VANCOMYCIN DOSING AND THERAPEUTIC DRUG MONITORING – CHW

PRACTICE GUIDELINE ©

DOCUMENT SUMMARY/KEY POINTS

- Vancomycin is an important antibiotic for methicillin-resistant Staphylococcus aureus (MRSA) infections where guidance on optimising therapy and minimising toxicity is required.
- This guideline is not intended for use in preterm neonates or patients admitted to the Grace Centre for Newborn Care (GCNC), where the Australasian Neonatal Medicines Formulary should be used

CHANGE SUMMARY

- Trough targets of 15-20 mg/L are NO longer recommended based on recent efficacy and toxicity studies
- The new trough target is 7 to 15 mg/L with updated dose adjustments
- Target Area Under the Curve (AUC) guided dosing is the preferred method of therapeutic drug monitoring in patients with:
  - MRSA bloodstream infection
  - PICU patients with unstable renal function (delta creatinine of ≥150%)
  - PICU patients on concurrent nephrotoxins
  - Patients with complicated pharmacokinetics driven by the AMS pharmacist
- Updated starting doses in patients with normal renal function
  - 1 month to 18 years of age: 15 mg/kg/dose (maximum of 750 mg/dose) 6 hourly
  - 6 hourly dosing is preferred in children and adolescents
  - These doses will achieve a target AUC ≥400 mg-hr/L in >75%
  - >12 years age dose of 30 mg/kg/dose 12 hourly is NO longer recommended
- The maximum daily dose with therapeutic drug monitoring is 100 mg/kg/DAY or 4.5 g/DAY

Approved by:	SCHN Policy, Procedure and Guideline Committee	
Date Effective:	6th of October 2021	**Review Period**: 3 years
Team Leader:	Antimicrobial Stewardship Pharmacist	**Area/Dept**: Antimicrobial Stewardship Team

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- **5/11/21** – minor review to fix spelling issue. No other changes made.
- **15/11/22**- minor review. Change of target level from 8.5 to 15 mg/L to 7 to 15 mg/L

READ ACKNOWLEDGEMENT

- Medical officers, nursing and pharmacists need to be aware of and understand the contents of this guideline.

TABLE OF CONTENTS

Background

- Vancomycin is a high-risk medicine and necessary glycopeptide antibiotic that is mainly indicated to treat serious infections caused by methicillin-resistant *Staphylococcus aureus* (MRSA).[1, 2]
- These infections range from boils, impetigo, wound infections, and cellulitis to severe infections such as bone and joint infections, pneumonia, endocarditis and bacteraemia.
- Our local and national rates of MRSA are 17-22%, and local modelling (Figure 1) indicates MRSA resistance rates are increasing. [3]

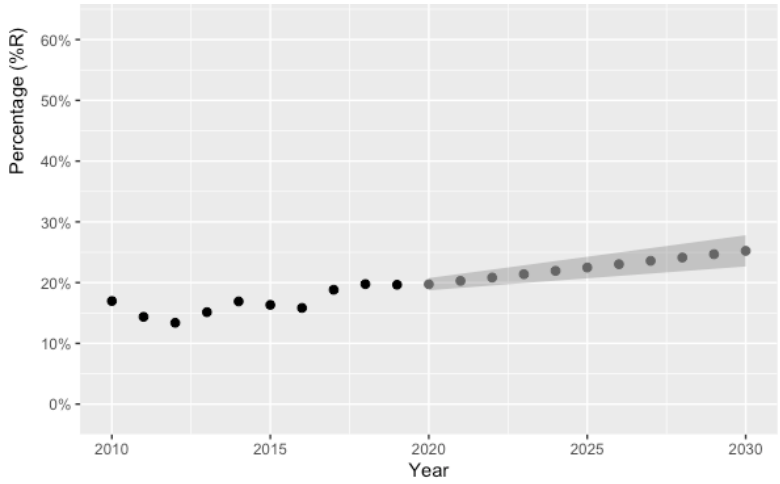


Figure 1: Percentage Staphylococcus aureus resistance to flucloxacillin (Acknowledgment: Dr Indy Sandaradura)

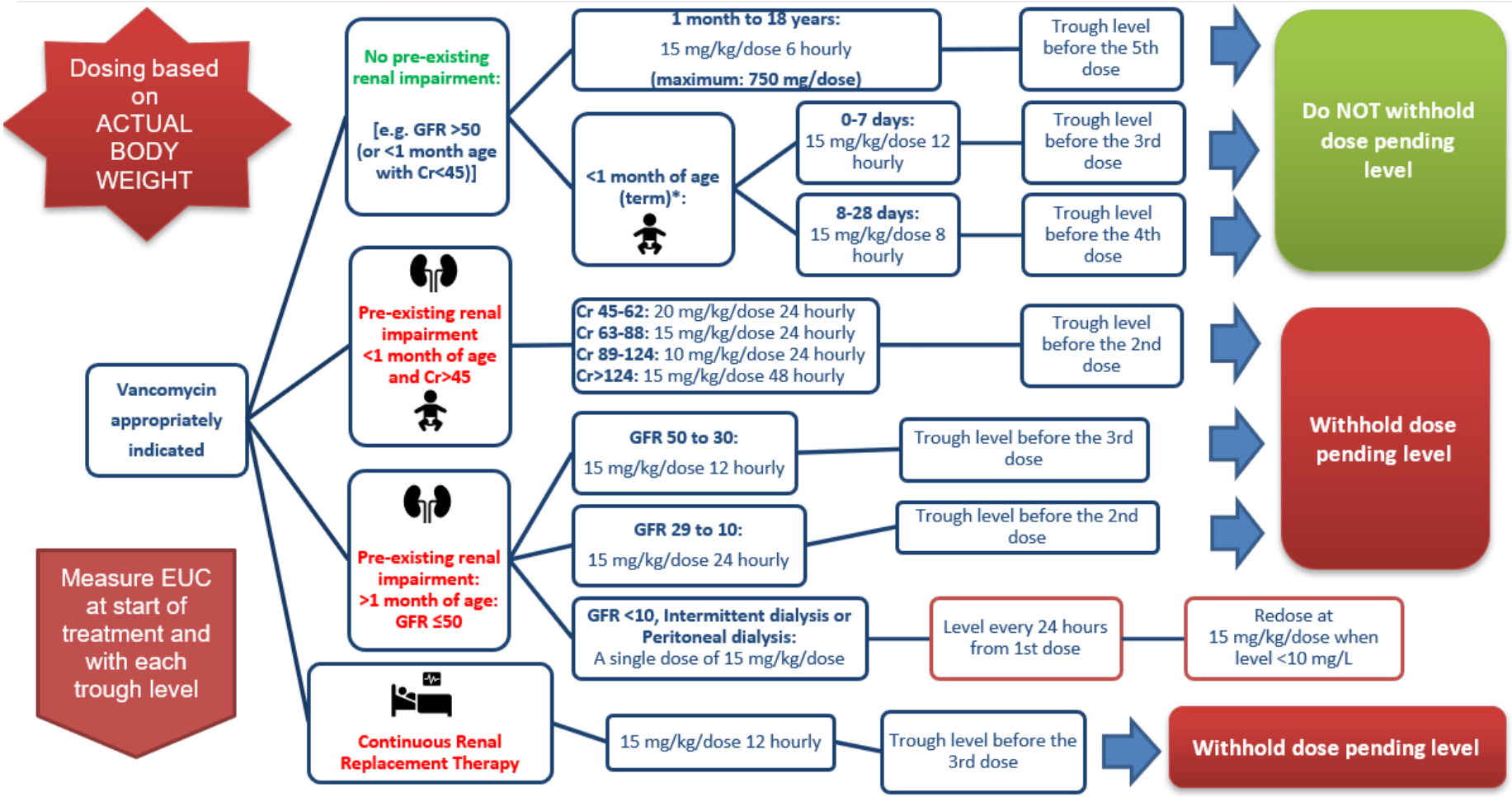
- The 30-day mortality of MRSA bacteraemia in Australian children is 8.5% (lower compared to adults 22.8%), and patients with MRSA bacteraemia are twice as likely to die compared to methicicillin-sensitive Staphylococcus aureus (MSSA) (4.1%) [OR 2.2 (95% CI 1.1-4.3)]. [4]
- Vancomycin is commonly prescribed at CHW with over 200 days of therapy per month and around 5-10 vancomycin inpatient prescriptions per day. It is consistently in the top 10 most prescribed antimicrobials based on annual point prevalence and eMM utilisation data at CHW.
- Despite over six decades of clinical use of vancomycin, recent studies have been published in 2020 that have changed the dosing recommendations of vancomycin and therapeutic drug monitoring (TDM).

Vancomycin for oral administration is available

but is out of scope in this guideline

Please note: Vancomycin given orally does not require therapeutic drug monitoring

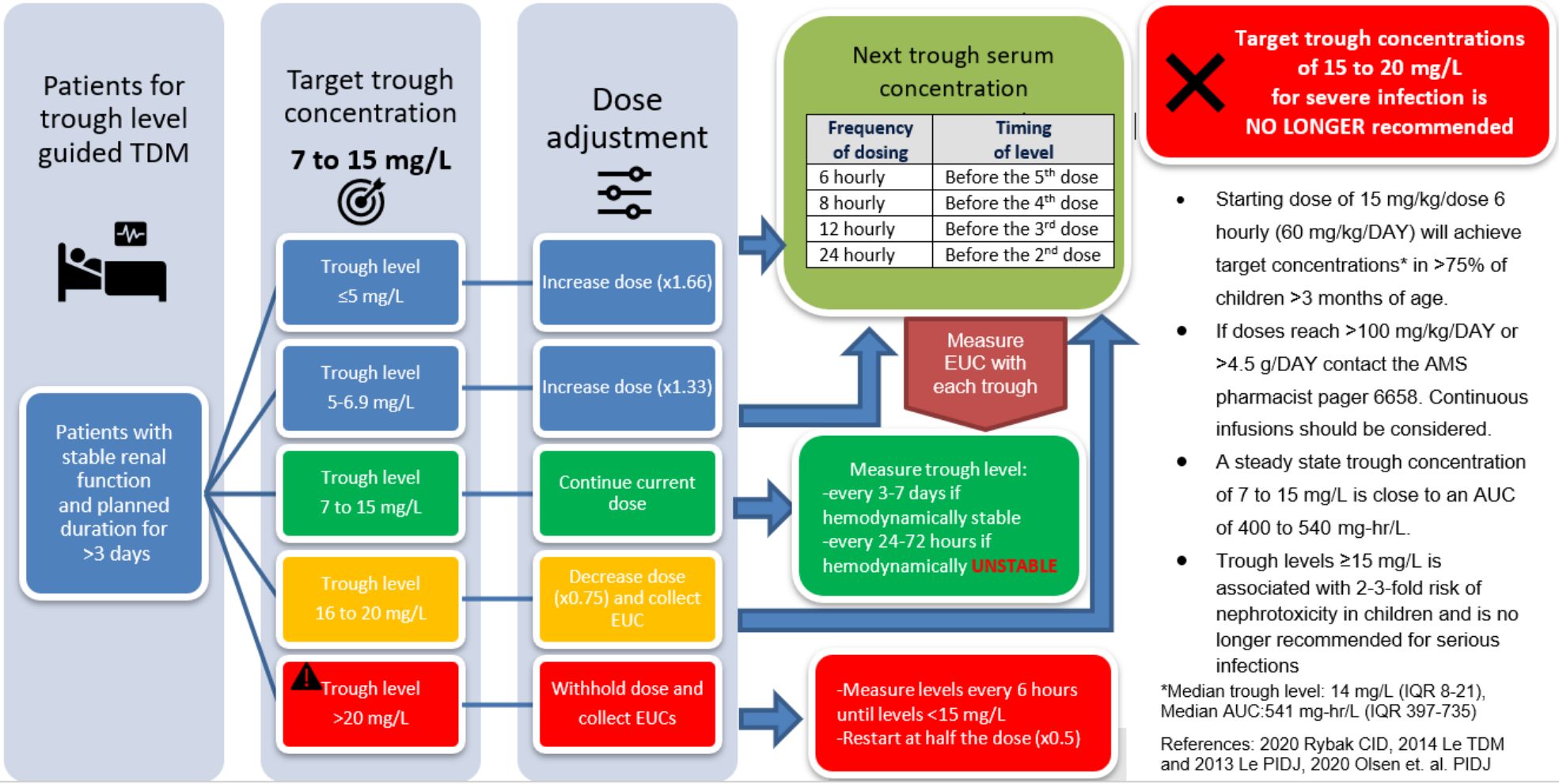
Starting dose and timing of trough serum concentration measurement



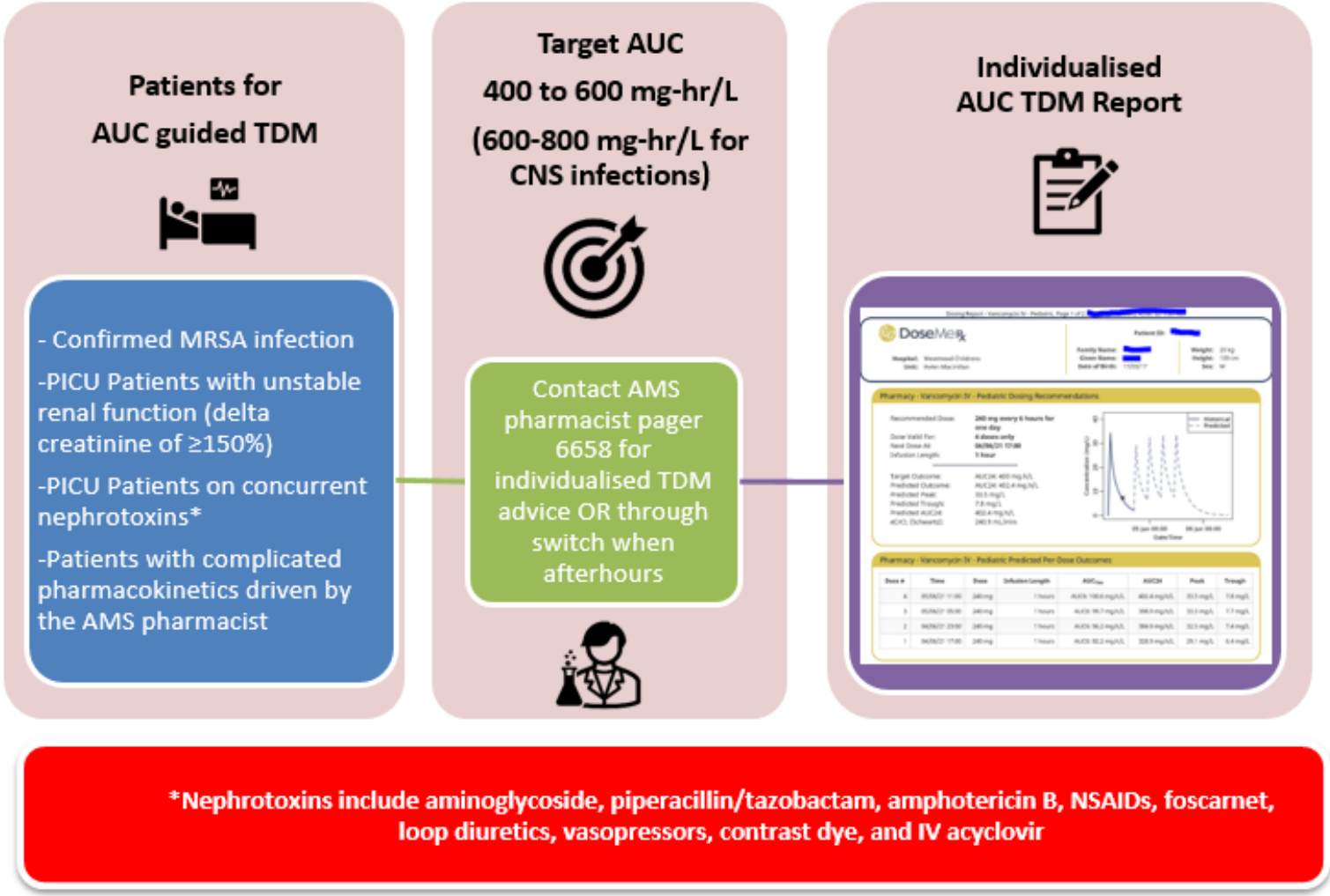
- GFR: estimated glomerular filtration rate based on Bedside Schwartz creatinine clearance (mL/min/1.73 m^2), Cr: serum creatinine (umol/L)
- *For pre-term neonates or patients in NICU, refer to Australasian Neonatal Medicines Formulary.
- **Trough level should be taken within 1 hour before the next dose.**
- If the recommended trough level measurement has been missed, measure a trough level on the subsequent dose

Dose adjustment and therapeutic drug monitoring (TDM)

1. **Trough guided therapeutic drug monitoring is recommended for:**



2. Area Under the Concentration (AUC) guided therapeutic drug monitoring (TDM) is recommended for:

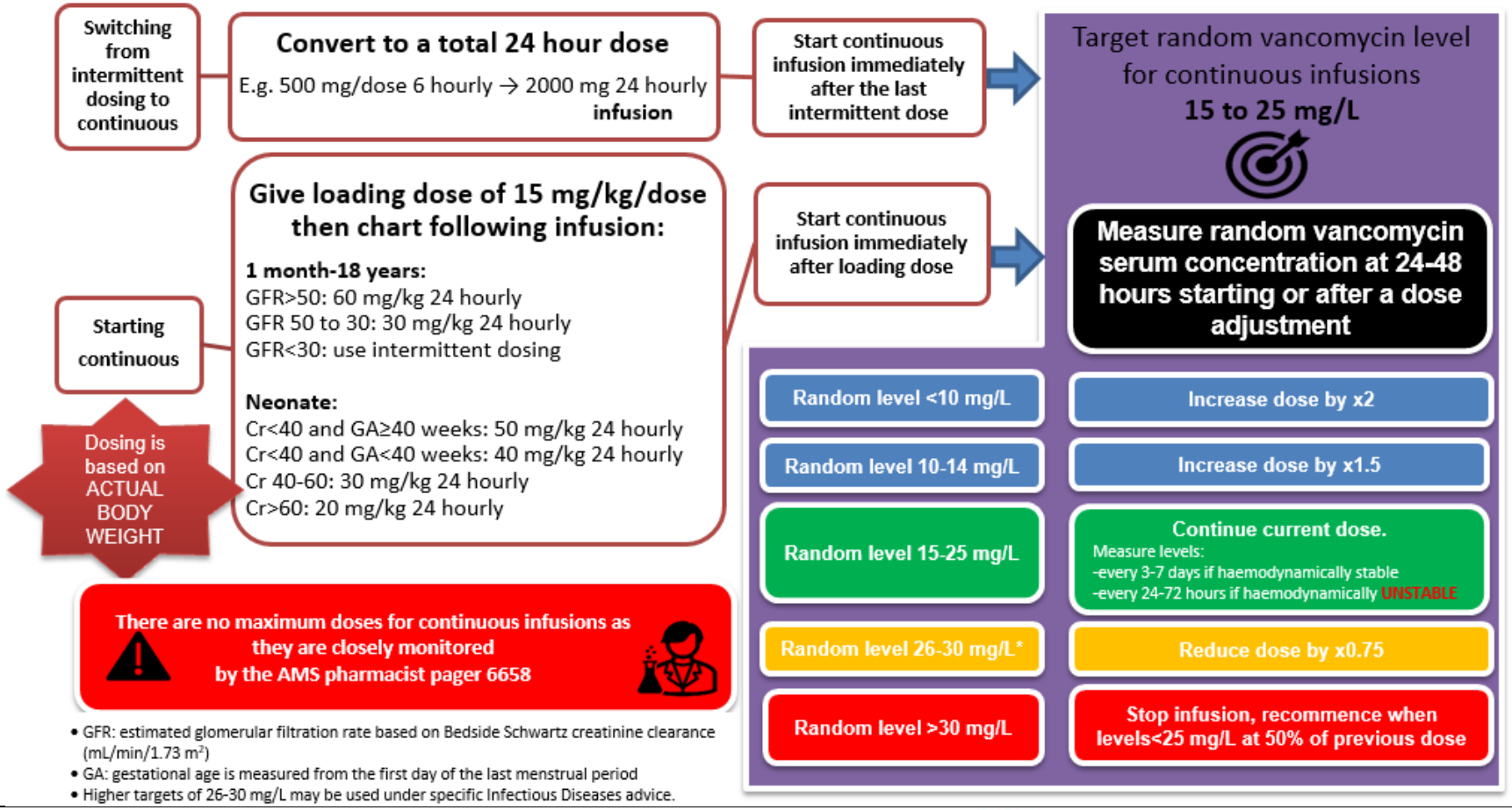


- AUC guided dosing of vancomycin is the preferred strategy to individualise therapy because it incorporates:
  - Age
  - Weight
  - Sex
  - Renal function
- Advantages of AUC vs. trough guided TDM include:
  - Less risk of acute kidney injury (AKI)
  - Reduced length of stay from AKI
  - Less blood draws
  - Shorter durations of vancomycin
  - Better and faster achievement of target AUC exposure
  - Levels can be taken at anytime
- Trough guided dosing will lead to unnecessary larger doses in 25-35% of patients who have already achieved target AUC exposure

References: 2020 Rybak et. al. CID, 2013 Le et. al. PIDJ, 2020 Olsen et. al. PIDJ, 2018 Neely et. al. AAC, 2014 Pai et. al. AdvDrugDel

Vancomycin continuous infusions (VCI)

- Vancomycin administered as a continuous infusion is useful in children having difficulty achieving target concentrations and CNS infections [5].
- It has been shown that VCI in children is twice as more effective at achieving target concentrations and requires less dose adjustments when compared to intermittent dosing. [6] A large adult study (n=1430) showed a lower risk of AKI compared to intermittent infusions [7].



Adverse effects

- Nephrotoxicity (Incidence 5-14%) [8-10]
  - Risk factors include: trough levels ≥15 mg/L, AUC >800 mg-hr/L, doses >4g/DAY, duration >7 days, obesity, pre-existing renal impairment, critical illness or concurrent nephrotoxins*
  - This is reversible and 3% of AKI episodes may require dialysis [11]
- Vancomycin infusion reaction ("red man syndrome" term should no longer be used) can occur in 4% of patients. [12-15]
  - Erythematous rash, generalised flushing
  - Severe reactions can include hypotension, chest pain and dyspnoea
  - Not a sign of allergy; a non-IgE mediated reaction caused by histamine release from mast cells
  - Onset: usually within 4-10 minutes after the start of infusion
  - Risk factors:
    - Associated with rapid infusion of vancomycin (<1 hour)
    - Drugs that induce histamine release (e.g. ciprofloxacin and opioids)
  - Management of reaction:
    - Stop the ongoing infusion; the reaction usually improves promptly after ceasing, and call medical officer immediately
  - Preventative measures:
    - Dilute vancomycin to <2.5 mg/mL
    - Infuse over ≥2 hours
    - No evidence of H_1-antihistamines as a preventive in children
    - Consider teicoplanin as an alternative
- Drug-induced neutropenia (Incidence: 2%)
  - Risk factors: prolong use >7 days, cross-reactivity with teicoplanin
- Ototoxicity (Incidence: 1%):
  - Associated with long duration (>27 days), age and use with aminoglycosides [16, 17]
- Drug-induced thrombocytopenia (Incidence: 1%)
- Anaphylaxis (Incidence: <1%)
  - IgE mediation reaction occurring within 1-6 hours of administration
- Delayed hypersensitivity reactions (Incidence: <1%):
  - Maculopapular rash, severe cutaneous adverse reactions (SCAR), Stevens-Johnson syndrome (SJS), toxic epidermal necrosis (TEN) or Drug reaction with eosinophilia and systemic symptoms (DRESS)
  - Onset is days to weeks after exposure—median latency of 7 days.
  - Cross-reactivity with teicoplanin

Monitoring:

Renal function:

- Electrolyte, Urea and Creatinine (EUC) should be measured at commencement then at least twice weekly while on vancomycin. More frequent monitoring is required in hemodynamically unstable patients or patients on concurrent nephrotoxins.
- These blood tests should be done when vancomycin levels are taken to reduce the number of venepunctures.

Presentation and formulary restrictions

- Vancomycin is available as:
  - 500 mg vial for intravenous infusion ($4.50/vial)
  - 1 gram vial for intravenous infusion ($7.80/vial)
- Vancomycin is a restricted antimicrobial, and the appropriateness of its use is regularly reviewed according to the CHW Antimicrobial Stewardship policy.

Administration

- Refer to Paediatric Injectable Medicines Handbook: Vancomycin monograph

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Appendix I: Pharmacology

	Children	Adult
CNS penetration	Normal meninges: Nil; Inflamed meninges: 0.2-17.3 mg/L CSF:blood ratio: 7.1%-68%	Uninflamed meninges: 0-4 mg/L Inflamed meninges: 6-11 mg/L CSF:blood ratio: 80%
Distribution	Distributes widely in body tissue and fluids	
Volume of distribution	Neonate, term: 0.57-0.69 L/kg Infants: 0.56 L/kg Children: 0.47-0.61 L/kg Adolescents: 0.49 L/kg	0.4 to 1 L/kg 0.3-0.5 L/kg (morbidly obese)
Protein binding:	55%	
Half-life (Significantly prolonged with renal impairment)	Pre-term neonates: 5.9-9.8 hours Term neonates: 6.7 hours Infants: 2.8 hours Children: 2.4-2.9 hours Adolescents: 3.2 hours	Adults: 4-6 hours; End-stage renal disease: 7.5 **days**
Excretion	Primarily via renal (glomerular filtration) 75%	

Antibacterial pharmacodynamics evidence:

The target Area Under the Curve (AUC) is ≥400 mg-hr/L for antibiotic effect

- The ratio of Area Under the Curve over 24 hours to the minimum inhibitory concentration (AUC/MIC) of ≥400 is the critical target for the bactericidal activity (e.g. 2-log reduction in bacterial inoculum) for vancomycin (Figure 2) [2, 18]

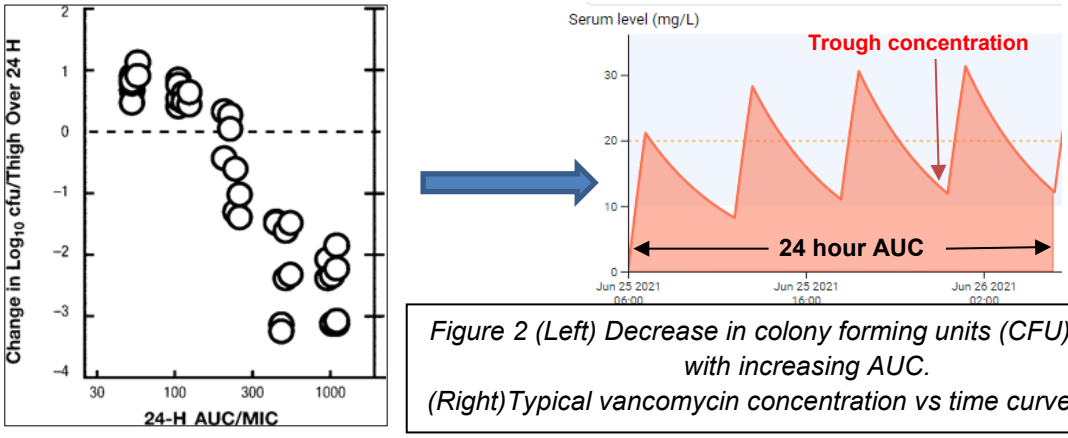


Figure 2 (Left) Decrease in colony forming units (CFU) of MRSA with increasing AUC.
(Right) Typical vancomycin concentration vs time curve.

Trough concentration of 7-10 mg/L is equal to an AUC of 400 mg-hr/L in children

- Trough serum concentrations are a modest surrogate measure for AUC, and a trough level of 8.5 mg/L (95% CI, 6-11) corresponds to an AUC of 400 for 6 hourly dosing from 3 months to 18 years. (19, 20)

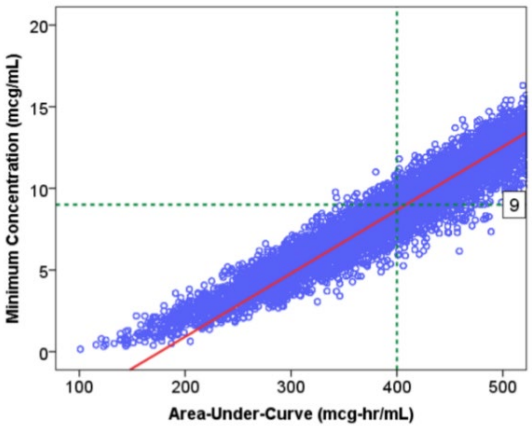


Figure 3: Correlation between AUC and trough serum concentrations for Vancomycin 6 hourly dosing in children

- This correlation is supported by another PK study where a trough level of 7-10 mg/L is equal to an AUC of 400 in children >1 month of age with 6 hourly dosing. (20)

Antimicrobial resistance pharmacodynamics evidence:

An AUC <400 mg-hr/L will lead to antimicrobial resistance

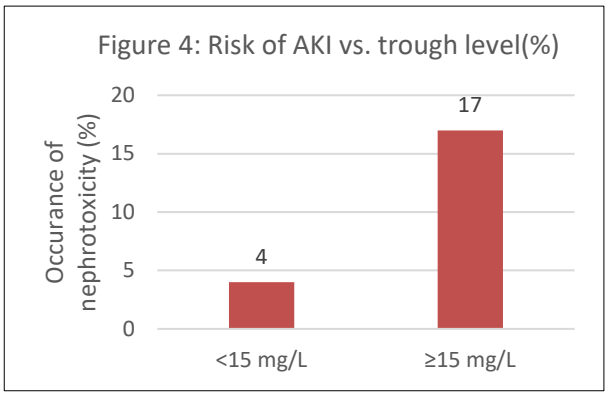
- In vivo and In vitro studies have found an AUC of <400 mg-hr/L potentiates the emergence of MRSA resistance and vancomycin-intermediate *S. aureus* strains.(21)

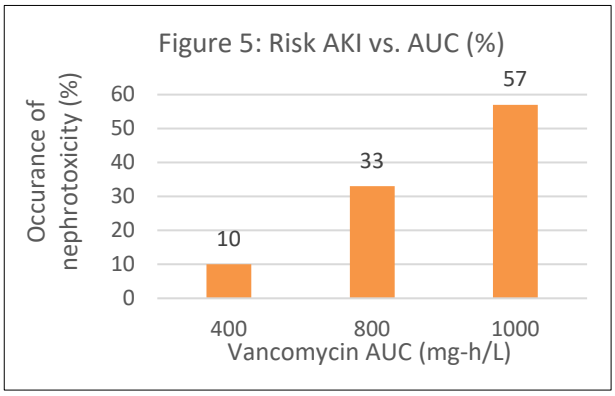
Toxicity pharmacodynamics evidence:

Trough levels of ≥15 mg/L and an AUC >800 mg-hr/L is associated with 2 to 3-fold increase of nephrotoxicity in children

PICU stay and concurrent use of nephrotoxins* are associated with a 1.5-fold increase in nephrotoxicity in children

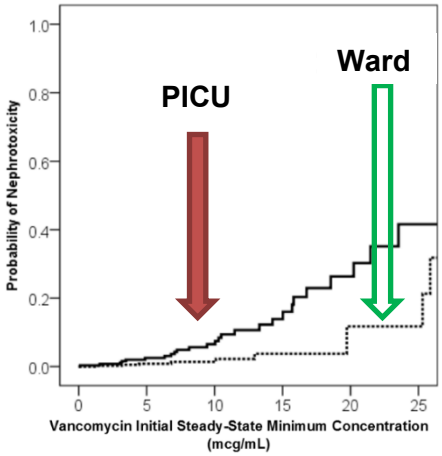
- A meta-analysis of vancomycin-induced acute kidney injury (AKI) in children showed a trough level of ≥15 mg/L is associated with significantly increased AKI compared to trough levels <15 mg/L ([OR], 2.67; 95% CI, 1.95 to 3.65). (22)
- The first paediatric study (n=167) in children (1 week to 19 years of age) had an overall AKI risk of 14%. Children with a trough level ≥15 mg/L had more AKI compared to children with a trough level <15 mg/L (28% versus 7.3%, P =0.0001). (9)
- A much larger study (n= 680) in children (2 to 13 years of age) found that a trough level ≥15 mg/L and an AUC ≥800 mg-h/L had an aOR 2.5;(95% CI, 1.1 to 5.8, p=0.028) and aOR 3.7;(95% CI, 1.2 to 11.0, p=0.018) increase risk of AKI, respectively. There is a positive correlation relation for AUC vs AKI. (10)





- Significant nephrotoxicity was seen in Intensive Care (62.2% vs 37.2%; p=0.001) and concurrent nephrotoxins* (71.1% vs 37.6%; P<0.001) compared to those without [10]

Figure 6 Kaplan-Meier of Vancomycin associated AKI in patient in or not in PICU



**nephrotoxins defined in the study included loop diuretics, vasopressors, aminoglycosides, contrast dye, and intravenous acyclovir*

Appendix II: Frequently Asked Questions

1. What is the evidence of the 15 mg/kg/dose 6 hourly dosing, and why is 30 mg/kg/dose 12 hourly from the eTG as a starting dose not recommended?

- 6 hourly has the most supporting literature in pharmacokinetic target attainment in children >1 month of age and paediatric clinical experience with most children achieving target concentration within 3000 mg/day [2, 19, 20, 23, 24]
- 8 hourly and 12 hourly dosing have been described in other guidelines and literature, but it is crucial to note they have different target trough concentration targets and are not interchangeable. Less frequent dosing will always require a lower trough level to achieve the same AUC. [1, 19, 20]
- 15 mg/kg/dose 6 hourly has been found to achieve a target ≥AUC 400 in over 75% of children >3 months of age. Monte Carlo simulations in children have shown that this dose will achieve a median trough level of 14 mg/L (IQR 8-21) and a median AUC of 541 mg-hr/L (IQR 397-735) (Figure 7). The remaining 25% of children that may require higher doses is discussed in Question 3. [19]
- Lastly, infusions of 30 mg/kg/dose may be associated with vancomycin infusion reaction [25], which discourages the higher 12 hourly dose despite being the same total daily dose.

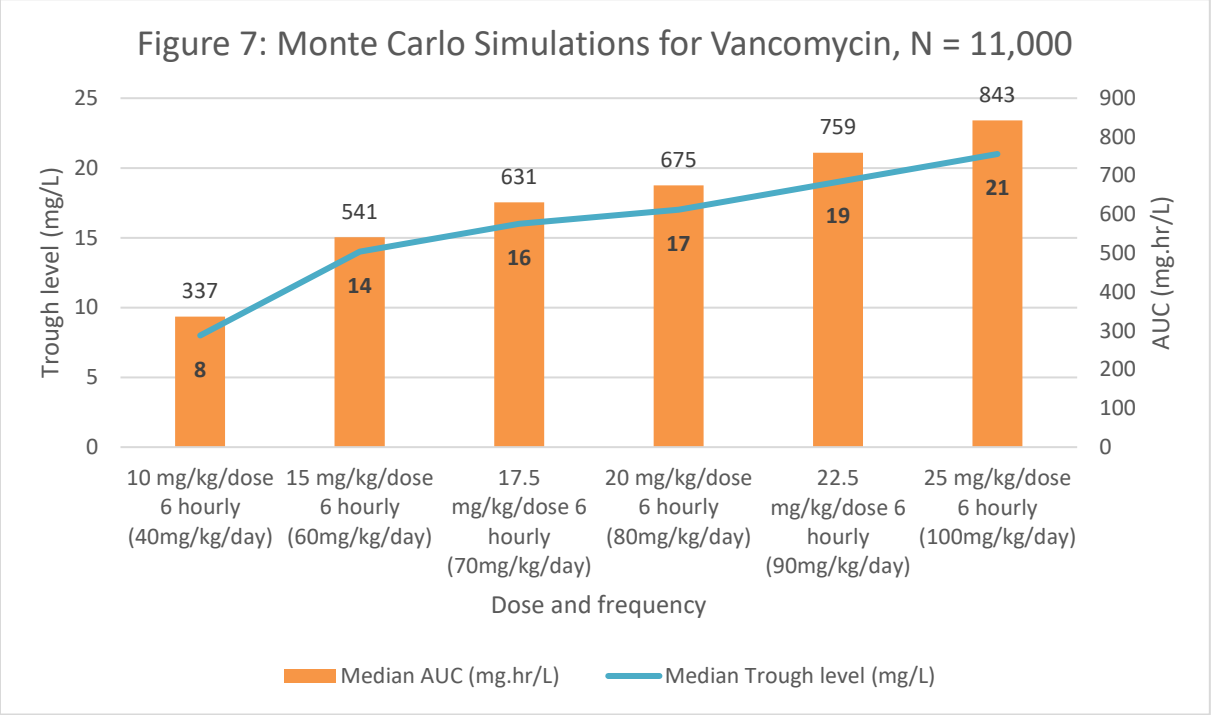


Figure 7: Monte Carlo Simulations for Vancomycin, N = 11,000
Trough level (mg/L)
AUC (mg.hr/L)
25
20
15
10
5
0
900
800
700
600
500
400
300
200
100
0
337
541
631
675
759
843
8
14
16
17
19
21
10 mg/kg/dose 6 hourly (40mg/kg/day)
15 mg/kg/dose 6 hourly (60mg/kg/day)
17.5 mg/kg/dose 6 hourly (70mg/kg/day)
20 mg/kg/dose 6 hourly (80mg/kg/day)
22.5 mg/kg/dose 6 hourly (90mg/kg/day)
25 mg/kg/dose 6 hourly (100mg/kg/day)
Dose and frequency
Median AUC (mg.hr/L)
Median Trough level (mg/L)

2. Why are the target troughs of 15 to 20 mg/L not recommended?

- A higher trough target of 15-20 mg/L was recommended in previous American guidelines [26] and the current eTG [1]. This was initially based on an adult study with the supervising author, Michael Rybak, describing an association with increasing treatment failures of MRSA bloodstream infections <15 mg/L.[27] Subsequently, Michael Rybak has now rescinded this recommendation in his most current guidelines based on the entirety of the evidence. [2]
- From a clinical perspective, there is clinical data that has debunked the target 15-20 mg/L range. Targeting a trough of ≥15 mg/L was not associated with an increase in treatment success in deep-seated MRSA infections [28], critically ill MRSA pneumonia [29] or MRSA bacteraemia.[30]
- A paediatric retrospective study (n=192) in MRSA bacteraemia from osteoarticular focus showed troughs >15 mg/L were not associated with improved clinical outcomes. The outcomes measured included: duration of fever, bacteraemia or need for repeat surgery. The authors found an association with AKI, increased length of stay. [31]
- The same authors published a larger prospective study in children with MRSA bacteraemia (n=340) found trough levels >15 mg/L had no clinical benefit. There was a clear proportional increased risk of AKI (Table 1) [32]

Table 1: Outcomes of MRSA Bacteraemia by trough levels in children

	Trough ≤ 10 µg/ml (n=55)	Trough 10–≤15 µg/ml (n=33)	Trough > 15 µg/ml (n=39)	P value
Median Age, Months (IQR)	15.6 (1.2–96)	2.4 (0.1–10.3)	9.4 (0.3–169.2)	0.3
Infectious Diagnosis of Endocarditis	7 (12.7)	10 (30.3)	4 (10.3)	0.07
Median Duration of Bacteremia, Days (IQR)	2 (1–4)	2.5 (1–5)	2 (1–4)	0.4
Median Time to Resolution of Fever, Days (IQR)	2 (1–4)	3 (2–4)	2 (1–5)	0.2
Median Length of Hospital Stay, Days (IQR)	17.5 (10–44)	47.5 (24–104)	43.5 (25–89)	0.01
AKI	9 (16.2)	11 (33.3)	24 (61.5)	<0.001
S. aureus Attributable Mortality	2 (3.6)	3 (9.1)	8 (20.5)	0.02

- From a nephrotoxicity perspective, recent meta-analyses of vancomycin induced nephrotoxicity in both adults and children have led the authors of the American guidelines to no longer recommend trough targets of 15-20mg/L for serious MRSA infections. Evidence summaries on page 13 [2, 11, 22]
- From a pharmacokinetic perspective, studies have shown trough targets of 15-20 mg/L are not necessary to achieve AUC>400 in children. 25-35% of children who have already achieve target AUC will be exposed to unnecessarily high doses [19, 20, 23, 33, 34]
- Based on the evidence of increased risk of nephrotoxicity and lack of clinical benefit (even in severe MRSA infections), a trough target of 15-20 mg/L has been reduced to 7-15 mg/L in this guideline. These target troughs are similar to an AUC of 400-540 mg-hr/L in paediatric studies. The eTG was published before Michael Rybak's American guidelines and will need to wait for the next edition to consider adopting this change. [1, 2]

3. Where did the trough level-based dose adjustments, maximum doses of 100 mg/kg/DAY or 4.5g/DAY, come from?

- The dose adjustments on page 4 follow a simplified version of linear dose adjustment, and the maximum doses studied. Vancomycin displays linear pharmacokinetics (e.g. dose directly proportional to serum concentration). (1)
    - For example. when trough levels are low (≤5 mg/L), the dose increase of multiplying the dose by 1.66, [(e.g. 15 mg/kg/dose 6 hourly (60 mg/kg/DAY) by 1.66= 24.9 mg/kg/dose 6 hourly (99.6 mg/kg/DAY)] is the maximum dose increase.
- Up to 25% of children may require higher doses of 60 to 100mg/kg/DAY studied in children with increased clearance (e.g. oncology and augmented renal clearance).(19)
- Higher doses of 100 mg/kg/DAY may be required for children with increased vancomycin renal clearance (augmented renal clearance). This may be up to 12% of children who have serum creatinine <30 microg/L or eGFR≥130 mL/min/1.73m^2. Children older than 8 years of age are more likely to have augmented renal clearance (17% vs 4.6%. p=0.002) and are more likely to have lower trough levels (5 mg/L vs 9 mg/L. p<0.001). (35, 36)
- Higher doses of 80 mg/kg/DAY may be required for paediatric cancer patients. Malignancy in children and infants have been shown to lead to an increased clearance by 30%. (37-39)
- Doses of >100 mg/kg/DAY have been poorly studied and will lead to toxic trough levels (>21 mg/L) and toxic AUCs (>843 mg-hr/L). Therefore 100 mg/kg/day is recommended as the maximum dose. (2, 19)
- eTG recommends a maximum dose of 70 mg/kg/DAY; this translates to a maximum dose increase multiplier of 1.17 for starting doses of 60 mg/kg/DAY (e.g. 70/60=1.17). (1)
- This real patient model illustrates the false logic in this recommendation: A 9-year-old 40.3 kg girl and a height of 125 cm with a Cr of 30 is started on vancomycin 15 mg/kg/dose 6 hourly and gets a trough level of 5 mg/L. Using the linear dose adjustment and being capped at 70 mg/kg/day according to the eTG, a dose increase of 1.17x would only produce a subtherapeutic trough level of 5.37 mg/L. and an AUC 316. (Figure 8)

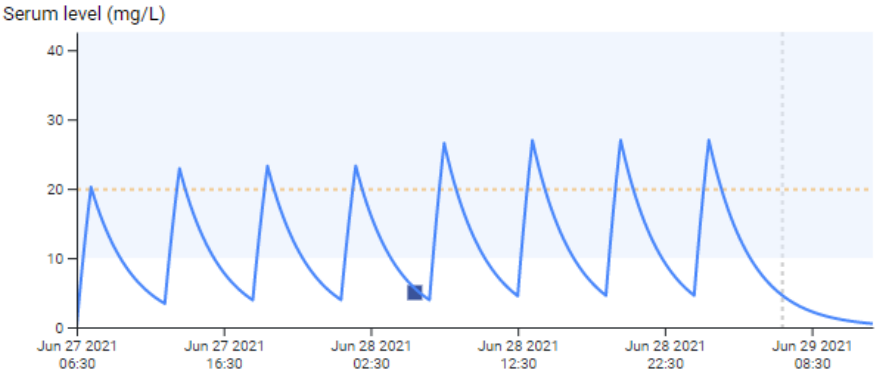
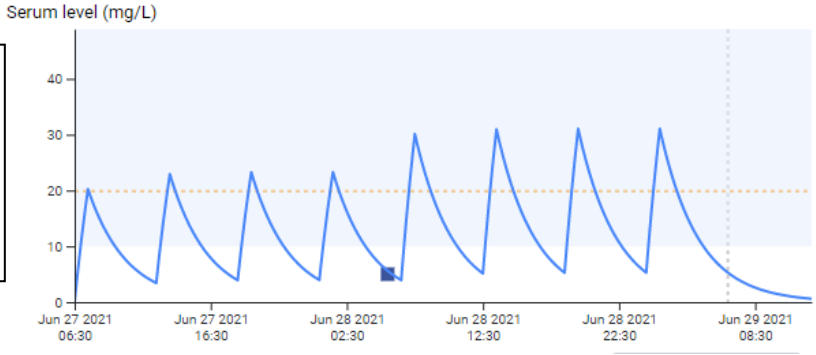


Figure 8 Bayesian forecast model of a dose increase according to eTG with a dose cap of 70 mg/kg/DAY

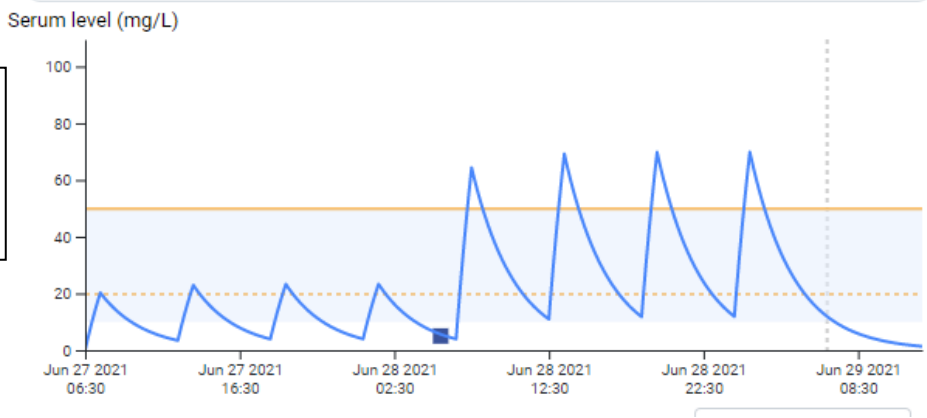
- A pharmacokinetic study has shown that 7-20% of children >3 months will not achieve target AUC≥400 mg-hr/L with a dose 70 mg/kg/DAY. Doses of 80-100 mg/kg/DAY may be required in patients with increase clearance, as previously discussed [19]
- A linear dose adjustment with a dose cap 80 mg/kg/DAY would only produce a trough of 6.6 mg/L and an AUC of 360 (Figure 9)

Figure 9 Bayesian forecast model of a dose increase according to eTG with a dose cap of 80 mg/kg/DAY



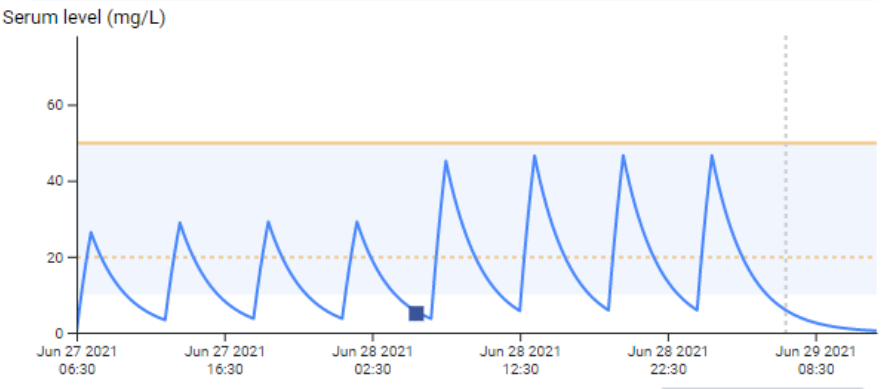
- A dose increase of 1.66x (the max dose of 99.6 mg/kg/DAY) according to this guideline would produce a trough level of 8.56 mg/L and an AUC of 429 (Figure 10)

Figure 10 Bayesian forecast model of a dose increase according to this guideline



A linear dose increase with no max dose cap for a target of 15 mg/L for "severe infections" according to the eTG (e.g. tripling the dose since the level is 5 mg/L) would produce toxic levels (trough 15.9 and AUC 800.23) (Figure 11)

Figure 11 Bayesian forecast model of a dose increase according to eTG with NO dose cap



- 4.5 g/DAY is the maximum vancomycin dose from studies in obese adults and is recommended to be an appropriate maximum dose for obese children [2, 40, 41]

4. Is there different dosing in obesity for children because it is not mentioned in the guideline?

- An earlier vancomycin pharmacokinetic study in obese children (n=87, 389 levels) showed that the differences between obese children and normal weights are not clinically relevant for dose adjustments. The authors concluded that actual body weight should be used regardless. [42] This was tested subsequently by the same authors, and they found 15 mg/kg/dose 6 hourly achieved an AUC ≥400 in 76% of obese children when actual body weight was used and 66% when ideal body weight was used.[2]
- In the largest pharmacokinetic study (n=1892, 5524 samples) with 301 that were obese children, the heaviest weighing 188 kg. The authors found that the clearance of vancomycin was directly proportional to the total body weight which supports the conclusion of earlier studies (Figure 12). They also proposed a dosing guideline, but this has not been tested or validated. [41]

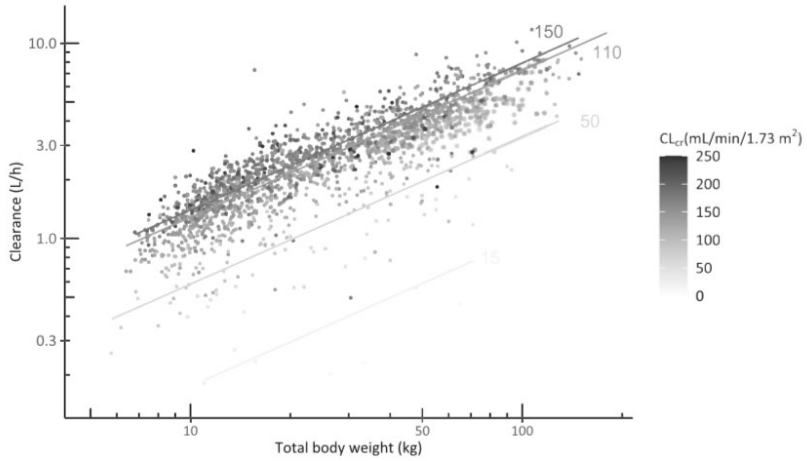


Figure 12: Vancomycin clearance (L/h) versus total body weight (kg) for varying creatinine clearance values in 1-18 years and a weight range of 6-188 kg

- The American guidelines recommend a loading dose of 20 mg/kg/dose in obese children, but this is based on a conference presentation, and alarmingly 20% of children had toxic AUCs of ≥800. This evidence has not been published or peer-reviewed. [2, 43]
- This guideline does not recommend specific dosing for obese children; using a starting dose of 15 mg/kg/dose 6 hourly will achieve a target AUC≥400 in 3 out of 4 obese children. Adjusting the dose based on troughs or AUC modelling with assist with the remaining 1 out of 4, significantly when the trough targets are lowered from 10-20mg/L to 7-15 mg/L. [19]
- 4.5 g/DAY is the maximum vancomycin dose from studies in obese adults and is recommended to be an appropriate maximum dose for obese children [2, 34, 40, 41]

5. Why are loading doses of vancomycin not recommended in this guideline?

- Loading doses have been shown to be safe and effective in adult practice. [2] The highest-level evidence for vancomycin loading doses in adults is an RCT (n=99) which found a higher percentage of early target attainment (34% vs 3%, p<0.01). There was no difference in AKI or clinical outcomes. [44] The largest adult vancomycin loading dose study (n=449) showed no different clinical outcomes (e.g. clinical failure, mortality, or AKI). [45]
- At the time of this publication, there is currently no robust clinical evidence to support loading doses of vancomycin in children. It is not recommended in American guidelines [2] but is recommended in the eTG [1]; this is based on expert opinion level evidence rather than the two primary studies.
- One small RCT in children (n=59) showed no earlier target attainment of vancomycin serum concentrations from the 30 mg/kg loading dose, despite using unnecessarily high trough targets of 15-20 mg/L, and, more importantly, there was no difference in AUCs in the first 24 hours. No difference in AKI was seen. The authors found a trend to more vancomycin infusion reactions from the loading dose (48% vs 24%, p=0.06). [25]
- A larger paediatric retrospective study (n=151) showed a loading dose of 25 mg/kg achieved higher trough levels of 13 mg/L vs. 9.2 mg/L (p<0.0001). Both trough levels are within newer target vancomycin concentrations (7-15 mg/L) which question the benefits of the loading dose and needs reevaluation. AUCs were not measured in this study as a key limitation. There was no difference in AKI. [45]
- The lack of utility of loading doses in children compared to adults can be explained based on fundamental pharmacokinetic principles. Children have shorter half-lives compared to adults (2-3 hours vs 4-6 hours), and therefore, the time to reach a steady-state concentration is much sooner in children (within 8-12 hours) compared to adults (within 16-24 hours). The purpose of the loading dose is to achieve target steady-state concentrations immediately, and this is achieved within 2 doses for 6 hourly dosing in children. This is the reason why loading doses are used in drugs with long half-lives like amiodarone or isavuconazole. The two primary studies are consistent with this explanation where the time to early target attainment is no different if a loading dose of vancomycin is given in children [25, 45].
- Figure 13 (next page) illustrates a Bayesian forecast modelled child where no loading dose still achieved an AUC>400 in the first 24 hours compared to if a loading dose of 30 mg/kg was given. One can see graphically, and by the trough levels, steady-state was achieved by the second dose (e.g. 12 hours) when loading dosing was not given.

Figure 13: Bayesian forecast model of a 3 year old boy, weighing 13 kg with a serum creatinine of 40 mmol/L

A one-compartment model with first-order kinetics model derived from a retrospective analysis including 702 patients (median age ~6.6 yo, age rage 2.2-13.4 yo, weight 12.6-46 kg, baseline SCr 0.3-0.6 mg/dL<0.9 mg/dL) with 1660 vancomycin serum concentrations. Covariates: weight, serum creatinine, age.

Reference: J Le, JS Bradley, W Murray, GL Romanowski, TT Tran, N Nguyen, S Cho, S Natale, I Bui, TM Tran, and EV Capparelli. Pediatr Infect Dis 2013; 32(4):e155-e163.

<table>
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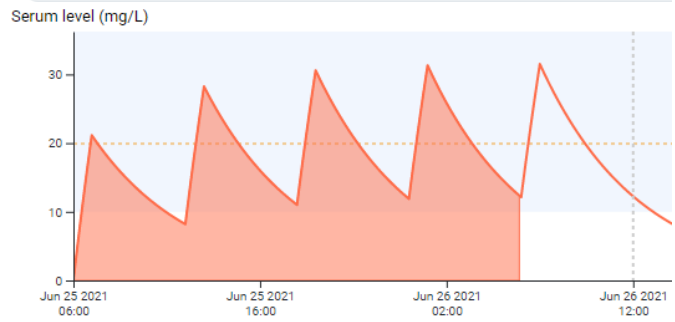
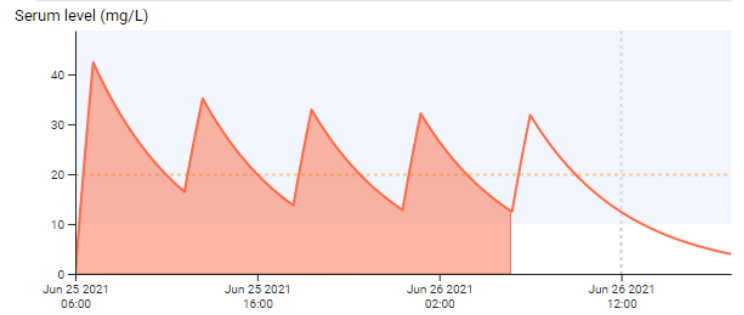
195 mg 6 hourly</td><td colspan="2"> 
</td></tr>
<tr><td>AUC 1st 24 hours: 430.38 mg-hr/L</td><td>Troughs:
1st 8.28 mg/L
2nd 11.10 mg/L
3rd 11.99 mg/L
4th 12.39 mg/L</td></tr>
<tr><td rowspan="2"><u>Loading dose:</u>
450mg then
195 mg 6 hourly</td><td colspan="2"> 
</td></tr>
<tr><td>AUC 1st 24 hours: 555.65 mg-hr/L</td><td>Troughs:
1st 17.18 mg/L
2nd 13.39 mg/L
3rd 12.85 mg/L
4th 12.51 mg/L</td></tr>
</table>

- The evidence for loading doses in children is limited only to use in obesity (20 mg/kg/dose) and when administering continuous infusions (15 mg/kg/dose). These doses are lower and near regular maintenance doses. [2, 6]
- The half-life of vancomycin in neonates is significantly longer 6-10 hours, so the time to reach a steady-state is later, and loading doses may be of utility in this age group. This needs to be further evaluated. [46]
- Ultimately, there is insufficient data to recommend loading doses in children, and the safety and efficacy are not translatable from adult studies. There is an evident lack of pharmacokinetic benefit and a suggestive risk of a vancomycin infusion reaction.