# Area under the curve-guided vancomycin monitoring and risk of nephrotoxicity in non-*Staphylococcus aureus* infections: A case-control study

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## Background

- Vancomycin is the most frequently used (25%) antibiotic for Gram-positive infections among hospitalized patients, particularly those caused by methicillin-resistant *Staphylococcus aureus* (MRSA)[1-2]
- Nephrotoxicity is a significant concern, with vancomycin-induced kidney injury (VIKI) rates ranging from 5-43%[3]
- Guidelines recommend AUC targets of 400-600 mg*hr/L for MRSA infections using two post-dose levels or Bayesian software[4]
- Little evidence available to support the benefit of AUC-based vancomycin monitoring in other Gram-positive (non-*Staphylococcus aureus*) infections

## Purpose

- Describe clinical risk factors (RFs) for nephrotoxicity among patients receiving area under the curve (AUC)-guided vancomycin for non-*Staphylococcus aureus* (non-SA) infections
- Evaluate the relationship between specific AUC targets and risk of nephrotoxicity in non-SA infections, which currently does not have well-established therapeutic guidance

## Methods

**Design:** Retrospective, single-center, case-control study evaluating RFs associated with VIKI in hospitalized patients receiving AUC-guided vancomycin for non-SA infections from February 2019 to October 2021 at Northwestern Memorial Hospital (NMH).

**Cases:**
- Found **with** AKI within 24 hours of vancomycin discontinuation

**Controls:**
- **No AKI** within 24 hours of vancomycin discontinuation

## Methods Continued

| | |
|---|---|
| **Inclusion Criteria:** | • Patients ≥18 years with serious infection caused by non-SA pathogen<br>• Received ≥72hrs of vancomycin<br>• ≥1 documented concentration & corresponding AUC(mg*hr/L) |
| **Exclusion Criteria:** | • Patients without available culture information or no identified pathogen<br>• AKI within 24 hours of vancomycin initiation<br>• Renal dysfunction requiring renal replacement therapy within 24 hours of vancomycin |

**Analysis:**
- Univariate & multivariable analysis of pre- & post-hospitalization RFs w/VIKI:
  - **Pre**: age, gender, weight ≥101.4 kg, baseline SCr, diabetes
  - **Post**: CrCl <86.6 mL/min, peak SCr on vancomycin, ICU admission, length of stay, mAPACHE-II score, AUC >515 mg*hr/L within 24 hrs of vancomycin discontinuation, daily dose of vancomycin ≥4 g, receipt of other nephrotoxins
- Optimal data analysis (ODA) and R Core Team (2020) were used to identify RFs associated with AKI

**Primary Outcome**: assess the distribution of RFs associated with nephrotoxicity in patients receiving vancomycin for non-SA infections

**Secondary Outcomes**:
- Median AUC threshold associated with AKI in patients with non-SA infections
- Mortality and treatment failure defined as worsening infection

## Results

- Leading indications: bloodstream (52.1%) and severe skin/skin structure (46.5%)
- Isolated pathogens from culture: coagulase-negative *Staphylococcus* (49.3%) and *Streptococcus* spp. (43.7%)
- Majority of vancomycin AUCs (52%) were collected within 24-48 hours of initiation
- Most patients (75%) experienced AKI within 72 hrs of vancomycin initiation, with a median time to AKI of 5 days (IQR 2.5-7)

| Risk Factors | Case (n=23) | Control (n=48) | P-value |
|---|---|---|---|
| **Pre-hospitalization** | | | |
| Body weight ≥101.4 kg, n (%) | 3 (13) | 9 (18.8) | 0.548 |
| Diabetes, n (%) | 8 (34.8) | 14 (29.2) | 0.632 |
| Baseline SCr, mg/dL, median (IQR) | 0.7 (0.6-0.8) | 0.7 (0.5-0.8) | 0.672 |
| **Post-hospitalization** | | | |
| Calculated CrCl ≤86.6 mL/min, n (%) | 3 (13.0) | 8 (16.7) | 0.693 |
| Vanc ≥4 grams/day, n (%) | 0 (0) | 3 (6.3) | -- |
| **AUC >515 mg*hr/L, n (%)** | **14 (60.9)** | **14 (29.2)** | **0.011** |
| Modified APACHE II Score, median (IQR) | 8 (6-12.5) | 7 (4-10) | 0.202 |
| ICU admission, n (%) | 7 (30.4) | 6 (12.5) | 0.067 |
| Days from admit to infxn, median (IQR) | 1 (1-2) | 1 (1-2) | 0.320 |
| Receipt of ≥1 nephrotoxin, n (%) | 22 (95.7) | 43 (89.6) | 0.390 |

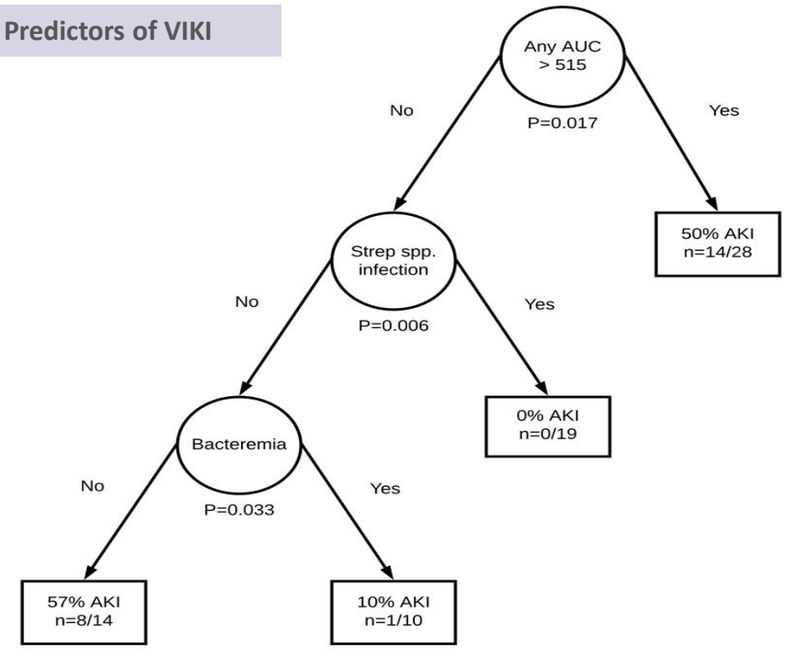
## Results Continued

| AKI Analysis | Case (n=23) | Control (n=48) | P-value |
|---|---|---|---|
| 1st AUC^, median (IQR) | 429 (365-581) | 385 (329-454.5) | 0.0019 |
| 2nd AUC^, median (IQR) | 573 (423-780) | 429 (382-485) | 0.0001 |

^mg*hr/L

| Secondary Outcomes, n (%) | Case (n=23) | Control (n=48) | P-value |
|---|---|---|---|
| Mortality | 6 (26) | 2 (4.2) | -- |
| Hemodynamic Instability | 5 (21.7) | 2 (4.2) | -- |

**Predictors of VIKI**




## Conclusions

- Higher AUCs increased the risk of VIKI in non-SA infections. The risk of VIKI varied by vancomycin indication. This supports previous studies in SA that demonstrates optimal vancomycin AUC should not exceed 515 mg*hr/L.
- The results can help inform modifiable patient-specific RFs and predict AUC thresholds associated with AKI, promote early de-escalation of vancomycin, and consider less aggressive vancomycin doses in non-SA infections.

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