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Vancomycin Clinical Pathway

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CONTRIBUTORS

PREPARATION

Scientific Group

Shahad Raslan

Reviewed by:

Alaa Mously, Wafa Alfahad,
Thamer Almangour, Sahar Almowaina

Supervision

Dr . Abdullah Alkhenizan

Review and Approval

- Council of Corporative Health Insurance
- Professional Council of Physicians
- Saudi Society of Clinical Pharmacy
- Supervision Council of Health Association

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الجمعية السعودية للصيدلة الإكلينيكية

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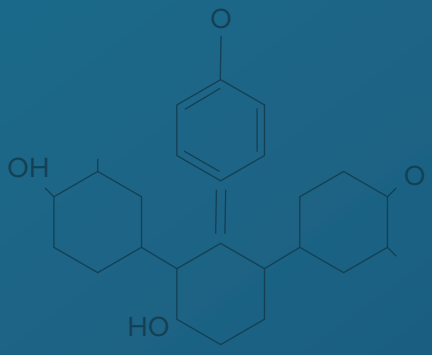
CORRESPONDENCE:

P.O. Box: 94656
Postal Code: 11614
Consolidated Communication Center: 920019393
International Contact Number: 00-966-114179900
Fax: 4800800
PSHA@SCFHS.ORG
Website: www.scfhs.org.sa



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The information included in this document has been adapted and compiled from various international sources and guidelines.

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ABBREVIATIONS

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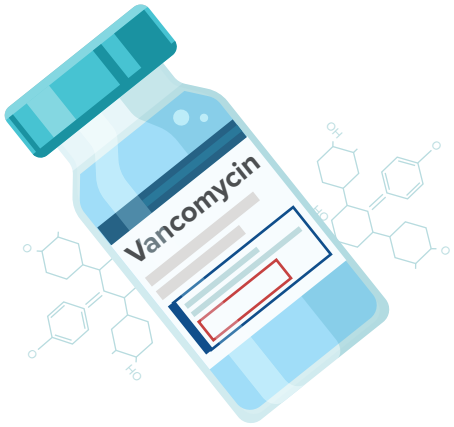
01	**ABW**	Actual body weight
02	**AUC/MIC_{BMD}**	Area under the 24-hour time-concentration curve to minimum inhibitory concentration
03	**BCG**	Bacille Calmette-Guerin
04	**BMI**	Body mass index
05	**CBC**	Complete blood count
06	**CrCl**	Creatinine clearance
07	**CRRT**	Continuous renal replacement therapy
08	**ESRD**	End-stage renal disease
09	**IHD**	Receiving intermittent hemodialysis
10	**MRSA**	Methicillin-resistant *Staphylococcus aureus*
11	**TDM**	Therapeutic drug monitoring

INTRODUCTION



- **Pharmacologic category:**
  Glycopeptide
- **Mechanism of action:**
  Inhibits bacterial cell wall synthesis by blocking glycopeptide polymerization by binding tightly to D-alanyl-D-alanine portion of cell wall precursor
- **Spectrum of coverage:**
  Gram-positive bacteria including diphtheroids, most Enterococcus species, staphylococci "MRSA" and streptococci. When used orally, it covers *Clostridioides difficile*
- **Target audience:**
  Physicians in secondary and tertiary hospitals, clinical pharmacists, nurses
- **Impact of vancomycin therapeutic drug monitoring (TDM):**
  TDM of vancomycin has significantly higher rates of clinical efficacy (OR=2.62, 95%CI 1.34–5.11 P=0.005) and decreased rates of nephrotoxicity, compared to no TDM
- **Side effects:**
  Hypotension, local phlebitis, eosinophilia, neutropenia, reversible ototoxicity, renal failure (limited data suggesting direct relationship), red man syndrome (infusion-related side effect)
- **Monitoring:**
  Periodic renal function tests, CBC, serum trough vancomycin concentrations or area under the 24-hour time-concentration curve to minimum inhibitory concentration (AUC/MIC) determined by broth microdilution
- **Warning and precaution:**
  Avoid concomitant use of vancomycin with BCG (intravesical) and cholera. Live, attenuated cholera vaccine should not be administered during or for at least 14 days after treatment with systemic antibiotics. Combination of vancomycin and aminoglycoside may increase the risk of neurotoxicity and renal dysfunction but may involve synergistic effect. While using vancomycin and colistimethate can increase risk of kidney and inner ear damage

Table I: Cost of Vancomycin

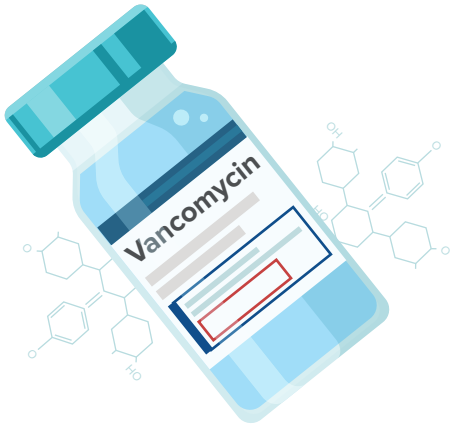
500 mg vial	**18–180 SAR**
1000 mg vial	**58–340 SAR**

The ADAPTE process was used, modified to Five Steps as developed by Kristiansen et al, which include:

1. Planning
2. Initial assessment of the recommendations
3. Modification
4. Publication
5. Evaluation

Multiple workshops were conducted over a one-year duration (2019-2020). The Five Steps adaptation process was selected because of its simple and practical approach. The final document was peer-reviewed and edited accordingly.

1. Loading dose



- Normal kidney function: 25–30 mg/kg (maximum 2500 mg) based on actual body weight (ABW)
- Patients with end-stage renal disease (ESRD) receiving intermittent hemodialysis (IHD) should be administered a one-time LD of 15–25 mg/kg (based on ABW) (maximum 2000 mg)
- Continuous renal replacement therapy (CRRT): 15–25 mg/kg (maximum 2500 mg) based on ABW
- Dosing in special populations:
  - Morbidly obese patients (BMI ≥ 40 kg/m^2): 25–30 mg/kg (maximum 3000 mg) based on ABW
- Can be considered for:
  - ICU patients
  - Clinical instability
  - Documented MRSA infections
  - Meningitis
  - Endocarditis
  - Bacteremia
  - Osteomyelitis
  - Pneumonia
  - When rapid attainment of target serum concentrations is desired

2. Initial maintenance dose

- **Creatinine Clearance by Cockcroft-Gault = (140 - Age[yr]) *Weight[kg] /Serum Creat [mcmol/LCr] *0.85 if female**
- A weight-based maintenance dosing (15–20 mg/kg) with a maximum initial maintenance dose = 2000 mg, based on ABW
- Round all doses to the nearest 250 mg increment

Table II: Suggested Regimen Based on Estimated Creatinine Clearance	
Estimated CrCl (mL/min)	Suggested Regimen
≥ 100	15–20 mg/kg q 8–12 hours
60–99	15–20 mg/kg q 12 hours
40–59	10–15 mg/kg q 12 hours, or 15–20 mg/kg q 24 hours
15–39	10–15 mg/kg q 24 hours, or 15–20 mg/kg q 48 hours
< 15 or acute renal failure (ARF)	15–20 mg/kg (one dose), then re-dose when serum concentration falls below the upper limit of the target trough concentration

- Patient on CRRT
  - 10–15 mg/kg (based on ABW) (maximum 2000 mg) IV every 24 hours
- Peritoneal dialysis: 1000 mg IV every 4–7 days
- Approach for vancomycin dose adjustment for patients on RRT

Table III: Suggested Regimen Based on Estimated Vancomycin Trough Concentration	
Estimated Vancomycin Trough Concentration (mcg/mL)	Suggested Regimen
<15	Increase dose by 250–500 mg
15–25	No change in therapy*
26–35	Decrease dose by 250–500 mg
>35	Hold vancomycin dose
Following dose adjustment, repeat vancomycin serum concentration prior to the third dialysis session (IHD), with subsequent adjustment (if necessary) according to the principles above *** Rechecked weekly**	

- In patients having severe infections with *S. aureus* (MRSA), the preferred approach is AUC-guided dosing involving the use of an AUC calculator (Bayesian or non-Bayesian), together with an individual patient's vancomycin concentrations, to calculate an individualized dosing regimen that is often performed by pharmacist.
  - This approach requires the hospital or health care system to:
    - Purchase software
    - Provide training for the pharmacist
    - Ensure adequate staffing to make daily dose adjustment for individual patient
- The second approach relies on the collection of 2 concentrations (obtained peak concentration at 1–2 hours after infusion and trough at end of dosing interval) preferably during the same dosing interval (if possible) and utilizing first-order PK equations to estimate the AUC.
- Dosing in special populations?
  - Morbidly obese patients (BMI ≥ 40 kg/m^2):
    - First dose: 10–12.5 mg/kg (maximum dose 2000 mg) based on ABW q 12 hours
    - Subsequent dosing based on serum concentration
  - For patients aged 50–89 years, the initial interval should not be more than every 12 hours
  - For patients aged ≥ 90 years, the initial interval should not be more than every 24 hours
  - Every 8 hour dosing can be considered for treatment of complicated infections in:
    - Patients with acute burn
    - Age ≤ 30 years and CrCl > 80 mL/min since rapid accumulation may occur with q 8 hours interval
    - Pregnancy
    - Cystic fibrosis
- Administration: administered over a period of at least 1 hour (1.5–2 hours), maximum concentration of the dilution: 5 mg/mL

Therapeutic Monitoring

- Serum concentration monitoring:
  - Serum vancomycin trough concentrations are recommended
  - Trough concentrations are the most accurate and practical method for monitoring efficacy
  - Troughs should be drawn at steady-state conditions (~24–30 hours after the initiation of therapy in patients with normal renal function), approximately by the 4th dose
  - Trough concentrations should ideally be obtained immediately prior to the administered dose (30 min)
- Serum trough concentrations may be drawn earlier in the course of therapy (e.g., prior to the 2nd or 3rd dose) to serve as an early marker for sub-therapeutic or excessive serum concentrations (with the understanding that trough concentrations will be rising without a change in the dosing regimen)
- Once trough concentration is within therapeutic range, repeat trough at least every 5–7 days and more frequently in patients with unstable renal function or hemodynamic status, lack of response to antimicrobial therapy, clinical deterioration, extremes of age and body weight, and those receiving aggressive diuresis or concomitant nephrotoxins
- Subsequent serum concentrations may be drawn every 24–48 hours based on the patient's clinical status and changes (improvement or decline) in renal function. If patient received q 48 interval, serum trough level should be drawn pre-second dose

Table IV: Optimal Serum Trough Concentrations	
Indication	Goal Serum Trough Concentration*
1. Uncomplicated (SSTI)	10–15 mcg/mL
2. Urinary tract infections	
3. Endocarditis infected with *Streptococcus gallolyticus* (bovis)	
All other indications †	15–20 mcg/mL

** Trough concentrations should be maintained above 10 mcg/mL to avoid the development of resistance.*

† Including, but not limited to

Bacteremia	Meningitis/CNS infections
Febrile neutropenia	Infections involving prosthetic material
Endocarditis	Abscesses
Osteomyelitis	Other endovascular infections
Pneumonia	Severe skin and soft tissue infection (SSTI) (e.g., necrotizing fasciitis)

For severe infections with *S. aureus* (MRSA) the optimal approach for monitoring is:

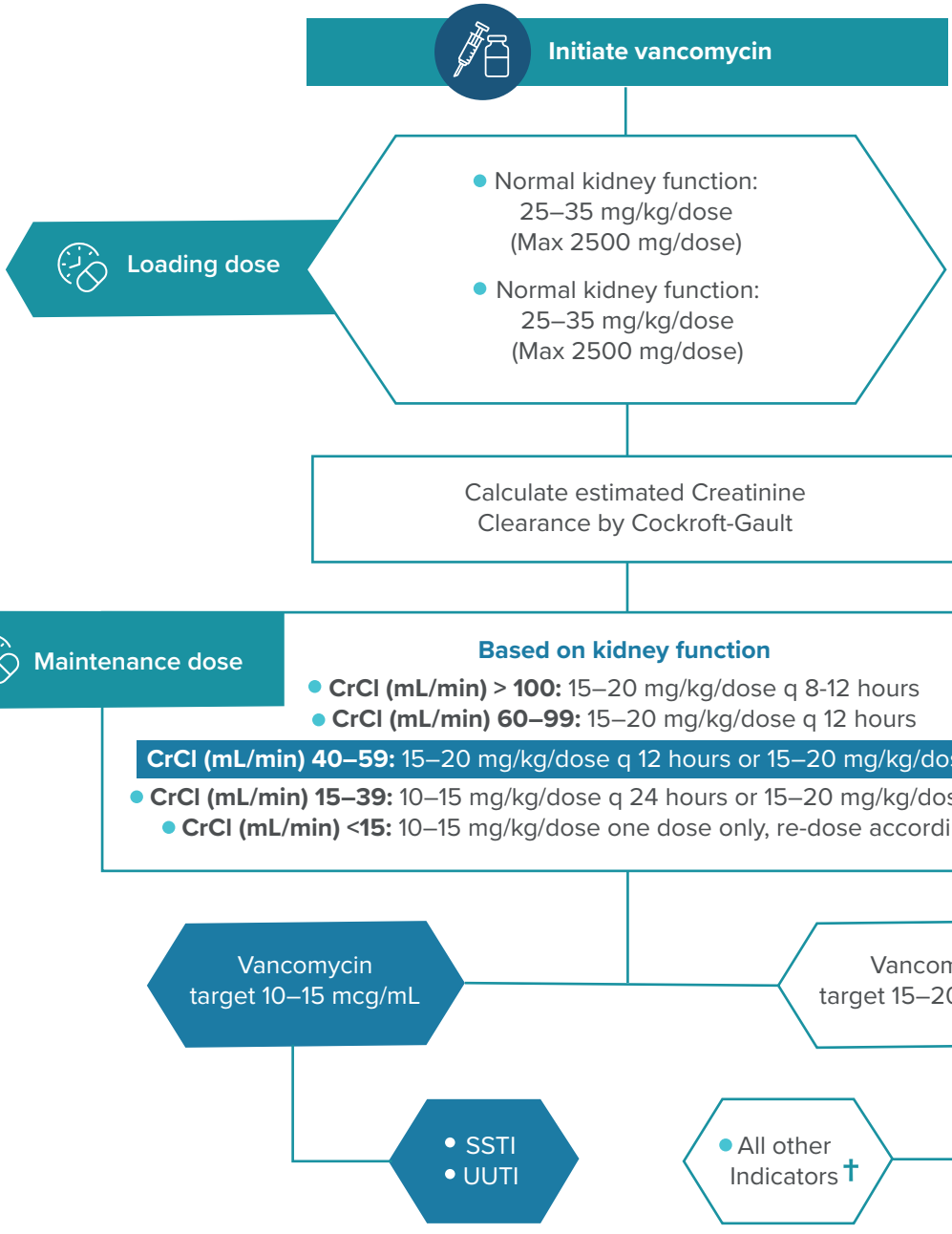
- Best predicted by area under the 24-hour time-concentration curve to minimum inhibitory concentration determined by broth microdilution (AUC/MIC_{BMD})
- Optimal pharmacokinetic/pharmacodynamic efficacy based on available data target is considered to be an AUC/MIC ratio of 400 to 600 mg * hour/L, (assuming vancomycin MIC_{BMD} of 1 mcg/mL)
  - When the MIC_{BMD} is > 1 mg/L, decision to change therapy should be based on clinical judgment
  - When MIC_{BMD} < 1 mg/L, decreasing the dose is not recommended
- Does not require steady-state serum vancomycin concentrations

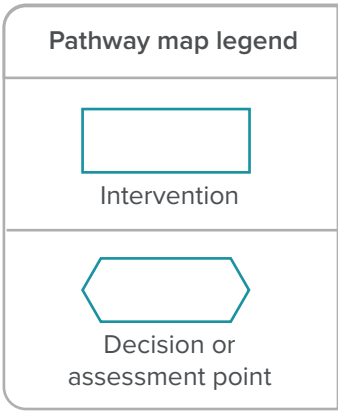
Case 1

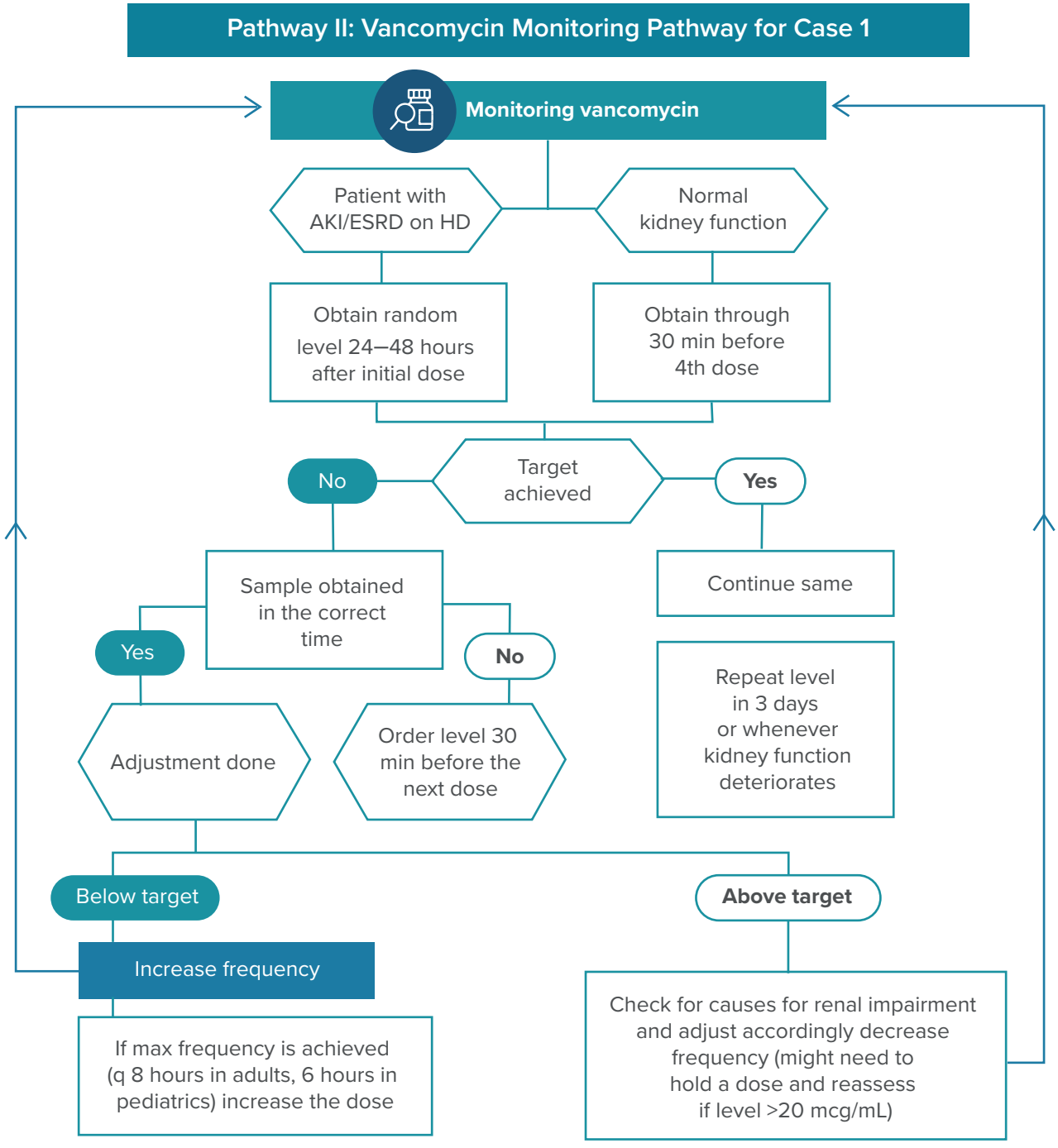
A 45-year-old female 65 kg diagnosed with SSTI, patient received vancomycin 1000 mg intravenously every 24 hours and has a trough concentration, obtained 30 min before the 4th dose, of 6 mg/L. How should you adjust the patient's vancomycin regimen?

Weight 65 kg, CrCl 45 mL/min, culture pending

Pathway I: Vancomycin Regimen Pathway for Case 1







Answer:

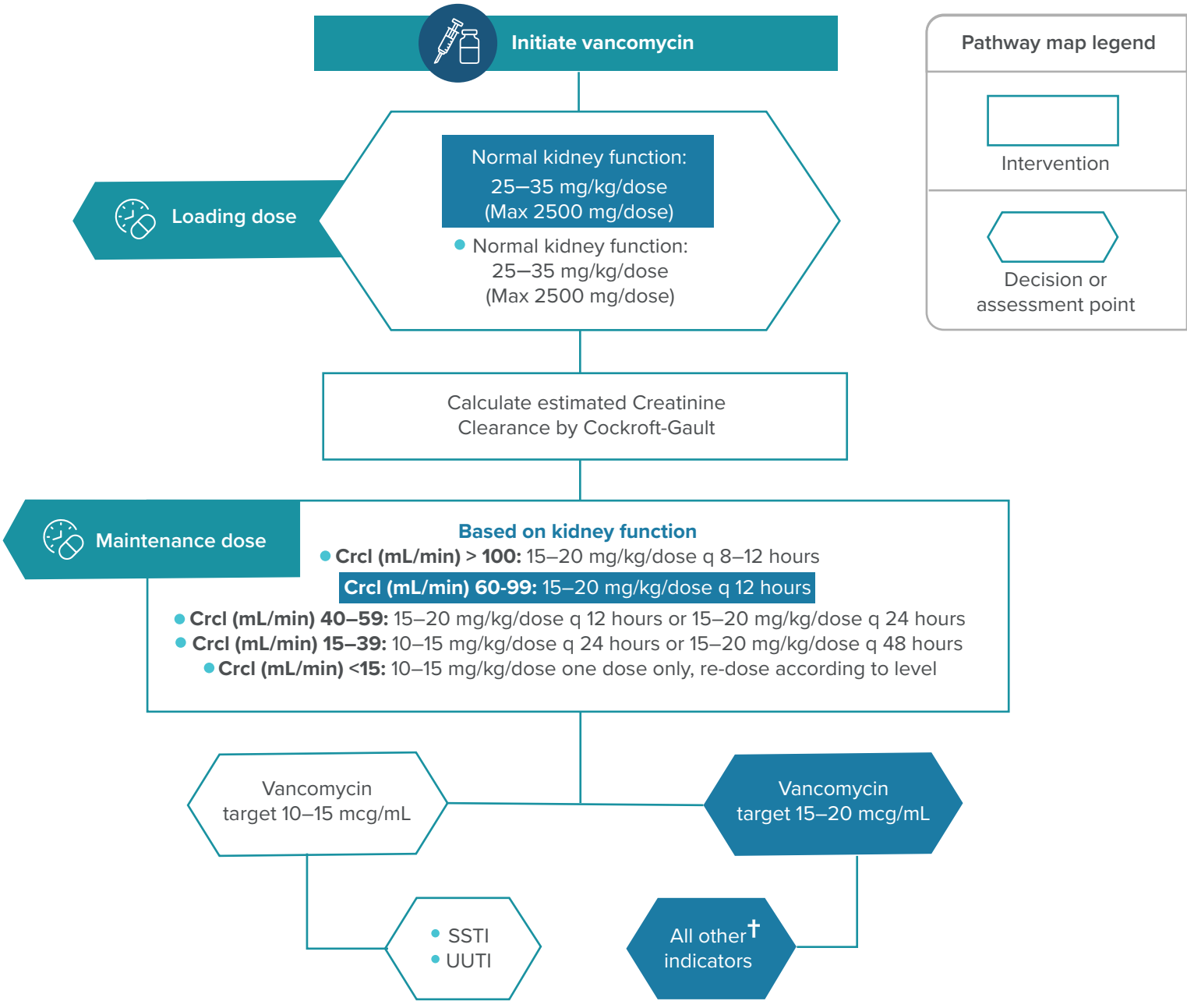
1. No need for loading dose
2. Based on CrCl patient should be on 10–15 mg/kg q 24 hours
3. Since patient has skin and soft tissue infection then goal is goal trough concentration is 10–15 mg/L
4. Since target cannot be reached and level was collected correctly then the frequency must be changed to q 12 hours and the level should be repeated 30 min before the 4th dose and adjusted accordingly

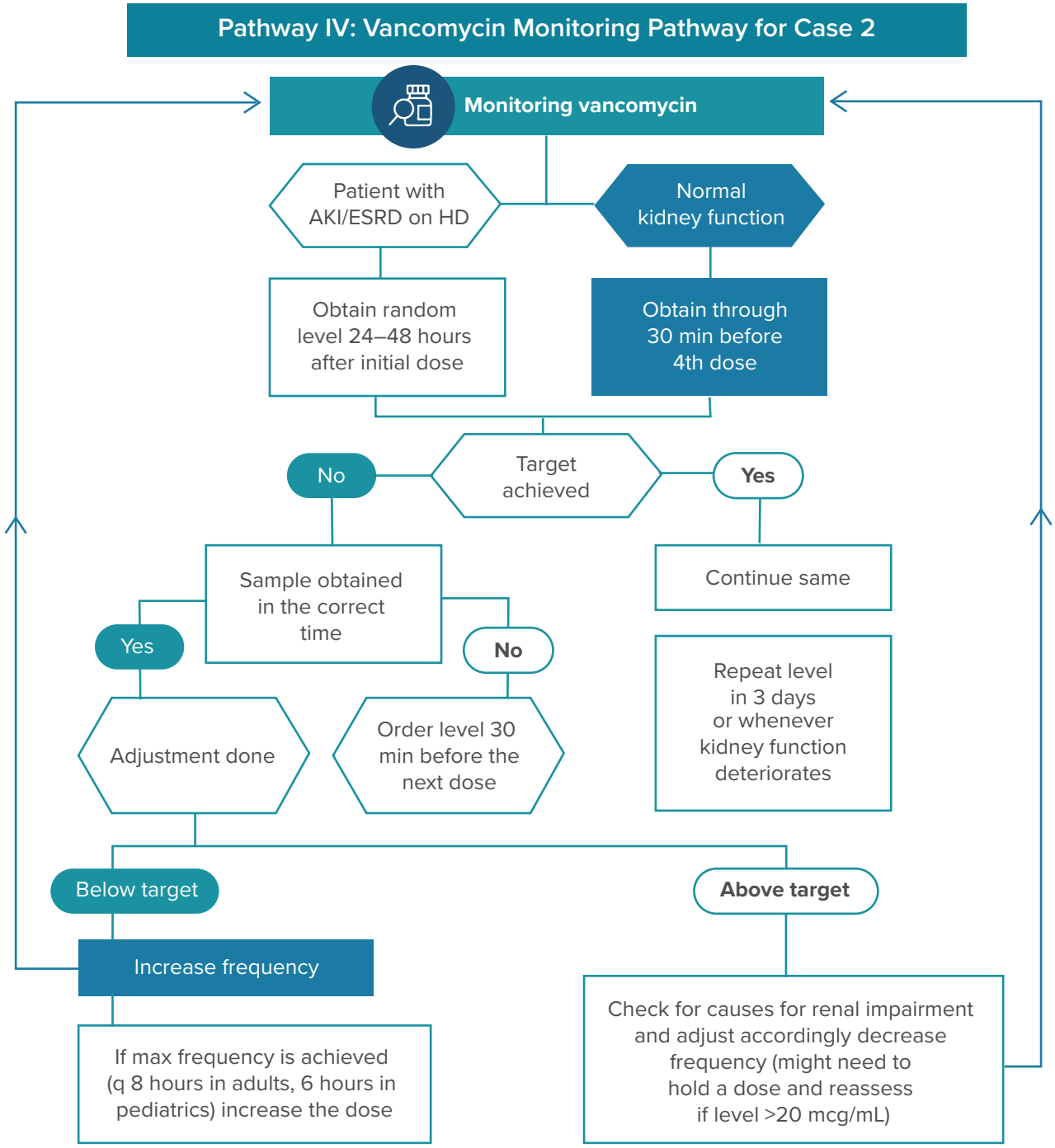
Case 2

An 23 year-old male k/c of end-stage liver disease day 3 post liver transplant developed sepsis while in the ICU, the team wants to start vancomycin empirically. What's the best regimen for this patient? When should a trough level be obtained?

Weight 45 kg, SrCr 87 mcmol/L, culture pending

Pathway III: Vancomycin Regimen Pathway for Case 2





Answer:

1. Loading dose is needed since patient is clinically unstable, in the ICU and rapid attainment of target serum concentration is needed (25 mg/kg = 1125 mg ~ 1000 mg)
2. Calculated CrCl for this patient is 74 mL/min
3. Based on CrCl patient should be on 10–15 mg/kg q 12 hours
4. Since patient has sepsis, the goal trough concentration is 15–20 mg/L
5. Level should be obtained 30 min before the 4th dose and adjusted accordingly

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