Utilizing PDSA cycles for Implementation of Vancomycin Area Under the Curve (AUC) Dosing in a Hospital Setting

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**Introduction and Objectives:**

Current practice is to dose Vancomycin according to trough levels. However, area under the curve (AUC) dosing of Vancomycin is preferred as it is associated with reduced nephrotoxicity with equivalent effectiveness. This preference is reflected in the upcoming IDSA guidelines. Given perceived benefits of AUC dosing over trough dosing, the aim of this project is to test the utility of an AUC calculator at Trillium Health Partners (THP).

**Method:**

Retrospective vancomycin dosing charts were analysed using DoseMeRX Bayesian kinetics software to determine the proportion of patients that were meeting AUC 400-600 targets with current trough dosing.

Based on the results of retrospective analysis a quality improvement initiative using the Plan-Do-Study-Act (PDSA) cycle methodology was used. In PDSA Cycle 1 and 2 AUC dosing was attempted in the ICU and non-ICU hospital population respectively to identify situations in which AUC dosing would be useful.

**Results:**

Of the patients retrospectively assessed 24/47(51%) had therapeutic AUC, 9/47(19%) had subtherapeutic AUC and 14/47(30%) had supratherapeutic AUC. Of the individuals with therapeutic AUC 15/24(63%) had a trough that would have required a dose increase inappropriately and of those with supratherapeutic AUC 50% (7/14) had a trough of 15-20mg/L.

During implementation of the AUC dosing program a total of 0/9 ICU patients and 5/12 general population patients were successfully enrolled during the study period. Of the 5 patients successfully enrolled in the general population, 4 received the same dose with trough and AUC dosing with no benefit. One patient with a subtherapeutic trough (5.8 mg/L) was determined to be therapeutic based on AUC (>400 mgH/L). Review of the patient determined he was in danger of receiving a nephrotoxic dose of Vancomycin if dosed based on trough levels. Patients that received AUC dosing required 1.7 fold more blood levels than patients dosed by trough levels.

**Conclusion:**

Implementation of AUC dosing in patients with subtherapeutic troughs has the potential of sparing some patients from an inappropriate increase in vancomycin dose at the expense of increased blood draws.
**Background information:**

Gram positive infections have been a consistent concern in community and hospital settings due to the opportunistic infections they can cause. Although they often exist as commensal colonizers of human skin and mucosal membranes, during episodes where the immune system is suppressed or homeostasis is perturbed, many of these organisms can become highly pathogenic. Of greatest concern in gram positive bacteria are *Staphylococcus* spp, *Enterococcus* spp, *Streptococcus* spp and *Clostridium difficile*. Of these *Staphylococcus aureus* and *Enterococcus faecium* represent the largest reservoir of gram positive infections that require IV vancomycin. However, other infections may require vancomycin treatment as well due to patient penicillin allergies (1).

Vancomycin is a glycopeptide that targets the cell wall similar to penicillin’s and cephalosporins but binds the D-ala resides in the peptide side chain of peptidoglycan rather than the transpeptidase directly. Preventing transpeptidation during peptidoglycan synthesis prevents peptidoglycan cross linking which in conjunction with bacterial hydrolases causes de-stabilization of the cell wall and lysis of the bacteria due to osmotic forces (2). Vancomycin has traditionally been thought of as having time dependant killing, however, this has not been reflected in laboratory or clinical evidence. Outcome analysis in neutropenic mice as well as human populations has shown that an Area Under the Curve (AUC) over Minimum Inhibitory Concentration (MIC) or AUC/MIC >400 is important for improved infection outcomes (1,3). Despite AUC being the best predictor of outcomes in infected individuals, the use of trough-based dosing has been adopted instead. This is based on the ease of using a single level to guide therapy and because levels were thought to correlate well with AUC measurements.

What are ideal Vancomycin AUC targets during bacterial infections?

Vancomycin area under the curve (AUC) is the relationship of vancomycin concentration over time. Multiple studies of lab and clinical data suggesting an AUC/MIC >400 as being the best pharmacokinetic measure for vancomycin effectiveness, however, these studies were mostly validated in Methicillin Resistant *Staphylococcus aureus* (MRSA) bacteremia and pneumonia (4,5,6,7). The target AUC in other conditions have not been well described and is an area of study requiring urgent further study.

A major source of variability in target AUC studies comes from heterogeneity in how MIC is calculated. MIC’s are usually obtained using broth dilution, E-test strips, or automatic methods which each come with caveats in interpretation. E-test strips have a tendency to over estimate MIC whereas automatic methods have a tendency to underestimate MIC with can lead to a 2 fold difference in MIC’s depending
on test type (8). This 2 fold variability can cause studies to have AUC/MIC to be different by a factor of two depending on the method of calculating MIC. This has made interpretation of vancomycin AUC data difficult despite broth microdilution method generally being considered the gold standard for MIC testing. Variability in testing is reflected in upcoming draft guidelines which have decided to abandon AUC/MIC targets for AUC only targets for vancomycin.

There has also been discussion about target AUC depending on the type/location of infection. Theoretically, attainment of target vancomycin AUC in the CNS and bone during meningitis or osteomyelitis should be more difficult due to diffusion limitations between these organs and the serum. AUC targets in these organs should possibly be higher as a result. Target vancomycin AUC in meningitis has not been investigated, however, one study of individuals with MRSA bacteremia and osteomyelitis found that time to bacterial clearance was 2 days faster if an AUC/MIC was >291 using E-test strips to determine MIC. Given E-test strips tendency to overestimate MIC the real target AUC/MIC is likely closer to 600 (9). Another study assessing patients with MRSA endocarditis found that AUC/MIC (using broth microdilution) > 600 was associated with less combined persistent bacteremia and mortality suggesting higher AUC might be needed in individuals with MRSA endocarditis.

Difficulty arises when interpreting best vancomycin AUC target in individuals with non-MRSA infections. One study has found that a target AUC/MIC of >381 (MIC determined with Etest) was associated with better mortality in individuals with Enterococcus faecium bacteremia (10). However, a further retrospective study assessing mortality due to E. faecium with vancomycin AUC less than or greater than 381 did not find a significant difference (Number of individuals with AUC <381 was 25.0% vs 15.2% in patients with 30 day mortality vs survivors respectively). However, the study was under powered to find significant differences in mortality and was complicated by AUC/MIC being calculated by automatic microdilution method (11). It is possible that based on these studies of E. faecium the target AUC may be significantly greater than 400 which in opposition to dosing at THP which has a target of 10-15mg/L in certain circumstances.

Dosing in critically ill patients is also complicated by observations that a higher target trough and AUC in septic patients is needed than what would be expected in non-critically ill patients. While an AUC>400 has been associated with good outcomes in most heterogeneous populations, Zelenitsky et al found that the probability of survival in MRSA infected septic patients was 53% in patients with AUC 451-577 and 82% in those with AUC>577 (12). This was corroborated by an additional study that found that the ideal AUC/MIC ratio for treatment success was >587 (13). The use of trough based dosing becomes
problematic since the trough of 15-20mg/L which is currently used and does not predict an AUC of >570. Based on these studies, there is potential to under dose vancomycin in critically ill patients with sepsis or bacteremia.

**Relationship of vancomycin AUC and trough level**

Multiple simulations have found that having a trough level of >15 mg/L is associated with a 95-100% chance of achieving an AUC >400 and would be acceptable for infections in which vancomycin MIC’s are 1mg/L or less (14,15,16). A major complicating factor of using troughs to control serum concentrations arises due to the poor correlation between AUC and trough levels. One study found that trough levels correlate with AUC with an R² value of 0.4 in a heterogeneous population (15). However, R² in adults, elderly and neonates have also been found to have R² of 0.38, 0.5 and 0.63, respectively (17,18,19). Class III obesity has also been associated with problems reaching target AUC vancomycin targets. A dose modeling study of patients with class III obesity found that obese patients required 3995 mg to reach target trough versus 2783 mg to reach target AUC. This signifies a 40% overdosing of vancomycin in obese patients that could potentially result in nephrotoxicity and poorer outcomes (20). Similar results were identified in an additional modeling study showing overdosing of vancomycin in obese patients (21) No study has been able to demonstrate a way to predict AUC from trough levels and begs the question of why we are using troughs as a surrogate for AUC dosing.

Treating patients in the intensive care unit is also a major challenge due to the variable pharmacokinetic properties they have. Several investigational studies have found that using standard dosing strategies in critically ill patients leads to patients with troughs less than 15 mg/L and AUC <400. For example, the DALI study found that of critically ill patients receiving intermediate dosing, only 50% of them achieved an AUC >400 (median 409, range 246-712) (22). The same study found that the correlation of dose/kg to trough was only R²=0.127 suggesting that it might not be possible to accurately dose vancomycin in ICU patients based on weight which is the standard of practice (22).

**Calculating Vancomycin Area Under the Curve:**

With the proliferation of adoption of AUC dosing of Vancomycin, there has been an increase in heterogeneity in the methods of determining AUC. Patient specific calculation of vancomycin AUC can be done in two ways: Single level Bayesian kinetics and two level vancomycin dosing.

Single level Bayesian kinetics: Bayesian kinetics is a method for calculating AUC based on a statistical platform that compares patient demographic data and a single vancomycin trough level to a database of
historical patients who have received vancomycin. The statistical model aims to match a patient in question to historical patients to match a kinetic model. Although this method can be challenging to learn and requires statistical software which can be expensive to acquire (software available are BestDose and DoseMeRx), it can be a very powerful tool. Bayesian kinetics have an advantage over other AUC calculation methods since only a single vancomycin level is needed, can be used retrospectively, is dynamic, and does not need steady state. Further, most upcoming studies have used Bayesian kinetics to calculate target vancomycin AUC for a variety of conditions which allows direct application of study results to ones institution.

Two Level Vancomycin Dosing: The alternative method of calculating patient specific vancomycin AUC is by using two vancomycin steady state serum levels. The value of this system is that it is easy to do with a validated calculator, is the most patient specific AUC calculation there is, and does not require expensive and difficult to use statistical software. This method is probably best for institutions where vancomycin dosing is not routine enough to warrant paying for statistical software. It, however, does require two blood levels which can cause confusion and extra work from the nursing staff.

Calculation of vancomycin AUC using two levels can be done in three different methods, the Sunnybrook method, the trapezoidal rule, and the linear-log trapezoidal rule. There is no evidence that any method is superior to the other, and in limited testing seem to yield similar AUC results that are likely not clinically different from each other. See Figure 1 for different calculation methods.
Figure 1: Calculation of AUC using 2 level kinetics: A) Representation of vancomycin is distributed over time with representation of where levels are to be taken and important time frames. B) AUC according to Sunnybrook method. C) AUC according to trapezoidal rule. D) AUC according to linear log trapezoidal rule.

C) 1) $K_e = \ln(\text{Level1}/\text{Level2})/\Delta T$
2) $C_{\text{max}} = \text{Level1}/e^{(-K_e \Delta \text{distribution})}$
3) $AUC_{\text{elim}} = (C_{\text{max}} + \text{Level2})/2 \times \Delta T$
4) $AUC_{\text{inf}} = (C_{\text{max}} + \text{Level2})/2 \times T_{\text{infusion}}$
5) $AUC_{\text{total}} = AUC_{\text{elim}} + AUC_{\text{inf}}$

D) 1) $K_e = \ln(\text{Level1}/\text{Level2})/\Delta T$
2) $C_{\text{max}} = \text{Level1}/e^{(-K_e T_{\text{distribution}})}$
3) $AUC_{\text{elim}} = (C_{\text{max}} - C_{\text{min}})/(\ln C_{\text{max}} - \ln C_{\text{min}}) \times \Delta T$
4) $AUC_{\text{inf}} = (C_{\text{max}} + \text{Level2})/2 \times T_{\text{infusion}}$
5) $AUC_{\text{total}} = AUC_{\text{elim}} + AUC_{\text{inf}}$
Evidence of Adoption of AUC Dosing in Clinical Practice

Dosing of vancomycin based on trough level has been the standard of practice at most institutions. Originally trough dosing was considered superior since it was easier to do and the risk of nephrotoxicity was considered minimal. This concept has been challenged as a trough of 10-15mg/L compared to a trough of >15mg/L is associated with a 2.7 fold lower risk in AKI (23).

The practice of trough dosing has been found to potentially be the cause of increased acute kidney injuries in recent studies. Zasowski et al conducted a retrospective study to determine what vancomycin AUC was associated with nephrotoxicity. It was found that an AUC >677 was associated with a nearly 4 fold increase in AKI (24). The practical application of this information was further demonstrated by Finch et al who found in a prospective study comparing trough dosing to AUC dosing resulted in a drop in AKI’s from 8% to 0-2% (ARR=6-8%, NNT=12-16) (25). Similar results were found in the PROVIDE observational trial in which an AUC >700 was associated with an increase in AKI (26). These studies have been the foundation for adoption of AUC dosing of vancomycin in many hospitals due to the high cost burden associated with Vancomycin induced AKI’s.

One ward where AUC may be of benefit is the ICU population since they are at potentially the highest risk of AKI which could be exacerbated by supratherapeutic vancomycin levels. Initial concern with using AUC dosing in critically ill patients was that Bayesian kinetic software packages could not accurately predict AUC from a single trough level in critically ill patients. However, Bayesian programs BestDose, and DoseMeRX have both been found to accurately predict critically ill vancomycin AUC’s opening this population to more AUC dosing (27). No studies have been done in critically ill patients to determine if vancomycin AUC dosing is a benefit and further support is waiting.

A surprising benefit of AUC dosing that has emerged is that it may also increase the ability to hit therapeutic AUC targets. One study found that with trough dosing only 55% of patients met initial therapeutic targets as compared to AUC dosing in which 73.5% met initial therapeutic targets. Additionally, the study found AUC dosing was associated with 10 fold fewer supratherapeutic targets and a trend to lower nephrotoxicity (the study was underpowered to detect nephrotoxicity) (28). Additionally, one study in Quatar also found that AUC dosing was associated with a 76.7% cure rate vs 48.6% in those treated with trough dosing suggesting there may also be treatment benefits associated with AUC dosing (study underpowered to detect mortality or AKI differences) (29).
The literature and upcoming draft guidelines for vancomycin dosing from the USDA both suggest that AUC dosing of vancomycin has superior safety endpoints as compared to trough dosing due to the reduced burden of nephrotoxicity. However, not many patients at THP require vancomycin and implementation of AUC dosing will require pharmacist teaching and infrastructure. A quality improvement initiative to explore implementation of a dosing strategy would be beneficial.

**General strategy:** Our Quality Improvement strategy will be to determine the feasibility of adopting vancomycin AUC dosing in THP.

**Aim Statement:** In 4 months we will be to validate the usefulness of a vancomycin AUC calculator in the inpatient population at THP.

**Methods:**

**Retrospective Analysis of Patient charts for Vancomycin AUC:**

Assessment of previous AUC target attainment at THP was a retrospective observational single site study at Trillium Health Partners (THP). To assess how THP was historically meeting AUC targets of 400-600 using a previous trough dosing nomogram Vancomycin dosing sheets submitted to the antimicrobial stewardship program were assessed. Vancomycin dosing sheets contain patient information that can be used to calculate patient AUC.

Vancomycin sheets were collected from patients who received pharmacist vancomycin dosing between September 2017 and September 2018. Inclusion criteria for patients in the analysis required at least 4 doses of vancomycin, have at least one steady state vancomycin trough level recorded, and have complete legible information on the dosing sheet.

Calculation of patient vancomycin AUC was done using Bayesian kinetics and the program BESTDOSERX (Available at https://doseme-rx.com/). Patient height, weight, age, SrCr, vancomycin dose, timing and number of doses given as well as first trough level were programed into the calculator. Predicted AUC at first steady state trough level were predicted using the program.

**Quality Improvement of Vancomycin AUC dosing at THP:**

**Study Design:**

To determine the likely success of implementation of AUC dosing at THP a quality improvement initiative using a prospective PDSA (Plan-Do-Study-Act) cycle format during the period of Feb 2019 to June 2019. To determine success outcome, balancing and process measures were assessed (see below). If the outcome, process and balancing measures are found to show areas for improvement or
infeasibility then a new PDSA cycle will be implemented with a new plan to improve the outcome, process and balancing measures.

**Dosing Protocol:**

For eligible patients, initial dose of vancomycin is being given as per the weight-based Trillium Vancomycin Nomogram (Appendix 1). Due to lack of access of Bayesian kinetics software for the entire program duration implementation the two level Sunnybrook method was used to calculate AUC. Following the third dose, one vancomycin level is collected 1h post infusion, and a second level was collected 30-60 min pre fourth dose. Once the levels have been collected, the Kel and Vd are calculated and the vancomycin AUC was calculated using the Sunnybrook method (Figure 1B). An AUC of 570-700 was targeted in ICU patients with an indication of sepsis due to data suggesting an AUC >570 has a mortality benefit in ICU septic patients. In other non-septic patients an AUC 400-600 was targeted. All calculations were done with an AUC calculator. If the target AUC 400-600 or 570 to 700 is reached based on initial vancomycin dose, the order will be unaltered. If the target was not met, it was adjusted based on ratio and proportion to meet the target AUC. If the dose was changed based on initial AUC then an additional AUC was calculated using an additional 2 blood levels as above after an additional 4 doses of vancomycin at the new dose (new steady state).

**Study Population:**

Inclusion criteria was all inpatients older than 18 years old admitted to Mississauga Site Trillium Health Partners. Patients must be indicated to be undergoing vancomycin monitoring and indicated to have a trough of 15-20 mg/L and receive at least 4 doses of vancomycin.

Exclusion criteria will be all individuals in which vancomycin is discontinued before third dose. In patients in which the dose of vancomycin required is larger than 4g/d or if the predicted Cmax is >40mg/L using the AUC calculator, then the patient will be excluded and conventional dosing will be used to avoid the potential of nephrotoxicity and nomogram dosing was used instead.

**Study Endpoints:**

*Outcome measure:*

1) Proportion of patients which receive a different dose of vancomycin using AUC dosing as compared to if they would have been dosed by trough

*Process measure:*
2) What proportion of patients meet inclusion criteria for AUC dosing vs. the trough based dosing

**Balancing measure:**

3) Compared to trough dosing, is there an increase in vancomycin levels (blood draws) taken with AUC dosing compared to trough dosing.

**Statistical Analysis**

The balancing measures will be analyzed by independent t-test compared to historical data collected between Sept 2017-Sept 2018.

**Results:**

**Retrospective analysis of patient charts:**

Guidelines suggest that a target AUC for vancomycin 400-600 should be implemented for all individuals with a target trough of 15-20mg/L. However, vancomycin dosing at THP is done using a trough targeting dosing nomogram and it is possible that AUC targets are still being met with this system. To determine how often patients were receiving a subtherapeutic, therapeutic or supratherapeutic vancomycin AUC with current trough dosing, Vancomycin dosing sheets from September 2017-2018 were analysed using DoseMeRX Bayesian AUC prediction software. Of the dosing sheets assessed, 47 met inclusion criteria. Of the patients that met inclusion criteria 51% (24/47) had therapeutic AUC, 19% (9/47) had subtherapeutic AUC and 30% (14/47) had supratherapeutic AUC based on first steady state trough measure (Figure 2).

It is possible that a patient’s AUC may be therapeutic (>400) despite a trough being <15mg/L. Additionally, a supratherapeutic AUC (>600) is possible despite a trough of 15-20mg/L. Both situations represent scenarios where incorrect doses can be given based on trough level only. Of the patients with therapeutic AUC, 63% (15/24) had a trough level <15mg/L and would possibly have had a dose increase inappropriately. Of the patients with supratherapeutic AUC, 50% (7/14) had a trough of 15-20mg/L and represent individuals who would have their vancomycin dose left the same inappropriately when they were supratherapeutic. Of the 47 total patients assessed, 47% (15/47) patients were dosed incorrectly based on trough levels and would have been potentially exposed to nephrotoxic levels of vancomycin as a result. No patients with a trough less than 15mg/L had an AUC >600 suggesting the likelihood of a nephrotoxic dose of vancomycin when a trough targeted is 10-15mg/L is unlikely.
**Figure 2:** Relationship of vancomycin trough level and vancomycin AUC in THP inpatients as calculated with Bayesian Kinetics
Quality Improvement Initiative: Implementation of AUC dosing at THP:

PDSA Cycle 1: Implementation in intensive care unit:

Preliminary analysis of patients receiving Vancomycin suggested that the existing protocol for vancomycin dosing was not meeting suggested AUC targets. Patients in the ICU have a higher incidence of acute kidney injuries which may be increased with supratherapeutic vancomycin AUC’s. Our hypothesis was that we could implement AUC dosing in ICU patients to reduce nephrotoxicity.

AUC dosing was implemented in the ICU over a period of 7 days in which a total of 9 patients were attempted to be enrolled. Of the 9 patients identified, the AUC calculator was used in 0 of 9 patients. Of these, 5 had CrCl <30ml/min or rapidly fluctuating CrCl, 3 had trough targets of 10-15mg/L and did not meet inclusion criteria, and 1 was enrolled too late in therapy to collect levels.

Based on these results we determined that the ICU may not be the most ideal ward to institute AUC dosing. As a result of first PDSA cycle we determined that AUC dosing would be better implemented in non-ICU wards. Additionally, due to issues encountered in patients with impaired renal function we determined that an additional inclusion criteria for the program should be individuals with CrCl >30ml/min and those with stable renal function.

PDSA Cycle 2: Implementation of AUC dosing in non-ICU patients:

We hypothesized that in the non-ICU population there is a population of patients that would benefit from AUC dosing. To determine if AUC dosing was feasible in non-ICU patients the AUC calculator was implemented in non-ICU floors over a 4 weeks period from February to March 2019. During this time a total of 22 patients were attempted to be enrolled. Of the 22 patients identified, 5 patients were successfully dosed using the AUC calculator.

Of the 5 patients who were dosed based on vancomycin AUC, only patient 1 received a dose of vancomycin that was different then what they would have received using trough based dosing (Figure 3). Based on trough based dosing they are projected to have needed a dose of 6g/day vancomycin to have a trough of >15mg/L. However, using AUC dosing they only required 2.5g/day. Assessment of their kinetics showed that if they had received a full 6g/day of vancomycin they would have had an AUC of 1080 which would have been potentially nephrotoxic. This individual was 25 years old and had CrCl of 143ml/min reflecting that the reason they had a low trough level of 5.8mg/L was due to their excellent renal function. Patients that did not benefit from AUC dosing were >65 years old and had reduced renal
function in 3 of 4 patients (Table 1). As a result of this PDSA cycle it was concluded that vancomycin AUC dosing may be useful in individuals that are young and have excellent renal function.

During implementation of AUC dosing, it was found that AUC dosing seemed to require more blood draws than trough dosing. Patients dosed by AUC required 0.622 (n=5) blood draws per day. In comparison, retrospective analysis of vancomycin dosing sheets found trough dosing required 0.34 (n=47) blood draws per day. This reflects a 1.7-fold (p=0.06) increase in blood draws per day for AUC dosing compared to trough dosing.

Figure 3: Dose of vancomycin given using AUC dosing program vs. dose of vancomycin that was predicted to be given based on trough based dosing

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Table 1: Patient Demographic Data of patients receiving AUC dosing
Discussion:

The adoption of vancomycin AUC dosing using either Bayesian kinetic approaches or two level kinetics has been documented in a litany of recent reports and has been suggested in the upcoming vancomycin dosing draft guidelines. Assessment of retrospective vancomycin dosing charts suggested that at THP there is a significant discrepancy between suggested dose given by AUC dosing vs. trough dosing and AUC dosing might confer benefit to patients receiving vancomycin. To test the utility of an AUC calculator we initiated a PDSA quality improvement initiative at THP. As a result of the study, a possible demographic group of patients were identified in which AUC dosing could be used, however, we found that AUC dosing is likely not useful in all patients and is associated with increased blood draws.

The push to implement AUC dosing for vancomycin has come from studies that showed that AUC dosing can result in a 50% reduction in incidences of acute kidney injuries (30). Further, a study showed that when AUC dosing was instituted in one institution the incidences of new AKI’s decreased from 8% per year to 0-2% per year (25). Guidelines suggest risk of AKI increases with AUC >600 and maintaining an AUC 400-600 is associated with fewer AKI’s and no reduction in effectiveness outcomes (25). In our analysis of retrospective patients we found that using Bayesian kinetics 47% of patients dosed with the THP vancomycin dosing nomogram would have had an inappropriate dose of vancomycin based on their trough level. Of those patients with therapeutic AUC, 63% (15/24) had a trough level <15mg/L and would possibly have had a dose increase inappropriately. Of the patients with supratherapeutic AUC, 50% (7/14) had a trough of 15-20mg/L and represent individuals who would have their vancomycin dose left the same inappropriately when they were supratherapeutic. This discrepancy in dose suggested by AUC vs trough dosing has been documented in the literature. A study from Stoessel et al found of patients with trough <15mg/L, 25% of them had an AUC <400 and required a dose increase (31). Implementation of AUC dosing at Sunnybrook additionally found that of patients with trough <15mg/L in MRSA pneumonia 33% of patients had a therapeutic AUC and did not require a dose increase (Unpublished data, personal correspondence). Our data agrees with these findings.

Most literature has used AUC dosing in individuals with trough <15mg/L that have AUC >400. However, there has less relative attention about individuals with trough 15-20mg/L and AUC >600. Interestingly, of the retrospective patients we assessed with trough 15-20mg/L 50% had an AUC greater than 600 which is greater than guideline recommended levels. The importance of AUC >600 is controversial as most CART analysis found that nephrotoxicity does not start until AUC is greater than 700-800 (24,26,32). An additional study found nephrotoxicity does not occur until AUC is >1300 unless patient is also obese.
Conservative AUC targets need to be weighed against higher AUC targets possibly being beneficial in individuals with MRSA sepsis, endocarditis, or osteomyelitis (9,11). Of patients in our analysis with trough of 15-20mg/L only one had an AUC>800 and at potential risk of nephrotoxicity. Implementing AUC dosing in all individuals with trough target of 15-20mg/L may not identify a meaningful number of patients with nephrotoxic AUC’s and may represent an increase in labor without benefit.

Contrary to the retrospective Bayesian analysis which suggested 47% of patients could benefit from AUC dosing, only 1 of the 5 patients enrolled from our prospective analysis received a different dose of vancomycin with AUC dosing as compared to trough. Assessment of the patient that received a lower dose of vancomycin with AUC dosing vs. trough dosing, the patient was young and had excellent renal function. Likely the patients trough of 5.8mg/L reflects high clearance due to good renal function. The other patients that did not benefit from AUC dosing were older (65-80 years old) and had reduced renal function in 3 of 4 patients (<80ml/h). Caution in using good renal function as a rational for selecting patients to use AUC dosing needs to cautioned against. Patient 3 had good renal function with CrCl of 118ml/min but did not have a subtherapeutic trough (Table 1). Patient 3 was obese (BMI=31.5) and likely had a larger volume of distribution and therefore lower clearance in comparison to patient 1 who was not obese. It is possible that AUC may be most useful in any patients with abnormally low trough levels, especially those that are young and have good renal function. An abnormally low trough level may be an indicator of abnormal vancomycin kinetics.

An issue identified in this study that has not been described in other studies is the fact that AUC dosing requires more blood draws than trough dosing using the two level method we implemented. Although the difference in blood draws between trough and AUC dosing did not reach significance, with only 5 patients it was underpowered to detect such a difference. The increased blood draws became an issue due to confusion with training the nursing staff who did not understand the need for an additional level. Despite attempts to educate the nurses, confusion persisted, especially during change over to night staff. Correspondence with Sunnybrook mentioned that AUC dosing is done enough in their institution that the nursing staff is comfortable with its use. However, at THP the use of vancomycin is rare enough that it may not be useful to train the nursing staff if AUC is only used in 1/5 patients receiving vancomycin. Additionally, the extra blood levels required had awkward timing to get pre and post levels resulted in patients being woken at odd hours for levels. The issue with increased blood levels needed using two level AUC vancomycin dosing has not been mentioned in previous literature and is a drawback of the program that should be assessed during implementation.
Although two level AUC dosing can be useful in a small subset of patients, two of the major issues encountered were the need for increased blood levels as well as the need for stable renal function or ability to establish steady state. Although two blood level AUC dosing requires less infrastructure and training to implement, the above mentioned weaknesses may severely limit its usefulness. Most studies in AUC dosing to date, especially the studies that have found reduced AKI’s were done with Bayesian kinetics. Bayesian kinetics requires only a single blood draw to get an initial AUC (more can be taken to get a better kinetic model) and does not require steady state/stable renal function. Considering the reason most patients did not meet inclusion criteria were due to poor or unstable renal function the applicability of the two level AUC dosing utility needs to be questioned. In 2 of 5 patients that were dosed with AUC dosing (patient 4 and 5), the patients suffered an AKI (CrCl reduced by >26 ml/min) which made dosing significantly more difficult using the two level method. Bayesian kinetics has two additional advantages: first, it is able to accurately predict the dose needed to reach a particular trough on patient demographic data before the first dose is given (Data not shown). There is limited data that attaining target vancomycin levels faster are associated with better outcomes in certain populations. For example, patients with predominantly MRSA infections who received drug monitoring where target vancomycin levels were reached in 3 days vs. 5 days also had shorter hospital stays (7 days vs. 14 days) and reached clinical stability faster (4 days vs 8 days) (34). Second, most upcoming studies assessing target AUC for different indications (sepsis, meningitis, etc) will report target AUC using Bayesian kinetics calculations. Although it is assumed that Bayesian kinetics and two level dosing are analogous to each other there may be an unknown advantage to applying results from Bayesian kinetic studies to ones institution using Bayesian kinetics.

Some commentaries have started to raise caution about the widespread implementation of AUC dosing. Despite studies finding improved AKI outcomes in AUC dosing, these studies found reduction in AKI when other nephrotoxic insults (other nephrotoxic drugs, volume depletion) were controlled for (25,30). Further, AUC dosing is suggested in patients with MRSA infections only, and evidence is only strong for individuals with bacteremia and pneumonia. For other indications the use of AUC dosing is suggested to be left to clinical judgment. AUC dosing may be useful in institutions where the incidences of MRSA or E. faecium are high, but may be of limited value in facilities where vancomycin use is less common or small facilities where patient burden is small. At THP most patients were given vancomycin empirically for 1-2 doses then discontinued. Of patients that stay on vancomycin, most patients were not continued on vancomycin past the first steady state level making adjustments of the dose pointless. Initiating two
level kinetics in these patients will expose them to more blood draws, and the pharmacist to more work, when the patient was only getting vancomycin empirically.

During implementation of AUC dosing using a calculator derived from the Sunnybrook method we did find sporadic success in its implementation. However, given the litany of potential drawbacks in implementation full implementation should be re-evaluated. The best use of the AUC calculator may be best applied under the umbrella of antimicrobial stewardship for patients where significant difficulty reaching trough targets are encountered.

References:


7) Jung Y1, Song KH2, Cho Je1, Kim HS3, Kim NH4, Kim TS5, Choe PG4, Chung JY5, Park WB4, Bang JH4, Kim ES6, Park KU7, Park SW4, Kim HB6, Kim NJ4, Oh MD Area under the concentration-time curve to minimum inhibitory concentration ratio as a predictor of vancomycin treatment


27) Turner RB1,2, Kojiro K2, Shephard EA1, Won R3, Chang E3, Chan D2, Elbarbry F view and Validation of Bayesian Dose-Optimizing Software and Equations for Calculation of the

28) Meng L1, Wong T1, Huang S1, Mui E1, Nguyen V2, Espinosa G3, Desai J1, Holubar M4, Deresinski S Conversion from Vancomycin Trough Concentration-Guided Dosing to Area Under the Curve-Guided Dosing Using Two Sample Measurements in Adults: Implementation at an Academic Medical Center. Pharmacotherapy. 2019 Apr;39(4):433-442.


34) Cardile AP1, Tan C2, Lustik MB3, Stratton AN1, Madar CS1, Elegino J1, Hsue G. Optimization of time to initial vancomycin target trough improves clinical outcomes. Springerplus. 2015 Jul 19;4:364.