Renal Function-Based Dose Adjustments - Adult - Inpatient/Ambulatory

Consensus Care Model

Population/Problem:
This document describes renal function evaluation in adults who are receiving medications that require dose adjustment to maximize outcomes and prevent toxicity. This includes patients receiving intermittent hemodialysis or peritoneal dialysis. Excluded populations are those with cystic fibrosis and those receiving extracorporeal continuous renal replacement therapy modalities [(e.g. continuous venovenous hemofiltration (CVVH), continuous venovenous hemodialysis (CVVHD), continuous venovenous hemodiafiltration (CVVHDF), slow-continuous ultrafiltration (SCUF), sustained low-efficiency dialysis (SLED), or extended daily dialysis (EDD)]. Renal function evaluation in adults is intended to facilitate renal dosing modifications that maximize outcomes by establishing and maintaining therapeutic drug concentrations while minimizing toxicity that may result from excessive accumulation of the drug or its metabolites. Renal dosing modifications further simplify and lengthen dosing intervals as appropriate to minimize errors and optimize medication use.

Intended Users:
Physicians, Advanced Practice Providers, Pharmacists, Nurses

Definitions:

1. **Abbreviations**
   - $AdjBW$ = Adjusted body weight in kilograms (as indicated)[1] = $\left[0.4 \times \left(TBW(kg) - IBW(kg)\right)\right] + IBW(kg)$
   - age = Age in years
   - BMI = Body Mass Index[2] = $\frac{TBW}{[Ht(m)]^2}$
   - Ht = Height of the patient; see the unit in parentheticals to follow
   - IBW = Ideal Body Weight
     - Ideal body weight (IBW) for **Males**[3,4] = $50\ kg + [(2.3\ kg) \times (Ht(in) - 60)]$
     - Ideal body weight (IBW) for **Females**[3,4] = $45.5\ kg + [(2.3\ kg) \times (Ht(in) - 60)]$
   - (in) = Inches; record the patient-specific value at left in terms of inches
   - (kg)= Kilograms; record the patient-specific value at left in terms of kilograms
   - (m) = Meters; record the patient-specific value at left in terms of meters
   - $MAX\ \{$ = Maximum; use the larger of the two values in brackets (separated by a comma) in the equation
   - $\left(\frac{mg}{dL}\right)$ = Milligrams per deciliter; record the patient-specific value at left in terms of milligrams per deciliter
   - (min) = Minutes; record the value at left in terms of minutes
   - $MIN\ \{$ = Minimum; use the smaller of the two values in brackets (separated by a comma) in the equation
   - (mL) = Milliliters; record the value at left in terms of milliliters
   - SCr = Serum Creatinine; the measured serum creatinine in milligrams per deciliter (as indicated)
   - TBW = Total (or "Actual") Body Weight; the measured patient weight in kilograms (as indicated)
   - UCr= Urine Creatinine; the measured urine creatinine in milligrams per deciliter (as indicated)
2. **Glomerular Filtration Rate (GFR)[5]**
   - The volume of blood that passes through the glomeruli each minute which is considered the best overall index of kidney function
3. **Estimated Glomerular Filtration Rate (eGFR)[6-9]**
   - An estimate of glomerular filtration rate that is normalized to body surface area
4. **Estimated Creatinine Clearance (CrCl)[10-12]**
   - An estimate of glomerular filtration rate based upon the estimated volume of blood plasma that is cleared of creatinine per unit time using serum creatinine
5. **Measured Creatinine Clearance[13,14]**
   - An estimate of glomerular filtration rate based upon the calculated volume of blood plasma that is cleared of creatine per unit time using serum and urine creatinine levels
6. **Hemodialysis[14-17]**
   - The extracorporeal process of removing uremic retention products using a semipermeable membrane
   - High permeability dialysis membranes
     - Membranes whose in vitro ultrafiltration coefficient (KUf) is greater than 8 mL/hr/mmHg
     - Include both high-flux and high-efficiency membranes
     - Routinely used in standard hemodialysis technology
7. **Peritoneal Dialysis[17]**
   - A dialysis technique utilizing peritoneum to filter blood and remove uremic retention products
   - CAPD: Continuous Ambulatory Peritoneal Dialysis
     - Requires manual exchanges of dialysis fluid every 4-6 hours
   - CCPD: Continuous Cyclic Peritoneal Dialysis
     - A cycler machine is utilized to perform dialysis exchanges 3-4 times per night during sleep

Recommendations:

1. Estimate the renal clearance of medications based on the patient's estimated creatinine clearance and/or dialysis modality.[18-23] *UW Health GRADE Moderate quality evidence, strong recommendation*
   - 1.1. The Cockcroft-Gault equation using total (actual) body weight should be used for estimating creatinine clearance in patients with BMI between 18 and 30 kg/m^2.[10,14,15,24] (Table 1; Appendix A) *UW Health GRADE Moderate quality evidence, conditional recommendation*
     - 1.1.1. Creatinine clearance often exceeds true GFR due to creatinine secretion.[10,12]
     - 1.1.2. Within HealthLink CrCl is calculated for adults by default using the Cockcroft-Gault equation with total (actual) body weight. Calculators are available to calculate CrCl using other equations and weights.
   - 1.2. The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) Creatinine equation (2009) or the Modification of Diet in Renal Disease (MDRD) equation may be used to calculate eGFR in patients with estimated clearance rate <60 mL/min/1.73 m^2. The CKD-EPI Creatinine equation should be used to calculate eGFR in patients with estimate clearance rate ≥60 mL/min/1.73 m^2.[5-9] (Table 1; Appendix A) *UW Health GRADE Moderate quality evidence, conditional recommendation*
     - 1.2.1. In general, eGFR equations provide a more accurate estimate of true GFR than creatinine clearance equations and measured creatinine clearance[7-9,14,15]
     - 1.2.2. Within HealthLink eGFR is calculated using the CKD-EPI Creatinine (2009) equation with respect to sex, but not race. For Black patients, the reported value should be multiplied by 1.159.
   - 1.3. The National Institute of Diabetes and Kidney Diseases and The National Kidney Disease Educational Program recommend dosing based on either CrCl or eGFR.[22]
   - 1.4. CrCl and eGFR are NOT interchangeable.[9] The equation chosen to estimate renal function should be selected based upon the renal function estimate used in the medication dosing adjustment recommendations (Table 1). *UW Health GRADE Low quality evidence, conditional recommendation*
2. Estimate renal function in obese patients with a BMI ≥30 kg/m^2 using predictive equations that take higher body weight into account:[11,12] *UW Health GRADE Moderate quality evidence, conditional recommendation*
   - 2.1. Either the Salazar-Corcoran equation or the Cockcroft-Gault equation (using adjusted body weight) can be used to estimate renal function in obese patients with a BMI ≥30 kg/m^2.[11,12] (Table 1; Appendix A)
   - 2.2. Obese patients have variable amounts of body fat versus muscle mass which makes estimating creatinine clearance even more challenging in this population. No one equation consistently demonstrates maximal precision or minimal bias.[12,25-27]
   - 2.3. Using total body weight in the Cockcroft-Gault equation will overestimate creatinine clearance, whereas using ideal body weight will underestimate clearance in the obese patient. The Salazar-Corcoran equation is more complex and estimates fat-free mass. If a precise estimate of creatinine clearance is required to improve efficacy or prevent toxicity, then a measured creatinine clearance is recommended.[27]
   - 2.4. These recommendations do not address dosing modifications that may be warranted based on obesity (BMI >30 kg/m^2) outside of the appropriate equations for estimating creatinine clearance.
3. Regularly evaluate renal function and adjust medication doses based on estimated renal function when clinically appropriate in patients with mild to severe renal impairment and end-stage renal disease including those receiving dialysis as indicated by evidence-based dosing recommendations detailed in the drug-specific Lexicomp Drug Monograph.[28] *UW Health GRADE Moderate quality evidence, conditional recommendation*
   - 3.1. Dose modifications are not limited to adjustments based on declining renal function. Dose adjustments should be made as renal function improves, including adjusting doses for normal renal function.
   - 3.2. Drugs that are listed as "no renal dose adjustment necessary" may require further investigation in the event of suspected adverse effects that may be due to drug accumulation in specific patients.

3.3. Medication dose adjustment for patients on renal replacement therapy (HD/PD) must be made based on type of replacement modality, not on reported serum creatinine or estimation of creatinine clearance/eGFR.

4. Consistently assess the applicability and accuracy of plasma/serum creatinine-based equations in the context of the individual patient.[14,15,18] *UW Health GRADE Moderate quality evidence, strong recommendation*
   4.1. In patients with renal impairment, plasma/serum creatinine-based equations are used routinely to estimate renal function in place of more accurate exogenous markers such as inulin or iothalamate.[14,15]
      4.1.1. Equations used to calculate creatinine clearance and estimated glomerular filtration rate represent approximations and are meant to provide a basis for clinical evaluation of the patient.
   4.2. These equations are intended for patients with stable renal function and are less accurate for patients with changing renal function.[7,8,10,11,18,26]
      4.2.1. Additional factors must be evaluated in patients with changing renal function such as urine output and medication efficacy and toxicity.[18]
5. Obtain a measured creatinine clearance in patients with renal impairment when estimated creatinine clearance may be inaccurate.[14,15,24] *UW Health GRADE Low quality evidence, conditional recommendation*
   5.1. Calculated clearances using serum creatinine may be inaccurate in patients with low creatinine, hypoalbuminemia, hypermetabolic conditions, decreased muscle mass (as seen in cirrhosis, spinal cord injury, anorexia, malnutrition, debilitation).[14,15]
   5.2. Renal function using predictive equations may be overestimated in situations associated with rapidly rising serum creatinine, which includes all cases of acute kidney injury (AKI) such as hepato-renal syndrome, ischemic injury, or drug-induced nephrotoxicity.
   5.3. Proper urine collection is challenging because all the urine needs to be collected and any deviation from collecting for 24 hours will affect creatinine estimation.
   5.4. Mixed data exists on the accuracy and usefulness of urine collections shorter than 24 hours. Some studies indicate that a 2-hour urine measurement is sufficient; another indicates that a minimum of 8 hours is required and yet others indicate 24-hour measurement is required. [29-34]
   5.5. Measured creatinine clearance may overestimate the true GFR in patients with advanced chronic kidney disease (CKD) due to increased creatinine secretion.[13,14]
6. Asses medication regimens and adjust administration schedules as appropriate for patients receiving dialysis.[21] *UW Health GRADE Low quality evidence, strong recommendation*
   6.1. To accommodate the administration of drugs that are removed by hemodialysis, administer the scheduled dose after hemodialysis (HD) is complete.[21] *UW Health GRADE Low quality evidence, strong recommendation*
      6.1.1. For example, a drug listed as “every 24 hours/once daily/three times per week post hemodialysis” could be scheduled for 1600 or later depending on the end of the dialysis session.
      6.1.2. A drug listed as “every 12 hours post hemodialysis” could be scheduled at 1200 and 2400 if morning HD is anticipated, or at 0600 and 1800 if afternoon HD is anticipated.
      6.1.3. If the HD schedule is altered, then a dose may need to be administered after the patient returns from HD and with subsequent administrations adjusted accordingly.
      6.1.4. If the schedule is “every 6 hours” or “every 8 hours,” no special scheduling needs to be done as the time is frequent enough that scheduling around HD is not necessary.
      6.1.5. Anti-hypertensive medications may be held before HD to allow for greater ultrafiltrate removal without precipitating hypotension during the procedure. The decision to hold or give an antihypertensive medication prior to HD should be individualized to the patient.
   6.2. When high permeability membranes are used for hemodialysis, consider that more drug may be required compared to cases in which conventional filters are used.[16] *UW Health GRADE Low quality evidence, conditional recommendation*
      6.2.1. Hemodialysis dosing information has been obtained primarily from studies conducted under conditions where conventional dialysis membranes have been used.

6.2.2. Drug removal from plasma is often enhanced with the use of high permeability membranes as compared to conventional membranes, especially in drugs with higher molecular weight.
6.2.3. Individualized therapeutic drug monitoring may be necessary in these instances; the clinician is referred to the primary literature for further details.

7. All of the above recommendations must be utilized in conjunction with clinical evaluation and adjustments must be made to account for the individual patient.
   7.1. Factors to consider include but are not limited to age, body weight, drug interactions, hepatic function, clinical response, and concurrent disease states.

Table 1. Renal Function Estimation Equation Selection[A,B]

Renal Dosing in terms of CrCl	**BMI <30kg/m^2**	Cockcroft-Gault equation using TBW
	BMI ≥30kg/m^2	Salazar-Corcoran equation **OR** Cockcroft-Gault equation using AdjBW
Renal Dosing in terms of GFR or eGFR	**eGFR <60 mL/min/1.73 m^2**	CKD-EPI Creatinine equation (2009) **OR** MDRD equation[C]
	eGFR ≥60 mL/min/1.73 m^2	CKD-EPI Creatinine equation (2009)

[A] Equations are described in Appendix A

[B] All listed equations are serum creatinine-based and may overestimate renal function in advanced CKD, cirrhosis, spinal cord injury, anorexia, malnutrition, debilitation, obesity, and rapidly rising creatinine (including AKI)[12,14,15,24-27]

[C] Equation may generally underestimate true renal function[7,8]

Disclaimer

Consensus care models assist clinicians by providing a framework for the evaluation and treatment of patients. This guideline outlines the preferred approach for most patients. It is not intended to replace a clinician's judgment or to establish a protocol for all patients. It is understood that some patients will not fit the clinical condition contemplated by a guideline and that a guideline will rarely establish the only appropriate approach to a problem.

Contact for Changes:
Name: Philip Trapskin, PharmD, BCPS - Pharmacy
Phone Number: (608) 263-1328
Email Address: ptrapskin@uwhealth.org

Guideline Authors:
Mikala Hillis, PharmD - Pharmacy
Sara Shull, PharmD, MBA, BCPS

Reviewers:
Tripti Singh, MD - Nephrology
Laura Maursetter, MD - Nephrology
Jason Bergsbaken, PharmD - Pharmacy
Jeff Fish, PharmD, BCPS - Pharmacy
Kimberly Holdener, PharmD - Pharmacy
Mary Mably, RPh, BCOP - Pharmacy
Marie H. Pietruszka, PharmD, BCPS, AAHIVP - Pharmacy
Anne Rose, PharmD - Pharmacy
Lucas Schulz, PharmD, BCIDP - Pharmacy
Martha Starzewski, PharmD, BCPS - Pharmacy
Philip Trapskin, PharmD, BCPS - Pharmacy

Committee Approvals:
Pharmacy and Therapeutics Committee: August 2020

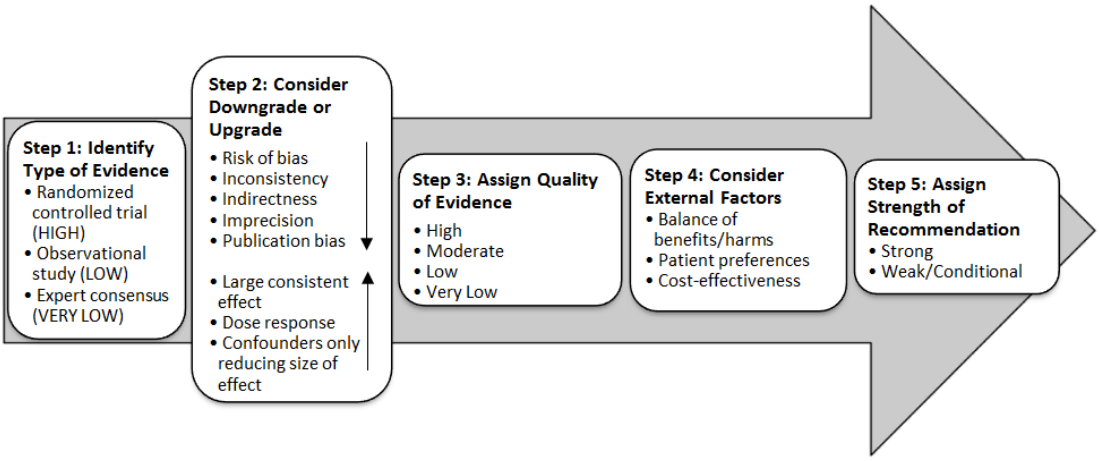

Table 2. GRADE Ranking of Evidence

High	We are confident that the effect in the study reflects the actual effect.
Moderate	We are quite confident that the effect in the study is close to the true effect, but it is also possible it is substantially different.
Low	The true effect may differ significantly from the estimate.
Very Low	The true effect is likely to be substantially different from the estimated effect.

Table 3. GRADE Ratings for Recommendations for or Against Practice

Strong (S)	Generally, should be performed (i.e., the net benefit of the treatment is clear, patient values and circumstances are unlikely to affect the decision.)
Conditional (C)	May be reasonable to perform (i.e., may be conditional upon patient values and preferences, the resources available, or the setting in which the intervention will be implemented.)

Collateral Tools & Resources

The following collateral tools and resources support staff execution and performance of the evidence-based model recommendations in everyday clinical practice.

Delegation Protocols

- Parenteral Nutrition Support – Developing, Ordering, and Monitoring Parenteral nutrition Support Care – Adult/Pediatric/Neonatal – Inpatient/Ambulatory [6]
- Renal Function-Based Dose Adjustment – Adult – Inpatient/Ambulatory [8]
    - **Drugs that can be dose adjusted per protocol based on renal function are listed within the Lexicomp drug monograph and specifically identified**
- Antimicrobial Dosing Based on Pharmacokinetic and Pharmacodynamic Principles – Adult – Inpatient/Emergency Department [9]
- Medication Therapeutic Interchange – Adult/Pediatric – Inpatient/Ambulatory/Emergency Department [13]
- Non-Thoracic Solid Organ Transplant Antiviral Prophylaxis – Adult – Inpatient [17]
- Anemia Management in Pre-Dialysis Chronic Kidney Disease Patients – Adult – Ambulatory [20]
- Therapeutic Medication Blood Concentration Monitoring – Adult/Pediatric/Neonatal – Inpatient/Emergency Department [31]
- Anemia Management in Abdominal Transplant Recipients – Adult – Ambulatory [32]
- Pharmacist Management of Electronic Medication Orders – Adult/Pediatric/Neonatal – Inpatient/Ambulatory/Emergency Department [74]
- Perioperative Antimicrobial Prophylaxis Adjustment – Adult/Pediatric – Inpatient/Ambulatory/Emergency Department [75]
- Non-Thoracic Solid Organ Transplant Rejection Antimicrobial Prophylaxis – Adult – Ambulatory [76]
- Lung Transplant Program Pharmacotherapy – Adult – Ambulatory [81]
- Heart Failure Medication Titration – Adult – Ambulatory [82]
- Diabetes Medication Titration in Primary Care – Adult – Ambulatory [87]
- Diabetes Medication Titration in Endocrine Diabetes Clinic/Health and Education Department – Adult – Ambulatory [88]
- Antihypertensive Medication Titration in Primary Care – Adult – Ambulatory [99]
- Transplant Management of Intravenous Iron Therapy – Adult – Ambulatory [106]
- Hepatitis B Prophylaxis for Non-Thoracic Solid Organ Transplant – Adult – Inpatient [118]
- Post-Hematopoietic Stem Cell Transplant (HSCT) Immunosuppressive Therapy – Adult – Ambulatory [125]
- Vancomycin Dosing and Monitoring – Adult – Inpatient/Emergency Department [129]
- Enoxaparin Dosing and Monitoring for Therapeutic Use – Pediatric – Inpatient [134]
- Pre-exposure Prophylaxis (PrEP) for HIV Prevention – Adult – Ambulatory [146]
- Management of Direct Oral Anticoagulants in Anticoagulation Clinic – Adult – Ambulatory [152]
- Primary Care Expanded Antihypertensive Medication Management – Adult – Ambulatory [164]
- Medication Therapeutic Interchange – Adult – Ambulatory [182]
- Heart Failure Medication Titration in Cardiology Clinic – Adult – Ambulatory [197]
- Vancomycin Dosing and Monitoring – Adult – Ambulatory [220]
- Antiseizure Medication Management – Adult – Ambulatory [225]

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Appendix A. Equations for Renal Function Estimation

Estimated Creatinine Clearance Equations	
Cockcroft-Gault equation using total (actual) body weight[1]	
CrCl **Males** mL/min =	$\left[\frac{(140-age)\times TBW(kg)}{SCr\left(\frac{mg}{dL}\right)\times 72}\right]$
CrCl **Females** mL/min =	$\left[\frac{(140-age)\times TBW(kg)}{SCr\left(\frac{mg}{dL}\right)\times 72}\right]\times 0.85$
Cockcroft-Gault equation using adjusted body weight[2]	
CrCl **Males** mL/min =	$\left[\frac{(140-age)\times AdjBW(kg)}{SCr\left(\frac{mg}{dL}\right)\times 72}\right]$
CrCl **Females** mL/min =	$\left[\frac{(140-age)\times AdjBW(kg)}{SCr\left(\frac{mg}{dL}\right)\times 72}\right]\times 0.85$
Salazar-Corcoran equation[3]	
CrCl **Males** mL/min =	$\left[\frac{(137-age)\times\left(0.285\times TBW(kg)\right)+\left(12.1\times Ht(m)^2\right)}{SCr\left(\frac{mg}{dL}\right)\times 51}\right]$
CrCl **Females** mL/min =	$\left[\frac{(146-age)\times\left(0.287\times TBW(kg)\right)+\left(9.74\times Ht(m)^2\right)}{SCr\left(\frac{mg}{dL}\right)\times 60}\right]$

Estimated Glomerular Filtration Rate Equations	
CKD-EPI Creatinine equation (2009)[4]	
eGFR **Males** mL/min/1.73m^2 =	$141\times\left(MIN\left\{\frac{SCr\left(\frac{mg}{dL}\right)}{0.9},1\right\}\right)^{-0.411}\times\left(MAX\left\{\frac{SCr\left(\frac{mg}{dL}\right)}{0.9},1\right\}\right)^{-1.209}\times 0.993^{\,age}\,[\times 1.159\;if\;Black\;race]$
eGFR **Females** mL/min/1.73m^2 =	$141\times\left(MIN\left\{\frac{SCr\left(\frac{mg}{dL}\right)}{0.7},1\right\}\right)^{-0.329}\times\left(MAX\left\{\frac{SCr\left(\frac{mg}{dL}\right)}{0.7},1\right\}\right)^{-1.209}\times 0.993^{\,age}\times 1.018\,[\times 1.159\;if\;Black\;race]$
MDRD equation[5,6]	
eGFR **Males** mL/min/1.73m^2 =	$186\times\left(SCr\left(\frac{mg}{dL}\right)\right)^{-1.154}\times(age)^{-0.203}\,[\times 1.212\;if\;Black\;race]$
eGFR **Females** mL/min/1.73m^2 =	$186\times\left(SCr\left(\frac{mg}{dL}\right)\right)^{-1.154}\times(age)^{-0.203}\times 0.742\,[\times 1.212\;if\;Black\;race]$

Measured Creatinine Clearance Equation[7,8]

CrCl mL/min = $$\left[\frac{UCr\left(\frac{mg}{dL}\right) \times (collected\ urine\ volume)(mL)}{SCr\left(\frac{mg}{dL}\right) \times (urine\ collection\ time)(min)}\right]$$

Appendix A References

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Appendix B. Selecting Appropriate Dosing Weight for Antimicrobial Medications

From: Renal Function-Based Dose Adjustments – Adult – Inpatient/Ambulatory – Consensus Care Model
Contact for Content: Lucas Schulz, PharmD, BCPS (AQ-ID); 608-890-8617; LSchulz2@uwhealth.org

Definitions and Equations:

- TBW = Total body weight (also called "Actual Body Weight")
- IBW = ideal body weight
  - $\text{IBW in kg (male)} = 50\ kg + 2.3 \times [Height\ (inches) - 60]$
  - $\text{IBW in kg (female)} = 45.5\ kg + 2.3 \times [Height\ (inches) - 60]$
- AdjBW = adjusted body weight
  - $\text{AdjBW in kg} = IBW(kg) + 0.4 \times [ABW(kg) - IBW(kg)]$

Appendix B: Selecting appropriate dosing weight for antimicrobial dosing (all recommendations are *UW Health GRADE Low-moderate quality evidence, conditional recommendation*)

	If patient TBW less than IBW, use this column	If patient is non-obese and TBW is greater than IBW, use this column	If patient is obese (BMI >30 kg/m^2), use this column
Aminoglycosides	TBW	IBW	AdjBW[1]
Colistin		IBW	IBW[2,3]
Daptomycin		IBW	IBW[4]
Polymyxin B		TBW	AdjBW[5-9]
Trimethoprim/Sulfamethoxazole		TBW	AdjBW[10]
Vancomycin		TBW	TBW[11,12]
Acyclovir	TBW	IBW	IBW[10]
Ganciclovir		TBW	AdjBW[10]
Foscarnet		TBW	AdjBW[10]; see footnote A
Liposomal amphotericin	TBW	TBW	AdjBW[13]; see footnote B
Flucytosine		IBW	IBW[14,15]
Voriconazole		TBW	AdjBW[16,17]
Bezlotoxumab	TBW	TBW	TBW[13]
Ethambutol		IBW	IBW[14]
Pyrazinamide		IBW	IBW[14,15]

[A] Use TBW for the indication of ganciclovir-resistant cytomegalovirus
[B] Consider IBW if risk of nephrotoxicity outweighs risk of infection

Appendix B References

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