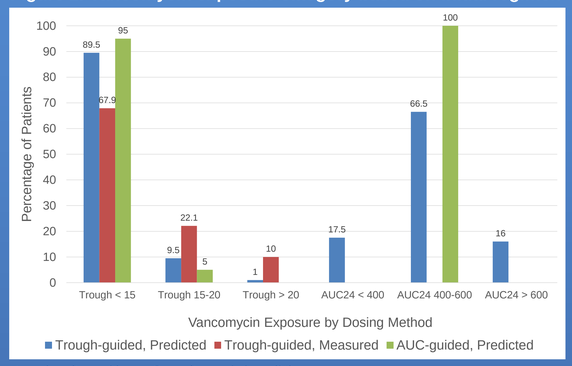
Table 3. Timing of serum vancomycin troughs by results category*

Vancomycin Concentration, Actual	Result Label*	
	Random (n = 11)	Trough (n = 213)
Spot, n (%)	11 (100)	44 (20.7)
Trough (true), n (%)	-	115 (54.0)
Trough (adjusted), n (%)†	-	54 (25.4)

*As described on laboratory results
† >1 and < 2 hours of next scheduled dose

Results

Figure 2. Vancomycin exposure category based on initial regimen



*trough units mg/dL; AUC_{24} units mg*hr/L; n (%)

Discussion

- Conservative dosing practices in the trough-guided cohort (including suboptimal loading doses in 33%) likely minimized differences in acquisition cost between dosing methods.
- Predicted troughs > 15 mg/dL (a known risk factor for nephrotoxicity) would be avoided in 27.1% of patients if executed by AUC_{24}-guided dosing.
- While AUC_{24}-guided dosing will require 2 samples (obtained in only 18% of trough-guided cohort within 96 hrs), this will likely improve timely patient-specific pharmacokinetic modeling and likely reduce the number of regimen changes.

Limitations

- AUC_{24}-guided dosing limited by retrospective data and dependent upon creatinine clearance estimation
- Cost minimization analysis limited to drug cost only and assumes equivalent efficacy

Conclusions

- Compared to trough-guided dosing, Bayesian AUC_{24}-guided vancomycin dosing was associated with comparable median costs of therapy while potentially improving the attainment of targeted AUC_{24} exposures.
- Lab reports describing trough vancomycin concentrations were accurate in only 54% of samples.
- Initial (measured) attainment of target concentrations utilizing trough-guided dosing occurred in only 22.1% of patients, likely due to suboptimal loading doses in patients with higher drug clearance than many hospitalized patients (as evidenced by normal and/or stable renal function).

References

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Disclosures

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