IREDELL HEALTH SYSTEM

Pediatric Pharmacokinetic Dosing Protocol	
Approved by: Dr. Katie Harknett, Pediatrician Diane Hamby, Director of 3N Laura Rollings, PharmD, BCPS, BCGP	Last Revised/Reviewed Date: N/A
Antimicrobial Stewardship Committee Department of Pediatrics P&T Committee	Date: 10/2021 Date: 03/2022 Date: 04/2022

Purpose:
To assure consistent and optimal dosing and monitoring of vancomycin and aminoglycosides, clinical staff pharmacists will provide a pharmacokinetic (PK) service for pediatrics including neonates.

Policy:
The Pediatric Pharmacokinetic Dosing Protocol will be initiated when the provider orders "Vancomycin - Pharmacy to Dose" or an equivalent order. It will also apply when the provider orders "Aminoglycoside – Pharmacy to Dose," "Gentamicin – Pharmacy to Dose" or an equivalent order. This order will initiate the ordering and monitoring of specified agent by pharmacists according to the following protocol. Pre-admission emergency department patients and those receiving vancomycin or aminoglycosides for surgical prophylaxis will not be included in this protocol.

Definitions:
Neonatal patient: a patient less than 28 days old
Pediatric patient: a patient greater than or equal to 28 days old

Procedures:

I. Processing New Orders - A "Vancomycin/Aminoglycoside-Pharmacy to Dose" order or "Gentamicin – Pharmacy to Dose" will be linked to the respective order for patients starting vancomycin or an aminoglycoside for which therapy is planned to continue.

1. The verifying pharmacist will review and verify the order and initiate an appropriate initial dosing regimen. Orders for doses and monitoring will be provided by a pharmacist prior to the next dose due.
2. Any order stating "pharmacy to dose" or "consult pharmacy" in regards to vancomycin/aminoglycoside orders will be interpreted as full dosing privileges as stated within this protocol.
3. Providers do have the option of opting out of the pharmacy to dose protocol by not ordering it as so, discontinuing the order or notifying the pharmacist who will then discontinue the order.

II. Patient Assessment/Data Collection/Monitoring

1. Upon receiving a new "Pharmacy to Dose" order, the pharmacist will review the appropriateness of the indication and dose the antibiotic as per protocol with consideration in the patient's specific information:
    a. Clinical Indication
    b. Age/Sex
    c. Height/Weight
    d. Renal function
    e. Estimated PK parameters
    f. Current or last known serum drug concentration

2. Routine monitoring will include the evaluation of clinical status, interpretation of relevant labs, drug concentrations, changes in renal function or fluid status, microbiology results, concurrent antimicrobial therapy as well as length of therapy. This information will all be recorded in an electronic pharmacy service on a daily basis.
3. The pharmacist will be expected to provide dosing and monitoring services until therapy is completed, discontinued or the patient is discharged.

III. Pharmacist Ordering

1. Doses - Upon selecting a dosing regimen, the pharmacist will enter applicable orders. All orders in response to "Pharmacy to Dose" will be entered or discontinued "per protocol-no cosign required."
2. Serum Drug Concentrations - The pharmacist will order serum drug concentrations for the drug as necessary "per protocol-no cosign required."
3. Labs - The pharmacist will ensure that relevant labs are ordered, collected, resulted, and recorded in an electronic pharmacy service. The pharmacist will ensure the relevant labs are utilized in the evaluation of appropriate dosing. Any labs ordered will be entered as "per protocol-no cosign required." Serum creatinine (SCr) and BUN will be ordered with each serum drug concentration and more frequently, if needed. The pharmacist will follow up on any labs not resulted in a timely manner. If not resulted by end of shift, the pharmacist will complete a handoff to the next shift pharmacist for follow-up.

IV. Documentation

1. Pharmacist will document in the patient's electronic medical record a progress note with initial dose, each resulting drug concentration values and any dose change.
2. Pharmacist will document in an electronic pharmacy service on a daily basis each monitoring task for that day.

V. Competency Standard - A pharmacy-based PK competency is required upon hire of all pharmacists participating in the PK protocol. Progress will be assessed annually as part of the annual performance review.

Procedure for *Vancomycin* Dosing and Monitoring

I. Initial Empiric Dosing

1. Initial vancomycin dosing will be based on the patient's age, weight, renal function, site of infection and other clinical indicators and diagnoses. The preferred dosing weight for vancomycin is based on total body weight. For obese patients (total body weight >125% ideal body weight), the adjusted body weight is preferred. (See **Appendix A**)
2. Estimates of creatinine clearance should be based on the Schwartz or Modified Schwartz equation instead of relying on estimates calculated through the electronic medical record:

$$CrCl\ (mL/min/1.73m^2) = K \times L/SCr$$

L = height or length (in cm)
SCr = serum creatinine concentration (mg/dL)
K = constant proportionality that is age specific (**Table 1**)

Table 1. Proportionality Constant (K) for Schwartz Equation

Age	K
Pre-term infants up to 1 year	0.33
Full-term infants up to 1 year	0.45
2 – 12 years	0.55
13 – 21 years female	0.55
13 – 21 years male	0.7

1 – 16 years with chronic kidney disease (Modified/Bedside)	0.413

3. For *pediatric* patients, initial Vancomycin dosing is based on age, weight, and type of infection assuming normal renal function of CrCl > 60 mL/min/1.73m^2. (**Table 2**).
    i. For children 2 – 12 years old, q6h may be required to achieve target levels.
    ii. For patients with significant renal dysfunction (SCr > 2, SCr > 1.5x baseline, increase of SCr by 0.3 mg/dL within 48 hours, anuria, or a history of nephrotoxicity with vancomycin or other agents), doses of 15 – 20 mg/kg once followed by spot level(s) to estimate vancomycin clearance is recommended.

Table 2. *Pediatric* Empiric *Vancomycin* Dosing Recommendations

Age	Empiric Therapy (uncomplicated)	Empiric Therapy (severe infections; e.g. sepsis, CNS, osteomyelitis, endocarditis, etc)
45 weeks CGA to Adolescents (12 years)	20 mg/kg/dose IV q8h Usual MAX Starting Dose: 1.25 grams IV q8h	20 mg/kg/dose IV q6-8h Usual MAX Starting Dose: 1.5 grams/dose OR 4 grams/day
Adolescents (13-18 years)	20 mg/kg/dose IV q8h Usual MAX Starting Dose: 1.25 grams IV q8h	20 mg/kg/dose IV q8h Usual MAX Starting Dose: 4 grams/day

CGA = corrected gestational age

II. Administration - All vancomycin infusions should be run over at least 60 minutes. Patients receiving >20 mg/kg of vancomycin, doses >1 gram, or those with history of Red Man's Syndrome should adjust the rate accordingly (e.g., approximately 90 – 120 minutes)

III. Therapeutic Monitoring

1. Goal trough concentrations (**Table 3**) are based on indication and patient status.

Table 3. *Vancomycin* Goal Trough Concentration Based on Indication

Indication	Target Trough Concentrations (mcg/mL)
Bacteremia (uncomplicated) Febrile neutropenia Line infection (clinically stable) Skin and soft tissue infections Urinary tract infections	10 – 15
Bacteremia (complicated, ill-appearing, severe; MRSA) Endocarditis Intra-abdominal infections/abscess Meningitis Pneumonia Osteomyelitis & join infections Sepsis (empiric) Severe SSTI	15 - 20

2. Trough concentrations should be drawn (30 minutes of next dose) at steady state (4th or 5th dose) in patients likely to receive vancomycin beyond 48 hours
3. Frequency of trough concentrations:
    i. If a patient has achieved a goal trough concentration at steady state and renal function is stable, vancomycin concentrations will be ordered at least every 5 days and renal function labs will be ordered at a minimum of every 3 days
    ii. If renal function is unstable, consider checking trough levels more frequently.
    iii. In circumstances of acute renal failure or concern for sub-/supra- therapeutic regimen, random concentrations may be utilized to determine the vancomycin concentration and determine when to re-dose.

IV. Vancomycin Dosing Adjustments

1. Before adjusting doses, verify that the vancomycin concentration was drawn appropriately and that recent doses have not been missed.
2. Refer to **Appendix A** for recommended vancomycin adjustment calculations.

Procedure for A*minoglycoside* Dosing and Monitoring

I. Initial Empiric Dosing

1. Initial aminoglycoside dosing in both neonatal and pediatric patients will be based on the patient's weight, site of infection, and other clinical indicators and diagnoses.
    a. The pharmacist must confirm the dosing strategy.
    b. The preferred dosing weight for aminoglycosides is based on how their total body weight (TBW) compares to their ideal body weight:
        1. For **underweight** patients (TBW < IBW) – use the TBW
        2. For **normal weight** patients (TBW = 100 -125% IBW) – use the IBW
        3. For **obese** patients (TBW > 125% IBW) – use the adjusted body weight
2. For patients with significant renal dysfunction (SCr > 2, SCr > 1.5x baseline, increase of SCr by 0.3 mg/dL within 48 hours, anuria, or a history of nephrotoxicity with aminoglycosides or other agents), a one-time dose may be indicated followed by a random level if subsequent doses are intended.
3. For *neonatal* patients, initial aminoglycoside dosing is based on agent, gestational age, chronological age, clinical status and indication (**Table 4**).

Table 4. *Neonatal* Empiric Aminoglycoside Dosing Recommendations

Agent	Gestational Age	Chronological age	Initial Dose	Interval
Gentamicin & Tobramycin	≤ 30 weeks	≤ 14 days	5 mg/kg/dose	Q48h
		≥ 15 days	5 mg/kg/dose	Q36h
	30 to 34 weeks	≤ 10 days	5 mg/kg/dose	Q36h
		≥ 11 days	5 mg/kg/dose	Q24h
	≥ 35 weeks	≤ 7 days	4 mg/kg/dose	Q24h
		≥ 8 days	5 mg/kg/dose	Q24h
Amikacin	< 30 weeks	≤ 14 days	15 mg/kg/dose	Q48h
		≥ 15 days	15 mg/kg/dose	Q24h
	30 to 34 weeks	≤ 60 days	15 mg/kg/dose	Q24h
	≥ 35 weeks	≤ 7 days	15 mg/kg/dose	Q24h
		≥ 8 days	17.5 mg/kg/dose	Q24h

4. For *pediatric* patients (e.g., greater than 3 months), initial aminoglycoside dosing is based on agent, age, clinical status and indication (**Table 5**).

Table 5. *Pediatric* Empiric Aminoglycoside Dosing Recommendations

Agent	Traditional Dosing
Gentamicin & Tobramycin	6 – 7.5 mg/kg/day divided Q8h
Amikacin	15 – 20 mg/kg/day divided Q8h

II. Therapeutic Monitoring

1. Goal peak and trough concentrations (**Table 6**) are based on indication and patient status. Patients who are presenting with severe infections should aim for higher concentrations in the outlined ranges.

Table 6. Aminoglycoside Goal Peak and Trough Concentrations Based on Agent Indication

Indication	Gentamicin & Tobramycin		Amikacin	
	Goal Peaks	**Goal Troughs**	**Goal Peaks**	**Goal Troughs**
Mild to Moderate Infections	Traditional: 6 – 8 mcg/mL	Traditional: 0.5 – 1.5 mcg/mL	Traditional: 20 – 30 mcg/mL	Traditional: 2 – 5 mcg/mL
Serious or Life Threatening Infections	Traditional: 8 – 12 mcg/mL	Traditional: 0.5 – 1.5 mcg/mL	Traditional: 25 – 40 mcg/mL	Traditional: 4 – 8 mcg/mL

2. Clinical situations to obtain serum concentrations:
    a. Patients on traditional therapy likely to receive aminoglycosides beyond 48 hours
    b. Patients with rapidly changing renal function or clinical status
    c. Concomitant nephrotoxic medications
    d. Patients with altered or variable volume of distribution
3. For traditional dosing:
    a. Trough concentrations should be drawn 30 minutes prior to the 3rd or 4th dose.
    b. Peak concentrations should be drawn 30 minutes after the end of the infusion.
4. Frequency of concentrations:
    a. If the patient has achieved goal concentrations at steady state and renal function is stable, aminoglycoside concentrations should be ordered at least every 5 days and renal function labs should be ordered at a minimum of every 3 days, if feasible.
    b. If renal function is unstable, consider checking levels more frequently.
    c. In the setting of acute renal failure or concern for sub- or supra-therapeutic concentrations, random concentrations may be utilized to determine aminoglycoside concentration and when to re-dose and schedule the interval.

III. Aminoglycoside Dose Adjustments

1. Before adjusting doses, verify that the aminoglycoside concentrations were drawn appropriately and that recent doses have not been missed.
2. Refer to **Appendix A** for aminoglycoside pharmacokinetic calculations that can be used to determine new dose and/or frequencies to achieve target concentrations.

Appendix A. Equations

Ideal Body Weight	Males: IBW (kg) = 50 + 2.3(# inches over 5 feet) Females: IBW (kg) = 45 + 2.3(# inches over 5 feet)	
Adjusted BodyWeight	ABW = IBW + 0.4(TBW-LBW)	
Creatinine Clearance	CrCL (mL/min/1.73m^2) = K x L / SCr L = length or height (in cm) SCr = serum creatinine concentration (in mg/dL) K = constant of proportionality that is age-specific (see **Table 1**)	
Two-Point Kinetic Equations		
ke	$ke = \frac{[\ln (C_1 / C_2)]}{T - t'}$	
t½	$t_{½} = 0.693/ke$	
Cp30	$Cp30 = \frac{C1}{e^{-ket}}$	t = time from level drawn (including 30 min after completion of the infusion)
Extrapolated Concentration (trough,etc.)	$C_p = C1e^{-ket}$	t = time difference between the level collection and the point to be estimated
Vd	Vd = Dose (mg) / Cmax (mg/L)	
Multiple-Dose Kinetic Equations		
Estimated NewCmax & Cmin	$Cmax = \frac{(Xo)(1 - e^{-ke\ t'})}{(t')(ke)(Vd)(1 - e^{-ke\ T})}$ $Cmin = Cmax\ [e^{-ke\ (T - t')}]$	Xo = drug dose (mg) t' = infusion time (hr) T = dosing interval (hr)
New Dosing Interval (T)	$T = \ln \frac{\{Cmax(desired)\ \ Cmin(desired)\}}{ke} + t'$	t' = infusion time
New Dose (Xo)	$Xo = \frac{(Ke)(t')(Vd)\{Cmax(desired)\}\ (1 - e^{-ke\ T})}{(1 - e^{-ke\ t'})}$	