Vancomycin Exposure and Utilization Following Implementation of AUC-guided Monitoring in Children

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Abstract

Background: 2011 IDSA guideline recommended targeting vancomycin (VAN) trough (TR) 15-20 mg/L as a surrogate marker for optimal area-under-concentration time curve, AUC over MIC ratio ≥ 400. Studies suggested attainment of target AUC ≥ 400 with TR 7-11 mg/L in children. In 2018, CHOC implemented VAN monitoring targeting AUC/MIC 400-600 or TR 7-15 mg/L. Our objectives are to evaluate differences in VAN utilization, exposure, nephrotoxicity and cost savings between pre (pre-guideline, pG) and post implementation (post-guideline, PG) of AUC-guided VAN monitoring guideline in children.

Methods: Retrospective review of patients prescribed VAN between Jan 2016 -Jun 2019. Primary objectives evaluated differences in pharmacokinetic (PK), AUC and nephrotoxicity in patients 3 mth to < 18 years.

Results: For the PK analysis, 35 in each pG and PG group were included. Highest daily dose (mg/kg) and AUC attained was significantly higher in pG compared to PG group (74.9 vs. 59.9, p = 0.002 and 647 vs. 469, p < 0.0001), respectively. AUC changes from the initial regimen to the final adjusted regimen was higher in pG group (532 vs. 647, p = 0.0008); there was no difference in PG group (459 vs. 469, p = 0.647). More patients experienced nephrotoxicity in pG compared to PG (11.4% (4/35) vs. 0 (0/35), p = 0.039). Logistic regression analysis identified AUC 800-900 as a significant risk for nephrotoxicity. Net reduction in VAN utilization of 19.7 DOT/1000pd, savings of $100,150 and 738 fewer levels drawn were observed in PG compared to pG.

Conclusion: AUC-guided VAN monitoring in children resulted in less exposure, utilization, and nephrotoxicity. Consistent with recommendations from the 2020 Consensus guideline, a threshold of AUC < 800 mg*h/L and TR < 15 mg/L to minimize risk of nephrotoxicity.

Objectives

Compare differences between **pre-guideline (pG)** and **post-guideline (PG)**

Primary – PK analysis	Secondary – Overall Utilization
• VAN daily dose (TDD) and DOT • VAN daily AUC • Highest TR attained • Rate of nephrotoxicity*	• VAN utilization (DOT/1000 pt days, $ spend) • VAN levels drawn

*Increase serum creatinine ≥1.5x or 0.3 mg/dL from baseline

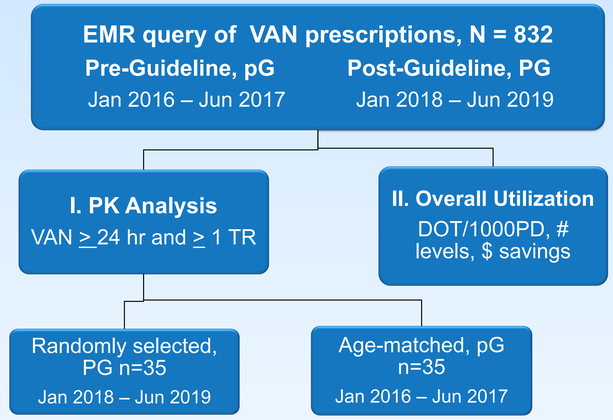
Methods

- Design: retrospective, cohort chart review
- Pre-Guideline (pG): target TR 15-20 mg/L
- Post-Guideline (PG): AUC/MIC 400-600 or TR 7-15 mg/L
- Inclusion: 3 mth – 17 yrs who received VAN
- Exclusion criteria: Patients who received renal replacement therapy (RRT) or ECMO

AUC24 = TDD (mg) / CL_{VAN}

$CL_{VAN} = 0.248*Wt^{0.75} *(0.48/sCr)^{0.361}*(ln(Age)/7.8)^{0.995}$

Figure 1. Study Groups and Data Query



Results

Table 1. Baseline Patients Characteristics – PK Analysis

Demographics Median (IQR)	Pre-Guideline (n=35)	Post Guideline (n=35)	P-value
Age (yr)	9.6 (2.7-13.5)	6.3 (1.6-13.5)	0.712
Weight (kg)	28.8 (11.9-50.5)	21.2 (12.5-39.3)	0.167
Male n (%)	21 (60)	21 (60)	1.000
Concur. nephrotox.*, n (%)	21 (60)	16 (45.7)	0.394
Serum Creatinine	0.4 (0.3 – 0.5)	0.3 (0.2 – 0.4)	0.599
ICU stay, n (%)	7 (20)	12 (34.3)	0.179
Hem/Onc, n (%)	16 (45.7)	15 (42.9)	0.810
VAN Indication, n (%)			
Febrile neutropenia	13 (37.1)	10 (28.6)	
Pneumonia	5 (14.3)	7 (20)	
CLABSI	9 (25.7)	6 (17.1)	
Sepsis unknown source	4 (11.4)	3 (8.6)	
CNS	3 (8.6)	6 (17.1)	
SSTI	2 (5.7)	2 (5.7)	

*Aminoglycosides, NSAIDs, contrasts, vasopressors, acyclovir, loop diuretics, amphotericin B, pip/tazo or methotrexate

Results

Table 2. Vancomycin Exposure and Nephrotoxicity

Variable, median (IQR)	pG (n=35)	PG (n=35)	CI (95%)	P-value
DOT, days	2 (2, 4)	3 (2, 4)	-1.8 - 0.5	0.243
Mean starting dose, mg/kg/day	65.5	58.3	0.5 - 13.8	0.343
Highest TDD, mg/kg/day	74.9 (35-122)	59.9 (30-100)	5.9 - 24	**0.001**
Highest AUC, mg*h/L	647 (364-1016)	469 (269-669)	114.4 - 241.4	**<0.001**
Highest TR, mg/L	13 (7-28)	11 (5-27)	-0.3 - 4.5	0.084
# levels drawn	1 (1, 2)	1 (1, 2)	-0.4 - 0.4	0.883
Nephrotoxicity n, (%)	4 (11.4)	0	0.01 - 0.2	**0.039**

Table 3. Initial vs. Final Dose Adjusted AUC

Group	Initial AUC (mg*h/L)	Final Adj. AUC (mg*h/L)	*p*-value	95% CI
Pre-Guideline	532	647	<0.001	**(-179.9, -49.2)**
Post-Guideline	459	469	0.646	(-55.6, 34.8)

Figure 2. AUC and Nephrotoxicity

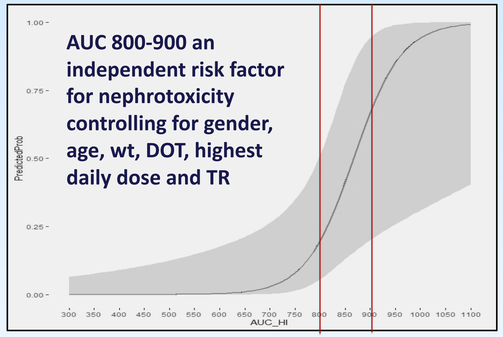
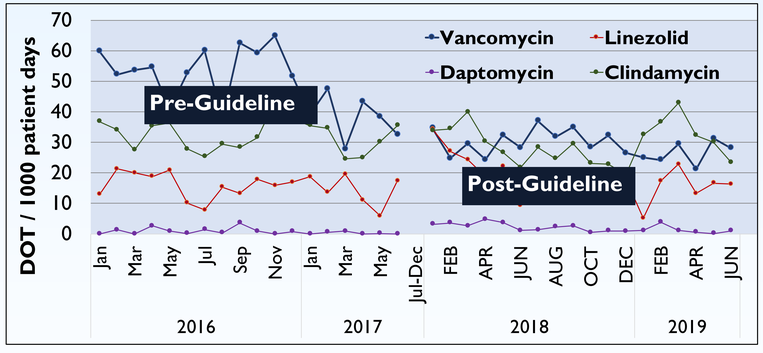


Figure 3. Utilization Trends of anti-MRSA agents



VAN Utilization post-Implementation of AUC-guided TDM

- ↓ 81% VAN purchased resulting in $100,150 net savings
- ↓ 59.2% TR drawn (1,247 to 509)
- ↓ 40.4% in VAN utilization (48.8 to 29.1 DOT/1000pt days)

Summary / Conclusions

- AUC-guided VAN monitoring in children resulted in:
  - Less VAN exposure (469 vs. 647 mg*h/L)
  - Lower nephrotoxicity (0 vs. 4 (11.4%))
  - Less utilization and fewer levels drawn
  - Net savings $100,150 in VAN purchased
- Logistic regression identified AUC 800-900 mg*h/L an independent risk factor for nephrotoxicity

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