It is recommended as a treatment for complicated skin infections, bloodstream infections, endocarditis, bone and joint infections, gastrointestinal and central nervous system infection caused by:

Selective Gram positive organisms:

1. Methicillin resistant *Staphylococci* and *Streptococci*
2. *Enterococci*
3. *Rhodococci*
4. *Clostridium*

Inherently resistant organisms:

1. Few species of *Enterococci*
2. *Lactobacillus*
3. *Leuconostoc*
4. *Pediococcus*
5. *Erysipelothrix spp*

KEY PARAMETERS:

Therapeutic Range	Refer to 'Indication and Therapeutic Range' section
Bioavailability (F)	Oral : < 5% [1] IV : 100 % [1]
Elimination Rate (Ke)	Ke (hr^{-1}) = 0.0044 + (CrCL x 0.00083) [3]
Volume of Distribution (Vd)	Vd (L)= 0.7L/kg
Clearance (CL)	Cl = 0.695 (CrCL, mL/min) + 0.05 [7]
Half-life ($t_{1/2}$)	Adult: 5 – 11 hours [4] Children: 2– 3 hours [4]

PHARMACOKINETIC

Bioavailability (F): [1]

Oral: < 5%

Intravenous: 100%

Volume of Distribution (Vd):

The average Vd for vancomycin in non-obese adults with normal renal function is 0.7 L/kg. However, it can be calculated using these equations:

$$Vd\ (L) = 0.17\ (age) + 0.22\ (TBW) + 15$$ [2]

or

$$Vd\ (L) = (0.5 - 1)\ L/kg \times BW\ (kg)$$ [2]

Clearance (Cl):

Cl = 0.695 (CrCL, mL/min) + 0.05 [7]

In healthy subject, 30% of the systemic vancomycin clearance is by non-renal mechanism and the non-renal clearance is concentration dependent. Assuming protein binding to be between 10% and 20%, renal vancomycin excretion is predominantly by glomerular filtration. [13]

Clearance can also be calculated using:

Cl = Vd/Ke (L/hr)

Half-life ($t_{½}$):

Neonates	6 – 10 hours [4]
Children	2 – 3 hours [4]
Adult	5 - 11 hours [4]
Adult, renal failure	120-140 hours [7]
Adult, obese	3-4 hours [7]
Burn patient	4 hours [1]

Indication and Therapeutic Range:

Vancomycin is used to treat severe gram positive infections. It exhibits time-dependent antibiotic. Thus, trough concentration combined with AUC_{24} estimation are the practical method for monitoring vancomycin effectiveness. AUC_{24} > 400 shows an optimal antibiotic exposure in ensuring the treatment efficacy, and a capping maximum limit in AUC_{24} of 600 signifies the treatment safety with vancomycin.

Trough:

General: 10 – 15 mg /L [5]

- The target trough level will depend on the ability to achieve AUC_{24} of 400-600 for optimal antibiotic exposure [20]
- For a pathogen with an MIC of 1 mg/L, the minimum trough concentration would have to be at least 15 mg /L to generate the target AUC_{24}/MIC of 400. (5)

For continuous infusion:

Conventional target: 15- 25 mg /L [16,17]

Critically ill and severe infection: 20-30 mg /L [16,25]

Conversion Factor: mg /L (~mg /L) x 0.69 = µmol/L

Pharmacodynamic Targets: goal AUC and Trough [20, 26]

Indication	Target Index
Most Indications	
Bacteremia (all sources, including SSTI) Endocarditis Bone/joint infection Necrotizing fasciitis Pneumonia Empiric therapy for neutropenic fever Sepsis, source unknown	Target AUC_{24} 400-600, with trough 10-20 mg/L **(AUC_{24} is primary target)**
Meningitis (Empirical or definitive), CNS infection MRSA infections with MIC = 2	
AUC_{24}-based protocol Trough-based protocol	600-800 15-20 mg /L

Renally impaired patients (AKI, CKD)	
AUC_{24}-based protocol	400-600
Trough-based protocol	15-20 mg/L
• In general, goal AUC_{24} 400-600 for *S.aureus* • Monitor closely with trough > 15 or AUC > 700: increased risk of nephrotoxicity • Vancomycin may be continued in clinically responding patients with MRSA with vancomycin MIC = 2	

DOSAGE

Pediatric:

Age	Dose
Neonate less than 29 weeks postmenstrual age	15 mg/kg OD [14]
29-35 weeks postmenstrual age	15 mg/kg BD [14]
Over 35 weeks postmenstrual age	15 mg/kg TDS[14]
Infant >1 month & children	10 -15 mg/kg every 6 h [4]

Adult:

Loading dose [5, 19, 26]

All patients initiated on vancomycin should be assessed to determine whether a LD is likely to improve outcomes. The two key components involved in making this determination include **indication for vancomycin** and **severity of illness**. The criteria below are meant to aid the clinician in making this determination. [26]

Patients meeting either criterion A or B should receive a vancomycin LD:	
A	Meeting **≥2** of the following (all indications except non-necrotizing fasciitis or bacteremic SSTI, UTI, or prophylaxis post-surgery): • Temperature > 38°C or < 36°C • Heart rate > 90 beats per minute • Respiratory rate > 20 breaths per minute • WBC > 12,000/mm3, < 4,000/mm3, or > 10% bands • Hypotension (systolic blood pressure < 90 mmHg, MAP < 60 mmHg, or requiring vasopressors)
B	Treatment of meningitis/CNS infection (suspected or documented)

In rare instances when such information cannot be obtained without a significant delay in treatment, it is reasonable to give a LD.

Recommendation for loading dose based on population:

LOADING DOSE	
Population	**Loading Dose (mg)**
CrCl > 30 mL/min and stable or improving	Weight-based: 25-30 mg/kg TBW*
CrCl ≤ 30 mL/min or declining, not on dialysis	Weight-based: 20 mg/kg TBW*
Intermittent Hemodialysis (IHD)	Weight-based: 20 mg/kg TBW*
Continuous Renal Replacement Therapy (CRRT)	Weight-based: 20 mg/kg TBW*
Peritoneal Dialysis (PD)	Intraperitoneally: 2 gram*
	Weight-based: 20 mg/kg TBW IV*

* (ASHP, Stanford)
Use total body weight (TBW) if TBW < IBW (ASHP, Stanford)
Use ideal body weight (IBW) for non-obese patients
Use adjusted body weight (ABW) for obese patients [total body weight (TBW) >20% of IBW or BMI >30 kg/m2]

Conventional Dosing: [4, 5, 18, 19, 23, 26]

MAINTENANCE DOSE						
BW(kg) / [a]CrCl (ml/min)	**>90**	**75-89**	**60-74**	**50-59**	**30-49**	**Sampling Time**
>60	1000 mg tds	750 mg tds	1000 mg bd	750 mg bd	500 mg bd	Pre level on 3rd dose
40-59	750 mg bd	750 mg bd	500 mg bd	750 mg od	500 mg od	
20-39	750 mg od	750 mg od	500 mg od	500 mg od	500 mg od	

<20 HD	ESRF: Initial dose: Give loading dose as chart (a) then sample blood for monitoring 24 hours after dose. [c](Re-dose 15-20 mg/kg when plasma concentration <20 mg/L and depending on the residual renal function)	Random level: • 24 hours after 1st dose. • 48 hours after subsequ-ent dose (pre HD preferred)
CAPD	ESRF: Initial dose: Give loading dose as chart (a) then sample blood for monitoring 24 hours after dose. (Re-dosing depends on the type of dosing (intermittent or continuous) and serum trough vancomycin concentration*) *Serum trough vancomycin concentration is advised to be kept between 15-20 mg/L	
[b]Dilution & Infusion Guide	• 500 mg/ 100cc NS/ 1hour • 750-1000 mg/ 200cc NS/ 2 hours • 1000-2000 mg/ 400cc NS/3 hours	

[a]Use Cockroft Gault formula. Not valid for SCr <60 umol/L and elderly >65 years of age. Get consultation from CPS pharmacist.
[b]Do not exceed 10 mg/min to avoid red man syndrome discomfort, hypotension, cardiac arrest.
[c]Subsequent doses to be recommended by CPS pharmacist.

Continuous Infusion [9]:

LOADING DOSE	
< 40 kg	500 mg IV in 100 mL 0.9% sodium chloride or 5% glucose over 1 hour
< 70 kg	1 g IV in 250 mL 0.9% sodium chloride or 5% glucose over 2 hours
≥ 70 kg	1.5 g IV in 250 mL 0.9% sodium chloride or 5% glucose over 2.5 hours

Central administration: the final concentration should not exceed 10 mg/mL
Peripheral administration: the final concentration should not exceed 5 mg/mL

Start the maintenance of IV infusion immediately after the loading dose. The dose depends on the patient's renal function. Infusions should be administered in 250 mL 0.9% sodium chloride or 5% glucose over 12 hours. The total daily dose should be split into two and the infusion rate set at 20.8 mL/hr.

MAINTENANCE DOSE		
Creatinine Clearance (mL/min)	**Daily maintenance dose**	**Dose in each 250 mL infusion bag for administration over 12 hours**
<20	500 mg	250 mg
20-34	750 mg	375 mg
35-59	1000 mg	500 mg
60-79	1500 mg	750 mg
80-99	2000 mg	1000 mg
>100	2500 mg	1250 mg

For dosage adjustments in continuous infusion [16, 19, 26]

Vancomycin Concentration	Suggested dosage change
< 15 mg/L	Increase the daily dose by 500 mg
15 – 25 mg/L	No change
> 25 mg/L	Decrease the dose by 500 mg*
> 30 mg/L	Stop the infusion and recheck serum concentration next morning. Restart at a lower dose

*If the patient is only receiving 500 mg/day, reduce the dose to 250 mg/day

Renal Impairment: [4, 18, 23]

CrCL (mL/min)	Dosage Adjustment
> 50	15 – 20 mg/kg/dose every 12 hours (usual : 750 – 1500 mg)
20 – 49	15 – 20 mg/kg/dose every 24 hours (usual : 750 – 1500 mg)
< 20	Need longer intervals, re-dosing determined by serum concentration monitoring

Dialysis (D)

Conventional: poorly dialyzable (0 – 5%) [4]

High-flux membranes & CRRT: increase vancomycin clearance & requires dosing replacement [4]

Type of Dialysis	Dosage
Haemodialysis (HD)[4]	Following loading dose of 15-20 mg/kg, given 500 mg to 1000 mg after each dialysis session. Pre dosing based on pre-HD level*: <10 mg/L: administer 1000 mg after HD 10 – 25 mg/L: administer 500-750 mg after HD >25 mg/L: Hold vancomycin *based on clinical judgement
CAPD[9,18]	**Intermittent dose** (once/day): 15 – 30 mg/kg every 5 – 7 days **Continuous dose** (per/L exchange): Loading : 30 mg/kg Maintenance : 25 mg/L OR 1.5 mg/kg/bag
CVVH[4]	Following loading dose of 15 – 20 mg/kg, give 1g every 48 hours
CVVHD / CVVHDF	Following loading dose of 15 – 20 mg/kg, give 1g every 24 hours

INTERACTION

Drug-drug interaction:

Increase effect/toxicity	Vancomycin may increase the concentrations/effects of: aminoglycosides, colisthimethate, gallium nitrate and neuromuscular-blocking agent [4]
Decreased drug concentration/effects	Vancomycin may decrease the concentrations/effects of thyphoid vaccine and BCG vaccine [4]

Drug- disease interaction:

Burn	Increase vancomycin CL, require more frequent dose [1]
Hepatic insufficiency	Reduce degree of vancomycin protein binding (20%), require higher than normal dose (>30 mg/kg/day in adult) [1]
Renal failure	Vancomycin total clearance decrease proportionally to decrease in CrCL[7]
Obesity	Increase vancomycin clearance, Vd dose not changes significantly with obesity and is best dosed with IBW for patient who are >30% overweight [7]

SAMPLING

Time to monitor serum concentration (at steady state):

Monitoring of both trough and peak concentrations is highly recommended as the first step in estimating patient's specific parameters (Ke and Vd) and AUC_{24}.

When to obtain serum vancomycin concentration (after dose initiation or adjustment):

Normal renal function: After 3rd dose or after 4-5 half lives [3, 5, 8]

Impaired renal function: After 24 hours

Intermittent dose:

Trough: just before next dose [4]

Peak: 1 hour after end of infusion [4]

Stat dose (unstable renal function):

Random depending on the serum concentration [4] or trough monitoring [8]

Continuous Infusion:

Take a sample after 12 – 24 hours of starting the continuous infusion then every 1 - 2 days, or daily if the patient has unstable renal function. [16]

MONITORING PARAMETER

i) Culture & sensitivity [7,8]
   a. Organism susceptibility towards vancomycin
   b. Clearance of bacteremia
ii) White blood cell count [4,7]
iii) Renal function [4,7,20]
   a. Serum creatinine incremental by 26.5 mcmol/L (AKI detection)
iv) Albumin concentration [27]
v) Symptomatic improvement [7,8]
   a. Vital signs (Temperature, heart rate, blood pressure)
   b. Hemodynamic stability
   c. GCS and alertness level
vi) Audiogram [4]

ADVERSE DRUG REACTION

Parenteral (4):

>10 % :	1 – 10 % :	<1%
CVS : hypotension accompanied by flushing	CNS : Chills, drug fever	Otoxicity, renal failure, thrombocytopenia, vasculitis
Dermatologic : Red man syndrome	Hematologic : Eosinophilia, reversible neutropenia	-

DILUTION AND ADMINISTRATION

Dilution of drug	Diluent: normal saline or D5W [4]. Reconstitute vials with 20 mL of SWFI for each 1 g of vancomycin (500mg/10mL). The reconstituted solution must be further diluted with at least 100 mL of compatible diluents per 500 mg of vancomycin prior to parenteral administration [4]. Maximum concentration : not to exceed 5 mg/mL[4] For fluid restriction patient, maximum concentration: 10 mg/mL[8] Stability: Reconstituted – room temperature or under refrigeration for 14 days [4] Diluted - under refrigeration for 14 days or at room temperature for 7 days [4]

Drug administration:

Infusion over at least 60 minutes [4,8] or a maximum infusion rates of 10 mg/min, whichever is longer [8]

CALCULATION

Trough & Peak level available [2]

a) $Ke = \frac{\ln Cpost - \ln Cpre}{T - (t2 - t1)}$

b) $t½ = \frac{0.693}{Ke}$

c) $Cmax = Cpost \times e^{ket'}$

d) $Cmin = Cmax \times e^{-KeT}$

e) $Vd = \frac{Dose\ (mg)}{BW \times Cmax(1-e^{-KeT})}$

f) $Expected\ Cmax = \frac{New\ Dose\ (mg)}{Vd \times BW(1-e^{-KeT})}$

g) $Expected\ Cmin = Expected\ Cmax \times e^{-KeT}$

Ke	Elimination rate constant (h-1)
T	Dosing interval (h)
t1	Pre sampling time
t2	Post sampling time
t½	Half life (h)
Cmin	Min conc. (mg/L)
Cmax	Max conc. (mg/L)
t′	Interval between end of infusion and post sampling time
Vd	Volume of distribution (L/kg)
BW	Body weight (kg)

Only trough level available [2]

a) $Cmax = Cmin + \frac{Dose\ (mg)}{V\ (L)}$

b) $Ke = \frac{\ln Cmax - \ln Cmin}{T}$

c) $t½ = \frac{0.693}{Ke}$

d) $New\ dose = \frac{Cmin\ target \times V(L) \times (1-e^{-KeT})}{e^{-KeT}}$

e) $Expected\ Cmax = \frac{S \times F \times New\ dose(mg)}{V(L) \times (1-e^{-KeT})}$

f) $Expected\ Cmin = Expected\ Cmax \times e^{-KeT}$

Cmin	Cpre (mg/L)
Cmax	Max conc. (mg/L)
S	1
F	1
V	(>18 years old) 0.17 (age) + 0.22 (TBW in kg) + 15
V	(< 18 years old) (0.5 – 1) L/kg X BW (kg)
Ke	elimination rate constant (h-1)
T	Dosing interval (h)
t½	half life (h)

Area Under the Curve 24 hours

4 methods:

- $\text{AUC } 24 = (24 \times \text{Cmin}) + \left[(0.5 \times \text{T})(\text{Cmax} - \text{Cmin})\left(\frac{24}{\text{T}}\right)\right](0.33)$

- $\frac{\text{AUC } 24}{\text{MIC}} = \frac{\text{Vancomycin total daily dose}}{\text{Cl (L/hr)} \times \text{MIC (mg/L)}}$

AUC_{24}	mg.h/L
CrCL	mL/min
Dose	Mg
Co	Conc. at start of infusion $Co = Cmax \times e^{Ke\ (t'')}$
t''	Interval between start of infusion and post sampling time
t`	Infusion time
inf	Infusion phase
elim	Elimination phase

Log Method

- $\text{AUC} = \frac{\text{Co} - \text{Cmin}}{\text{Ke}}$

$\text{AUC } 24 = \text{AUC} \times \text{dosing frequency}$

Linear-log / Trapezoidal method

- $\text{AUC(inf)} = \text{t`} \times \frac{\text{Cmin} + \text{Cmax}}{2}$

$\text{AUC(elim)} = \frac{\text{Cmax} - \text{Cmin}}{Ke}$

$\text{AUC } 24 = (\text{AUC}inf + \text{AUC}elim) \times \frac{24}{\text{T}}$

- $\text{New TDD} = \text{Current TDD} \times \frac{\text{AUC desired}}{\text{AUC Calculated}}$

*TDD: Total Daily Dose

RESULT EVALUATION

CONCENTRATION	RESPONSE	CONTRIBUTING FACTOR	RECOMMENDATION
Subtherapeutic	**Poor**	• **Fluid overload** • **Ascites** • **Wrong sampling time** • **Insufficient dose** • **Drug interaction** • **Burn**	➢ **Correct the fluid imbalance (if fluid overload), increase the dose appropriately & resample** ➢ **Repeat another sample for confirmation** ➢ **Increase the dose appropriately & resample** ➢ **Use alternative drug if possible, if unavoidable, increase the dose appropriately & resample** ➢ **Increase the dose appropriately (use conventional dosing) & resample**
	Good		**Continue current dose**
Within normal therapeutic range	**Poor**		**If sampling time is satisfactory & hydration status is fair, increase the dose (not more than max recommended)**
	Good		**Continue current dose**
Potential Toxic/ Toxic	**Toxic effect:** • **Nephro-toxicity** • **Ototoxic-ity** • **Red man syndrome** • **Neutro-penia**	• **Dehydration** • **Over dosage** • **Underlying disease/ factors** • **Renal failure** • **Possible drug interaction**	➢ **Withhold treatment (if necessary), hydrate the patient (if dehydrated) then reduce dose accordingly** ➢ **Withhold treatment then reduce dose accordingly** ➢ **Use alternative drug if possible, if unavoidable, withhold treatment (if necessary) then reduce dose accordingly**

The evaluation of result is a general approach in managing clinical pharmacokinetic cases. Do not evaluate the case based on the result only. Basic pharmacokinetic principles and patient's clinical condition should be considered before making any recommendations.

CASE DISCUSSION

A 19-years old Malay male with a body weight of 70 kg and height of 170 cm was hospitalized for 3rd degree burn with 39% total body surface area (TBSA). Past medical, social and medication histories are unremarkable and he was admitted to Burn ICU due to the burn complications that arisen afterwards.

He was initially started on IV Vancomycin 750 mg BD 4 days later based on the MRSA positive from his blood culture and sensitivity, and deterioration of condition despites of early treatment with IV Piperacillin-Tazobactam 4.5g QID. His serum creatinine was stable at 64 mcmol/L.

1. The first Vancomycin sampling taken on the fourth dose yields such results:

   Pre sampling @ 5.30am: 15.9 mg/L, dose given @ 6am over 1 hour

   Post sampling @ 8am: 29.3 mg/L

a) $\text{Ke} = \frac{\ln \text{Cpost} - \ln \text{Cpre}}{\text{T} - (\text{t2} - \text{t1})}$

$\text{Ke} = \frac{\ln 29.3 - \ln 15.9}{12 - (8 - 5.5)}$

$\text{Ke} = 0.0643\text{hr}^{-1}$

b) $\text{t1/2} = \frac{0.693}{\text{Ke}}$

$\text{t1/2} = 10.78 \text{ hours}$

c) $\text{Cmax} = \text{Cpost} \times e^{\text{ket}'}$

$\text{Cmax} = 29.3 \times e^{(0.0643)(1)}$

$\text{Cmax} = 31.25 \text{ mg/L}$

d) $\text{Cmin} = \text{Cmax} \times e^{-\text{KeT}}$

$\text{Cmin} = 31.25 \times e^{-(0.0643)(12)}$

$\text{Cmin} = 14.44\text{mg/L}$

e) $\text{Co} = \text{Cmax} \times e^{\text{ket}''}$

$\text{Cmax} = 31.25 \times e^{(0.0643)(2)}$

$\text{Cmax} = 35.53 \text{ mg/L}$

f) $\text{Vd} = \frac{\text{Dose (mg)}}{\text{Cmax}(1-e^{-\text{KeT}})}$

$\text{Vd} = \frac{750\ (\text{mg})}{33.32(1-e^{-(0.0643)(12)})}$

$\text{Vd} = 41.86\ \text{L}\ (0.59\ \text{L/kg})$

g) $\text{AUC} = \frac{35.53-14.44}{0.0643}$

$\text{AUC} = 328$

h) $\text{AUC 24} = 328 \text{ x } 2$

$\text{AUC 24} = 656$

Since estimation of Cmin at steady state is within the range and the AUC_{24} achieved the target of 400-600, maintenance of the dose is suggested. Subsequent resampling of pre Vancomycin concentration was suggested to be conducted after five days of the first sampling for monitoring purpose.

2. The second sampling of pre Vancomycin concentration was withdrawn

Pre sampling @ 5.45am: 18.8 mg/L

a) $\text{Cmax} = \text{Cpre} + \frac{\text{Dose (mg)}}{\text{Vd (L)}}$

$\text{Cmax} = 18.8 + \frac{750\text{mg}}{41.86\text{L}}$

$\text{Cmax} = 36.72\ \text{mg/L}$

b) $\text{Ke} = \frac{\ln \text{Cmax} - \ln \text{Cpre}}{\text{T}}$

$\text{Ke} = \frac{\ln 36.72 - \ln 18.8}{12}$

$\text{Ke} = 0.0558\ \text{hr}^{-1}$

c) $\text{t1/2} = \frac{0.693}{\text{Ke}}$

$\text{t1/2} = 12.42\ \text{hours}$