PEDIATRIC CLINICAL CARE GUIDELINES

Alberta Children's Hospital

Alberta Health Services

GUIDE FOR PICU STAFF: THINGS TO KNOW ABOUT VANCO(MYCIN)

KEY MESSAGES

- Ensure Vancomycin is truly indicated for patient/presentation.
- Ensure appropriate dosing schedule (Q6H, Q8h, Q12H or intermittent dosing with levels) based on presentation, concern for MRSA/resistant organism and renal function.

WHEN SHOULD I CHECK A LEVEL OR CONSIDER CHECKING A LEVEL SOONER?

- Pre 5th dose in a well perfused child with no renal dysfunction (rarely the PICU patient).
- Pre 3rd dose and Pre 5th dose in hemodynamically unstable or major changes in volume of distribution (i.e. very negative fluid balance or aggressive diuresis).
- Pre every dose in AKI (and give dose based on level)

WHEN SHOULD I HOLD VANCOMYCIN DOSE UNTIL THE LEVEL IS REPORTED?

- Patients with known AKI (new-onset or pre-existing)
- receiving renal replacement therapy
- with recent previously supra-therapeutic levels (i.e.:>20 mg/L)
- with diminished (i.e. <0.5 cc/kg/hr) or no urine output
- presenting with altered fluid status (i.e.: dehydration or fluid overload)
- with hemodynamic compromise (heart failure or receiving inotropes/vasopressors)
- recent BMT with concerns around renal function
- receiving concurrent furosemide, acyclovir, cyclosporine or piperacillin-tazobactam*

*Please consult PICU clinical pharmacist for clarification which medications are nephrotoxic

WHEN SHOULD I NOT HOLD VANCOMYCIN DOSE UNTIL THE LEVEL IS REPORTED?

- If renal function normal (i.e.: within normal limits and no changes from baseline S_{Cr}) with normal urine output and no expected major changes in volume of distribution, draw level ONE hour prior to dose and DO NOT hold the dose.

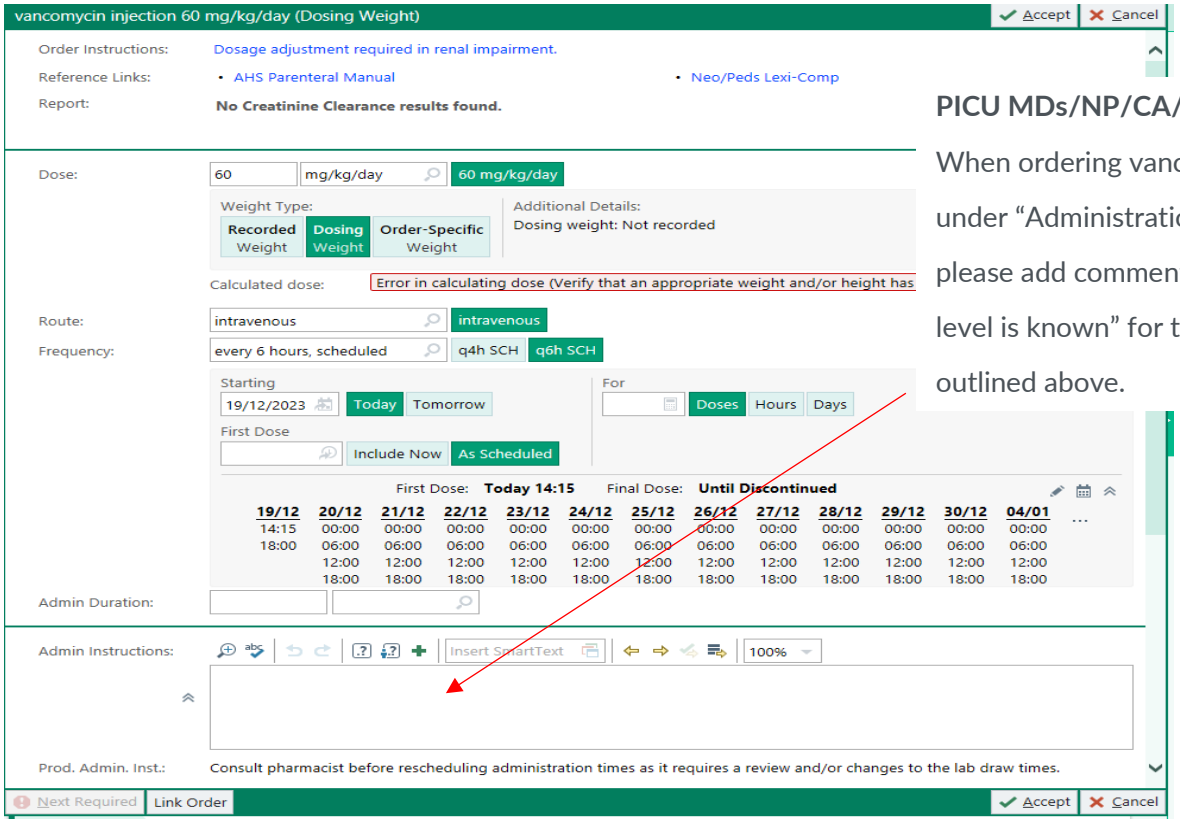
I HAVE A PATIENT WITH AKI, HOW SHOULD I MONITOR THEM?

- Trough levels ideally should be done prior to each dose until therapeutic steady state is attained (i.e. 4 or more doses at target concentration)
- If ++concerning abnormal renal function, order one dose of vancomycin only (consider dose adjusting to 10mg/kg), order level 8-12 hours after dose given and order next doses of vancomycin only after level is known

FOR PICU RNs

If abnormal renal function (elevated urea and creatinine), concerns around renal function (multiple nephrotoxic medications such as lasix, acyclovir, piptazocin or cyclosporine), previously high vancomycin level (greater than 20), or prolonged vancomycin course with changes in fluid balance + use of diuretics + concerns about renal dysfunction please draw level STAT **ONE hour prior to dose and hold dose until level reviewed. (RN please page resident/PICU MD once level is available).**

For PICU MDs/NPs/Residents:



PICU MDs/NP/CA/Resident

When ordering vancomycin dosing under "Administration Instructions" please add comment "hold dose until level is known" for the circumstances outlined above.

Vancomycin is a glycopeptide antibiotic primarily used to treat Gram-positive infections caused by methicillin resistant staphylococci (MRSA), coagulase-negative staphylococci (CONS) and ampicillin-resistant enterococci, as well as against (Cl)oxacillin-sensitive or penicillin-sensitive Gram-positive organisms in patients allergic to penicillin[1]. Vancomycin exerts its bactericidal effect in the bacterial cell wall by inhibiting the polymerization of peptidoglycans weakening bacterial cell walls and ultimately causes leakage of intracellular components, resulting in bacterial cell death.
The minimum concentration of drug needed to inhibit bacterial growth is called the minimum inhibitory concentration (MIC) and is the parameter used to describe antibiotic activity of vancomycin against a

pathogen. Area under the curve (AUC) is a term used to describe the total drug exposure across a specific period of time. Area under the concentration curve (AUC) divided by the MIC (AUC/MIC) is the best predictor of the activity of vancomycin. An AUC/MIC value of ≥400 is associated with a successful outcome, whereas an AUC/MIC value of <400 is associated with a lower eradication rate and a higher mortality rate of gram positive infection[2]. A study of children treated with vancomycin for invasive Methicillin-Resistant Staphylococcus Aureus (MRSA) infections found a trough vancomycin level of 7-10 mg/L predicted achievement of AUC/MIC >400 in >90% of children[5]. Consensus guidelines on vancomycin therapeutic drug monitoring, published in 2009, suggest a serum trough concentration range of 15 to 20 mg/L as a surrogate goal for an AUC/MIC ≥400 in patients with moderate to severe *S aureus* infections[3]. For moderate – severe infections (including CNS & MRSA) the desired target trough level is 15-20 mg/L[5]. For all other infections 10-20 mg/L is the desired trough level[3].

Vancomycin serum trough concentrations are serum vancomycin levels drawn 30-60 minutes before the next scheduled dose, are considered the most practical method for monitoring efficacy when the pathogen is susceptible. A trough level is reflective of how much vancomycin is in the blood (central compartment) of the patient at the lowest point in the dosing interval and is reported as concentration in mg/L. This trough level is dependent on 3 variables: time prior next dose (i.e. lowest concentration in the body), how much vancomycin (mg) is in the central compartment and how much volume is in this central compartment (L)[4]. This central compartment can be impacted by the multiple variables within the PICU setting including dehydration/fluid-overload and placement of chest tubes in complicated pneumonias to name a few.

In the PICU setting levels are frequently ordered pre-3rd dose and pre-5th dose of the dosing regimen. Simply put, the pre-3rd level is a "Safety Check" or non-steady state level to ensure the patient is not at toxic levels. Typically, dose adjustments are not made on this level unless it reported above therapeutic target (i.e.: ≥ 15 mg/L) which can necessitate reducing vancomycin dose or holding therapy. Pre-3rd levels are typically ordered in most PICU patients due to changes in renal status or fluid status that can impact vancomycin.

Pre-5th levels or steady-state levels are when vancomycin has reached "equilibrium" with the body granted there are no dosing, renal or fluid status changes. These levels can be used for safe therapeutic dose adjustment. Pre-3rd and 5th levels should be done ideally with each vancomycin dose change. Once therapeutic target has been attained, consider re-checking steady-state trough levels every 48 hours unless renal or fluid status changes occur then a level should be drawn earlier.

Vancomycin is primarily cleared by the kidney via glomerular filtration[6]. Vancomycin clearance correlates well with creatinine clearance with 80%–90% recovered unchanged in urine within 24 h after administration of a single dose[2]. The elimination half-life of vancomycin is significantly prolonged in patients with renal dysfunction. Additionally, vancomycin use has been associated with drug-induced acute kidney injury (AKI) but the exact mechanism of vancomycin-induced renal damage is still unknown, but it is postulated that proximal renal tubular cell necrosis occurs by vancomycin accumulation causing oxidative stress[6-7]. Oxidative stress is an imbalance between free radicals and antioxidants within cells that leads to mitochondrial dysfunction and cellular apoptosis[7]. It has been previously reported 23.4% of patients admitted to ACH PICU receiving vancomycin have developed AKI[6]. Concomitant use of furosemide with vancomycin was associated with AKI (adjusted OR: 3.52; 95% CI: 1.88-6.62)[6]. Additionally, there is recent literature suggesting concurrent vancomycin and piperacillin-tazobactam administration can precipitate AKI[8].

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