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Comparison of initial vancomycin costs between trough- and area under the time-concentration curve (AUC_{24})-guided dosing

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Abstract

Background: Vancomycin is the treatment-of-choice for most invasive methicillin-resistant *Staphylococcus aureus* (MRSA) infections. Although serum trough concentration-guided vancomycin dosing is the current standard, dosing based on 24 hour area under the concentration-time curve (AUC_{24}) to minimum inhibitory concentration ratio best predicts efficacy while often reducing trough concentrations associated with increased nephrotoxicity. Data regarding the impact of AUC_{24}-guided dosing on drug costs is sparse. We compared the relative initial acquisition cost of vancomycin when utilizing AUC_{24} - vs trough-guided dosing. We also sought to describe current dosing practices relative to attainment of targeted vancomycin exposures.

Methods: A retrospective, single-center cohort study was performed on 200 randomly-selected hospitalized adults 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 utilizing DUH wholesale vancomycin acquisition cost through 48 hours as determined from prescribed trough- and Bayesian computer-simulated AUC_{24}-guided dosing. Descriptive statistics were utilized to characterize dosing, serum concentration monitoring practices and attainment of goal vancomycin exposures.

Results: In the 200 enrolled subjects, the median ($IQR_{25,75}$) cost difference per patient among trough- and AUC_{24}-guided dosing was $0.00 (-15.02, 15.02). Serum vancomycin troughs were labeled correctly in 54% of samples, while 20.7% exceeded two hours of the next scheduled dose. Mean loading doses were 21.0 mg/kg and 24.8 mg/kg, respectively. Goal steady state troughs were achieved in 22% of subjects. Initial dosing was predicted to achieve an AUC_{24} within 400-600 mg.hr/L in 66.5% and 100%, respectively. Troughs ≥ 15 mg/dL (a known risk factor for nephrotoxicity) were measured in 32.1% of trough-guided dosing regimens while predicted in 5.0% of AUC_{24}-guided dosing regimens.

Conclusion: When compared to trough-, AUC_{24}-guided dosing may lead to improved attainment of vancomycin target exposures, including potential reductions in excessive and incorrectly labeled trough concentrations, without impacting drug acquisition costs.

Background

- 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.

Primary Objective

- 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 Objectives

- 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 initial steady-state trough serum concentrations

Methods

- Retrospective, single center, parallel design
- 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
  - creatinine clearance (CrCl) estimated utilizing modified Cockcroft-Gault formula (see footnote Table 1)
  - preference to regimens with least frequent administration

Inclusion

- ≥18 years of age admitted to DUH 1/1/17 to 12/31/17 (inclusive)
- Total body weight < 110 kg
- Inpatient initiation and receipt of IV vancomycin for suspected or confirmed invasive MRSA for ≥ 96 hours

Exclusion

- Unstable renal function as evidenced by:
  - baseline SCr < 2 mg/dL or CrCl ≥ 50 mL/min
  - 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

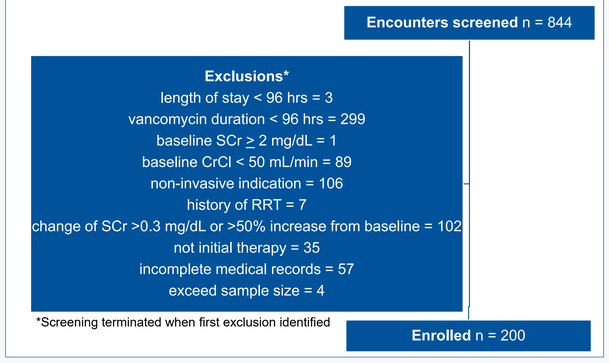
Primary Analysis

- Endpoint: DUH acquisition cost of vancomycin within the first 48 hours of therapy
- Analysis: Cost-minimization from the hospital perspective inclusive of dosing at 00:00 thru 48:00 hrs

Secondary Analyses

- Endpoints
  - calculated or measured steady-state serum vancomycin trough concentrations
  - loading doses (mg/kg)
- Descriptive statistics among dosing cohorts and for endpoints describing dosing practices

Figure 1. Patient screening and enrollment



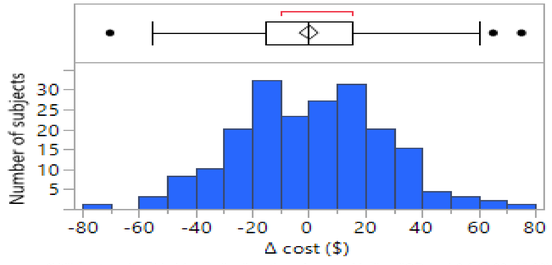
Results

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)
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 2. Cost difference per patient (n=200)*



*Utilizing trough-guided (prescribed) as the reference. 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

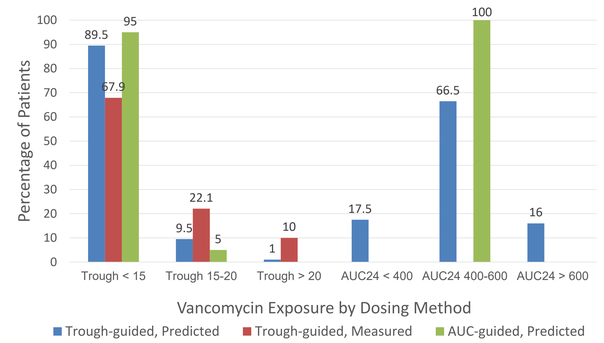
Table 3. Timing of vancomycin troughs by results category*

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 3. Vancomycin exposure category based on initial regimen via Bayesian analysis



*trough units mg/L; 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.
- Measured troughs > 15 mg/L (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

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

1. Rybak MJ, et al. *Clin Infect Dis.* 2009;49(3):325-327. 2. Álvarez R, et al. *Antimicrob Agents Chemother.* 2016;60(5): 2601-2609.. 3. Neely MN, et al. *Antimicrob Agents Chemother.* 2017;62(2): e02042-02017. Pai MP, et al. *Adv Drug Deliv Rev.* 2014;77:50-57.

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