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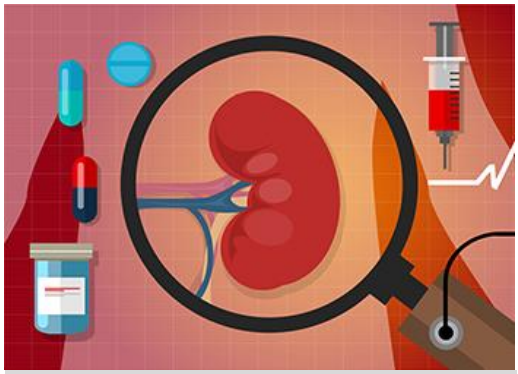
Antimicrobial Stewardship Strategy: Dose optimization

Review and individualization of antimicrobial dosing based on the characteristics of the patient, drug, and infection.



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Priority Level: **A**

Difficulty Level: **2**

Program Stage:

- ✓ Early
- Intermediate
- Advanced

Antimicrobial Stewardship Outcomes:

- Drug utilization outcomes
- Clinical outcomes

For more information on these criteria and how they were developed, please see the Antimicrobial Stewardship Strategy Criteria Reference Guide.

Updated June 2016

Description

This is an overview and not intended to be an all-inclusive summary. As a general principle, patients must be monitored by the health care team after changes to therapy resulting from recommendations made by the antimicrobial stewardship team.

Although antimicrobials are often prescribed in standard doses for adults, there is now more attention being paid to individualized dosing as a stewardship initiative for improving clinical outcomes and minimizing antimicrobial resistance.

Attention to the dose of the antimicrobial is very important when treating an infection. A dose that is too low will compromise the chances of successful treatment and increase the risk of the development of resistance. A dose that is too high can increase the patient's risk of adverse effects.

Dose optimization involves "optimization of antimicrobial dosing based on patient characteristics (e.g., weight, renal/liver function), causative organism, site of infection (e.g., central nervous system, blood) and pharmacokinetic and pharmacodynamic characteristics of the drug (e.g., concentration or time dependent activity)…"[1]

Dose optimization is a common antimicrobial stewardship strategy and is often integrated into the drug-review process by pharmacists. It frequently involves the reduction of doses for renally eliminated agents in patients with renal dysfunction; however, increasing doses for certain disease states (central nervous system infections, endocarditis, bone and joint infections), specific organisms (methicillin-resistant *Staphylococcus aureus*, multi-drug-resistant *Pseudomonas aeruginosa*) and obesity is also important.

Recommended doses and regimens should be incorporated into empiric treatment guidelines, clinical pathways and predefined orders to ensure the appropriate regimen is prescribed for specific infections. Some institutions may have medical directives for pharmacists to adjust antimicrobial doses and simplify the process.

Dosing and administration schedules that maximize the pharmacokinetic and pharmacodynamic profiles of the antimicrobial are important for optimizing their effect. For example, using once-daily or extended dosing of aminoglycosides instead of traditional dosing (lower doses administered two or three times daily) can improve bacterial eradication and decrease the risk of nephrotoxicity and ototoxicity.[2,3]

A more advanced dose optimization strategy involves the use of extended/prolonged or continuous infusions of beta-lactam antibiotics instead of the traditional bolus administration. This approach has been shown to improve clinical outcomes (including decreased mortality) for critically ill patients and individuals infected with more resistant organisms. This is a more labour-intensive program to implement and in practice is often limited to academic centres and critical care units. Beta-lactam infusion programs are of higher difficulty and lower priority than other dose-optimization initiatives and should not be considered an essential component of this strategy.

Advantages

- Improved likelihood of pharmacodynamic target attainment.
- Potentially improved microbiological and clinical cure rates, including improved mortality outcomes.
- Decreased risk of development of resistance.
- Decreased risk of adverse events from excess dosing (e.g., aminoglycoside related nephrotoxicity).
- Avoidance of underdosing in obese patients.
- Can be done centrally if sufficient information is available at time of dispensing (e.g., if renal function is available in electronic medical record).

Disadvantages

- May be difficult to obtain patient-specific information (e.g., renal function, weight, indication for antimicrobial) to make adjustments.
- Clinical trials that define optimal dosing and administration schedules are not available for all antimicrobials and indications (however, guidelines exist for most infections).
- Recommendations for dosing in special populations (e.g., renal dysfunction, obesity) are not always available or consistent.
- Prolonged/continuous beta-lactam infusions may be logistically difficult (e.g., drug stability and compatibility issues) and labour-intensive to implement.

Requirements

- Access to patient-specific data (weight, renal function, indication for antimicrobial therapy).
- Dosing charts/nomograms for aminoglycosides, dosing in obesity, renal dosing of antimicrobials, etc.

- Education for pharmacists and prescribers regarding pharmacokinetic/pharmacodynamic targets and how to optimize therapy to increase likelihood of achieving these targets.
- Development of protocols, necessary equipment (e.g., infusion pumps) and education of medical and nursing staff for extended/prolonged infusions of beta-lactams.

Associated Metrics

- Percentage of patients receiving an appropriate dose/adherence to dosing recommendations.
- Ease of implementation of new dosing protocols/policies and procedures.
- Clinical outcomes before and after implementation of a new dosing protocol (including extended/prolonged infusion of beta-lactams) (advanced).

References

1. Dellit TH, Owens RC, McGowan JE Jr, Gerding DN, Weinstein RA, Burke JP, et al; Infectious Diseases Society of America; Society for Healthcare Epidemiology of America. Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America guidelines for developing an institutional program to enhance antimicrobial stewardship. Clin Infect Dis. 2007;44(2):159–77. Available from: http://cid.oxfordjournals.org/content/44/2/159.long
2. Owens RC Jr, Shorr AF. Rational dosing of antimicrobial agents: pharmacokinetic and pharmacodynamic strategies. Am J Health Syst Pharm. 2009;66(12 Suppl 4):S23–30.
3. Barza M, Ioannidis JP, Cappelleri JC, Lau J. Single or multiple daily doses of aminoglycosides: a meta-analysis. BMJ. 1996;312(7027):338–45. Available from: http://www.bmj.com/content/312/7027/338.long

Additional Useful References

Select articles to provide supplemental information and insight into the strategy described and/or examples of how the strategy was applied; not a comprehensive reference list. URLs are provided when materials are freely available on the Internet.

- Xamplas RC, Itokazu GS, Glowacki RC, Grasso AE, Caquelin C, Schwartz DN. Implementation of an extended-infusion piperacillin-tazobactam program at an urban teaching hospital. Am J Health Syst Pharm. 2010;67(8):622–8.

  Describes the successful hospital-wide introduction of an extended-infusion piperacillin-tazobactam program; the amount of piperacillin-tazobactam purchased by the pharmacy decreased following implementation.

- MacVane SH, Kuti JL, Nicolau DP. Prolonging β-lactam infusion: a review of the rationale and evidence, and guidance for implementation. Int J Antimicrob Agents. 2014;43(2):105–13.

- Drew RH, White R, MacDougall C, Hermsen ED, Owens RC Jr; Society of Infectious Diseases Pharmacists. Insights from the Society of Infectious Diseases Pharmacists on antimicrobial stewardship guidelines from the Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America. Pharmacotherapy. 2009;29(5):593–607.
- Polso AK, Lassiter JL, Nagel JL. Impact of hospital guideline for weight-based antimicrobial dosing in morbidly obese adults and comprehensive literature review. J Clin Pharm Ther. 2014;39(6):584–608. Available from: http://onlinelibrary.wiley.com/doi/10.1111/jcpt.12200/full

Tools and Resources

- Division of Nephrology and Hypertension. Adult drug book [Internet]. Louisville, KY: University of Louisville; c2015 [cited 2015 Sep 23]. Available from: https://kdpnet.kdp.louisville.edu/drugbook/adult/?node=4361

  Provides recommendations for dose adjustments of antimicrobials in renal dysfunction.

- Scottish Antimicrobial Prescribing Group (SAPG). Gentamicin and vancomycin [Internet]. Glasgow, UK: Scottish Medicines Consortium; [cited 2015 Sep 23]. Available from: http://www.scottishmedicines.org.uk/SAPG/Quality_Improvement/Gentamicin_and_Vancomycin

  Guidance documents for the use of vancomycin and gentamicin, including online calculators.

  Guidance for both intermittent (pulsed) and continuous infusion of vancomycin.

  Provides both the Hartford and Greater Glasgow and Clyde nomograms, as well as administration and monitoring charts for gentamicin.

Samples/Examples (updated June 2016)

- Example 1: Vancouver Coastal Health and Providence Health Care, BC - Vancomycin Empiric Dosing Guidelines
- Example 2: Markham Stouffville Hospital Corporation - Policy for Medication Renal Dose Adjustment Guidelines in Adults
- Example 3: Sunnybrook Health Sciences Centre - Antibiotic Dosing Charts in Renal Replacement Therapy
- Example 4: Royal Victoria Regional Health Centre - Piperacillin + Tazobactam (Tazocin®): Guidelines for Use 2013

These documents have been generously shared by various health care institutions to help others develop and build their antimicrobial stewardship programs. We recommend crediting an institution when adopting a specific tool/form/pathway in its original form.

Examples that contain clinical or therapeutic recommendations may not necessarily be consistent with published guidelines, or be appropriate or directly applicable to other institutions. All examples should be considered in the context of the institution's population, setting and local antibiogram.

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Links with Other Strategies

- Disease-specific treatment guidelines/pathways/algorithms and/or associated order forms
- Empiric antibiotic prescribing guidelines
- Prospective audit with intervention and feedback
- Therapeutic drug monitoring (with feedback)

Disclaimer

Citation

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For further information

Antimicrobial Stewardship Program, Infection Prevention and Control, Public Health Ontario.

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Example 1: Vancouver Coastal Health and Providence Health Care, BC - Vancomycin Empiric Dosing Guidelines

Vancouver Coastal Health
Promoting wellness. Ensuring care.

Providence Health Care
How you want to be treated.

Pharmacy
VANCOMYCIN EMPIRIC DOSING GUIDELINES
April 2016, 3rd edition

For more information, please contact Pharmacy
Or visit: www.vhpharmsci.com

KEY
1. Establish patient age, weight, and serum creatinine.

2. Using Table 1, identify initial loading dose and maintenance dose per interval according to patient weight and target pre-vancomycin level.

3. Using Table 2, determine target pre-vancomycin level based on clinical indication.

4. Using Tables 3 or 4, identify initial dosing interval according to target pre-vancomycin level, age, and serum creatinine.

5. Using Table 5, determine dialysis dosing.

TABLE 1 INITIAL DOSE PER INTERVAL

TOTAL BODY WEIGHT	LOADING DOSE (suggested maximum 2500 mg/dose)		MAINTENANCE DOSE
kg	Target pre-level 10-15 mg/L (20 mg/kg)	Target pre-level 15-20 mg/L (25 mg/kg)	(15 mg/kg)
40-50	1000 mg	1250 mg	750 mg
51-60	1250 mg	1500 mg	1000 mg
61-70	1250 mg	1750 mg	1000 mg
71-80	1500 mg	2000 mg	1250 mg
81-90	1750 mg	2250 mg	1250 mg
91-100	2000 mg	2500 mg	1500 mg

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Example 1: Vancouver Coastal Health and Providence Health Care, BC - Vancomycin Empiric Dosing Guidelines (continued)

TABLE 2 SUGGESTED TARGET PRE-VANCOMYCIN LEVELS BASED ON INDICATION

Pre-vancomycin Level 10-15 mg/L	Pre-vancomycin Level 15-20 mg/L
• Skin and soft tissue infection • Urinary tract infection (UTI) (if catheter-associated; rule out bacteremia)	• Catheter-associated bacteremia • Central nervous system infection • Deep-seated or sequestered infection (e.g. abscess) • Endocarditis • Osteomyelitis • MRSA bacteremia or pneumonia • MSSA bacteremia (penicillin allergic patient)

TABLE 3 FOR SKIN AND SOFT TISSUE INFECTION & UTI
LOW-TARGET 10-15 mg/L INITIAL DOSING INTERVAL (hours)

SCr (mcmol/L)	Age Group (years)					
	20-29	30-39	40-49	50-59	60-69^	70-79^
40-60	8	8	12	12	12	18
61-80	8	12	12	12	18	18
81-100	12	12	12	18	18	18
101-120	12	12	18	18	18	24
121-140	12	18	18	18	24	
141-160	18	24	24	24		
161-180	24	24				
181-200	24					
Above 200						
Dialysis	See TABLE 5 (back of card)					

TABLE 4 FOR ALL OTHER INDICATIONS (COMPLICATED INFECTIONS)
HIGH-TARGET 15-20 mg/L INITIAL DOSING INTERVAL (hours)

SCr (mcmol/L)	Age Group (years)						
	20-29	30-39	40-49	50-59	60-69^	70-79^	80-89^
40-60	6	6-8	8	8	8-12*	12	12
61-80	8	8	8-12*	12	12	12	12-18*
81-100	12	12	12	12	12-18*	18	18
101-120	12	12	12-18*	18	18	18	18
121-140	12	18	18	18	18	18-24*	
141-160	18	18	18	18-24*	24		
161-180	18-24*	24	24	24			
Above 180							
Dialysis	See TABLE 5 (back of card)						

^In elderly patients with low muscle mass, use clinical judgment as SCr may not reflect renal function accurately.
*If more aggressive therapy is desired, select more frequent dosing interval.

Shaded boxes: These patients have unstable and/or reduced renal function, and the nomogram may not be as predictive.
- For those with an interval stated, patients should receive a loading dose followed by 3 hour and pre-2nd dose serum levels to determine appropriate dosing.
- For those with no dosing interval stated, patients should receive a loading dose followed by 3 hour and 24 hour post-dose serum levels to determine subsequent dosing.
- A clinical pharmacist should be contacted for assistance with dosing and interpretation of levels.

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Example 1: Vancouver Coastal Health and Providence Health Care, BC - Vancomycin Empiric Dosing Guidelines (continued)

TABLE 5 DIALYSIS DOSING

	Hemodialysis (HD)	Continuous Ambulatory Peritoneal Dialysis (CAPD)
Loading Dose	25 mg/kg	Intraperitoneal (IP): 30 mg/kg **OR** Intravenous (IV): 20 mg/kg
Maintenance Dose	**weight < 70 kg:** 500 mg QHD **weight ≥ 70 kg:** 750 mg QHD	IP: 30 mg/kg every 5-7 days **OR** IV: 20 mg/kg every 4-7 days
When To Draw Level	Pre-second maintenance dose	3-4 days after first dose
Target Vancomycin Level	Pre-HD level: 15-20 mg/L	Trough level: 15-20 mg/L

THERAPEUTIC DRUG MONITORING

Vancomycin serum levels should be ordered in the following situations:

1. Pre-vancomycin level on 3rd or 4th dose (within 48 hours) if:
   - a higher level of 15-20 mg/L is desired **OR**
   - patient is at risk for accumulation (e.g. Q6-8H interval) **OR**
   - patient is receiving other nephrotoxic agents **OR**
   - serum creatinine is above normal, renal function is changing or uncertain **OR**
   - patient is obese (>125% IBW), pregnant, pediatric or hypermetabolic (e.g. burn patient, cystic fibrosis)

   Repeat at least weekly to ensure pre-vancomycin level is within desired therapeutic range

2. Pre-vancomycin level after 7 days of therapy (for prolonged course) if aiming for levels < 15 mg/L **AND** no other risk factors as per above

3. Pre-vancomycin level if patient is not responding to therapy

4. Pre- and 3 hour post-vancomycin level (target 20-40 mg/L) if calculation of precise kinetic parameters are necessary (e.g. in a case when a target pre-vancomycin level of 15-20 mg/L cannot be achieved while on prolonged therapy, or in an obese, pregnant or pediatric patient, especially when aggressive dosing is required)

Revised April 2016

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Example 2: Markham Stouffville Hospital Corporation - Policy for Medication Renal Dose Adjustment Guidelines in Adults

INTERDISCIPLINARY MANUAL

AUTHOR:	Patient Care Director, Pharmacy Services	**FOLDER:**	Medication Guidelines & Protocols
APPROVED BY:	Medical Advisory Committee	**REVIEW FREQUENCY:**	3 years
ELECTRONIC RESPONSIBILITY:	Patient Care Director, Pharmacy Services	**ORIGINAL APPROVAL DATE:**	3/11/2005
POLICY HISTORY/ NUMBER CHANGES:		**REVIEWED**	22/01/2014
		REVISED DATE:	

290.914.916.195 MEDICATION RENAL DOSE ADJUSTMENT GUIDELINES IN ADULTS

POLICY: To ensure proper adjustment of renally eliminated medications for patients with renal impairment.

GUIDELINES: Many medications require adjustment of dose in the setting of impaired renal function. Renal impairment is the main reason for reducing the doses of drugs in the elderly as they will often have moderate renal impairment despite a serum creatinine value within the normal range. Adjusting doses according to renal function can eliminate adverse effects and can provide cost savings by avoidance of excessive dosing. Recommended doses are available for these medications based on estimated creatinine clearance.[1,2,3,4] This policy would grant the authority for pharmacists to automatically adjust the dose of designated agents.

PROCEDURE:

1) Review patient's chart and laboratory record
2) Obtain height, weight and serum creatinine to calculate estimated creatinine clearance based on the Cockroft-Gault equation*
3) Refer to the suggested dosing schedules in chart attached and identify appropriate dosing regimen based on estimated creatinine clearance

Example 2: Markham Stouffville Hospital Corporation - Policy for Medication Renal Dose Adjustment Guidelines in Adults (continued)

4) Write order in patient chart "Automatic renal dose adjustment by pharmacist, change _____(medication name) to _____ (new dose and interval)
5) Documentation will be made in electronic chart including estimated creatinine clearance and rationale for dose adjustment.
6) Order BUN and serum creatinine on day 2 and then as required. Order drug levels as required.
7) Adjustments will be made to medication regimen as needed based on subsequent serum creatinine measurements or drug level results.

Exceptions:

a. Physician indicates 'no substitution' on order
b. Patients with a diagnosis of meningitis or endocarditis
(See aminoglycoside policy for dosing of gentamicin in endocarditis)
c. Patients in Intensive Care Unit with presumed sepsis

For above situations, any suggested dosing changes require review and acceptance by most responsible physician.

*Cockroft-Gault equation:

$$\text{Creatinine clearance (CrCl)} = \frac{(140-\text{age}) \times \text{weight (kg)}}{\text{Serum creatinine } (\mu\text{mol/L})}$$ Multiply by 1.2 if male

References:

1. Aronoff GR, Bennett WM, et al. Drug Prescribing in Renal Failure: Dosing Guidelines for Adults, Fourth Edition. Philadelphia, PA; American College of Physicians. 1999.
2. Compendium of Pharmaceuticals and Specialties, electronic version (eCPS). Canadian Pharmacists Association, 2007.
3. Micromedex. Thomson Healthcare Inc. 2005.
4. Guidelines for Antimicrobial Use. Antibiotic Subcommittee, University Health Network, 2003.

ENDORSEMENTS:
Antibiotic Stewardship Subcommittee
Drugs and Therapeutics Committee

Example 2: Markham Stouffville Hospital Corporation - Policy for Medication Renal Dose Adjustment Guidelines in Adults (continued)

Antibiotic	Creatinine Clearance (CrCl) (mL/min)			
	Greater than 50	**25-49**	**10-24**	**Less than 10**
acyclovir (IV)	5-10 mg/kg q8h	5-10 mg/kg q12h	5-10 mg/kg q24h	50% dose q24h
(PO) *genital herpes*	400 mg TID	400 mg TID	400 mg TID	200 mg BID
(PO) *varicella zoster*	800 mg 5 x / day	800 mg 5 x / day	800 mg TID	800 mg BID
aminoglycosides	*see aminoglycoside dosing in adults guideline (policy # 290.914.916.025)*			
amoxicillin-clavulanate	500-875 mg BID	500-875 mg BID	250-500 mg BID	250-500 mg q24h
ampicillin	1-2 g q4-6h	1-2 g q6-12h	1-2 g q6-12h	1-2 g q12-24 h
amoxicillin	250-500 mg TID	CrCl less than 30: 250-500 mg BID	250-500 mg BID	250-500 mg q24h
azithromycin	*no adjustment required*			
cefazolin	1-2 g q8h	1-2 g q12h	1-2 g q12h	1-2 g q24h
cefotaxime	1 g q8h	1 g q12h	1 g q12h	1 g q24h
ceftazidime	1-2 g q8h	1-2 g q12h	1-2 g q24h	500 mg-1 g q24h
ceftriaxone	*no adjustment required*			
cefuroxime (IV)	750 mg q8h	750 mg q8h	750 mg q12h	750 mg q24h
cefuroxime axetil (PO)	500 mg BID	500 mg BID	500 mg BID	500 mg q24h
cephalexin	500 mg QID	500 mg TID	500 mg BID	250 mg BID
ciprofloxacin (IV)	400 mg q12h	CrCl less than 30: 400 mg q24h	400 mg q24h	400 mg q24h
ciprofloxacin (PO)	500-750 mg BID	CrCl less than 30: 500-750 mg q24h	500-750 mg q24h	500 mg q24h
clarithromycin	250-500 mg BID	CrCl less than 30: 50% of dose BID	50% of dose BID	50% of dose BID
Clindamycin	*no adjustment required*			
cloxacillin	*no adjustment required*			
cotrimoxazole (IV)	8-10 mg/kg/day in 2-4	CrCl Less than 30: 50% of dose in	50% of dose in	not recommended
(of TMP component)	divided doses	2 divided doses	2 divided doses	
PCP pneumonia	15-20 mg/kg/day in 2-4	CrCl Less than 30: 50% of dose in	50% of dose in	not recommended
	divided doses	2 divided doses	2 divided doses	

Example 2: Markham Stouffville Hospital Corporation - Policy for Medication Renal Dose Adjustment Guidelines in Adults (continued)

Antibiotic	Creatinine Clearance (CrCl) (mL/min)			
	Greater than 50	**25-49**	**10-24**	**Less than 10**
cotrimoxazole (PO)	1 DS tablet BID	CrCl Less than 30: 1 DS tablet daily	1 DS tablet daily	not recommended
ertapenem	1 g q24h	CrCl Less than 30: 500 mg q24h	500 mg q24h	500 mg q24h
fluconazole	100-400 mg q24h	50% of dose q24h	50% of dose q24h	25% of dose q24h
meropenem	500 mg q6h	500 mg q8h (CrCl Less than 30 - q12h)	500 mg q12h	500 mg q24h
moxifloxacin	*no adjustment required*			
metronidazole	*no adjustment required*			
nitrofurantoin	100 mg PO BID	*should be avoided if ClCr less than 50 ml/min*		
Oseltamivir – Treatment	75 mg BID	75 mg daily	30 mg daily	Not recommended
Oseltamivir- Prophylaxis	75 mg daily	30 mg daily	30 mg every second day	Not recommended
penicillin G	1-4 Milli units q4-6h	1-4 Milli units q8-12h	1-4 Milli units q8-12h	1-4 Milli units q12h
piperacillin/tazobactam	4.5 g q8h	CrCl less than 40: 3.375 g q8h	CrCl less than 20: 3.375 g q12h	
piperacillin/tazobactam for HAP/VAP *HAP= hospital acquired pneumonia *VAP= ventilator associated pneumonia	4.5 g q6h	CrCl less than 40: 3.375g q6h	CrCl less than 20 2.25g q6h	
Valacyclovir Herpes zoster	1000 mg q8h	CrCl less than 30: 1000 mg q12h	1000 mg q12h	
Genitial herpes (initial)	1000 mg q12h	CrCl less than 30: 1000 mg q24h	1000 mg q24h	
Genitial herpes (recurrent)	500 mg q12h	500 mg q12h	500 mg q12h	
Herpes Labialis (cold sores)	2000 mg q12h x 2 doses	1000 mg q12h x 2 doses	500 mg q12h x 2 doses	
vancomycin	CrCl greater than 65 - 1 g q12h	CrCl 31-40 - 1 g q36h	CrCl 10-15 - 1 g q72h	
	CrCl 41-64 - 1 g q24h	CrCl 16-30 - 1 g q48h	CrCl less than 10, rpt dose when level less than 12	

Example 2: Markham Stouffville Hospital Corporation - Policy for Medication Renal Dose Adjustment Guidelines in Adults (continued)

Miscellaneous Medications	Creatinine Clearance (CrCl) (mL/min)			
	Greater than 50	**25-49**	**10-24**	**Less than 10**
Allopurinol	200-400 mg q24h	200 mg q24h	100 mg q24h	100 mg q2-3 days
Gabapentin	300-900 mg TID	200-700 mg BID	200-700 mg daily	100-300 mg q24-48h
Ranitidine (PO)	150 mg BID	150 mg daily		
Ranitidine (IV)	50 mg q8h	50 mg q12-24h		
Sotalol (for VT)	CrCl greater than 60 40-160 mg BID	CrCl 30-60 40-160 mg daily	CrCl 10-30 40-160 mg q36-48h	Patient specific – discuss with MD
Sotalol (for AF)	CrCl greater than 60 40-160 mg BID	CrCl 40-60 40-160 mg daily	CrCl less than 40 *Not recommended*	

Example 3: Sunnybrook Health Sciences Centre - Antibiotic Dosing Charts in Renal Replacement Therapy

Antibiotic dosing charts

Sunnybrook
HEALTH SCIENCES CENTRE
when it matters MOST

Antimicrobial	Usual Dose	CRRT	SLED	HD	ESRD or PD
Aminoglycosides	Standard dosing of Tobramycin / Gentamicin 2mg/kg at interval appropriate for renal function Standard dosing of Amikacin 8mg/kg at interval appropriate for renal function ODA: Gentamicin / tobramycin 5-7mg/kg q24h Amikacin 15mg/kg q24h P/T levels with third dose	**CRRT and Continuous SLED:** •2-3mg/kg iv gentamicin or tobramycin OR 8-10mg/kg iv for amikacin given iv q24h •Obtain P/T with 3rd dose •Usually require q24-48h dosing with CRRT and the same is likely with continuous SLED **For intermittent SLED:** •Give 2-3mg/kg x 1 dose, get peak following dose and trough level after SLED completion, re-dose with 2mg/kg after getting the trough level, since likely trough <2mg/L with negligible accumulation, since 70-90% removed. •Adjust dosing based on P/T level. •5-7mg/kg iv gentamicin or tobramycin OR 15-20mg/kg iv amikacin has been recommended in SLED, due to higher Vd with 2mg/kg gentamicin or tobramycin OR 8mg/kg iv amikacin give after each 8h SLED (But data is very limited) •~70-90% removed with CRRT and SLED		2-3mg/kg iv for gentamicin and tobramycin OR 8-10mg/kg iv for amikacin x 1 dose •Obtain peak and 24h level, calculate half-life, give next dose in 2-3 half lives to drop trough <2 mg/L. Choose a convenient dosing interval based on the 2-3 half lives. [If HD due in the 24h period obtain peak and trough before dialysis and then decrease by ~30% removed by HD (more convenient for patient) then determine when next dose due based on half life.] •Then with the next dose given at the calculated dosing interval, do 3-point PK: get trough before the second dose, then get peak and trough with after the second dose). Now the pharmacist can calculate the Vd and required steady state dosing. •Usually dose q48-72h in IHD/ESRD/PD and ~30% removed during 4h with IHD •More complicated dose determination than vancomycin, because peak AND trough matter with AMGs.	

Example 3: Sunnybrook Health Sciences Centre - Antibiotic Dosing Charts in Renal Replacement Therapy (continued)

Antimicrobial Beta-Lactams	Usual Dose	CRRT	SLED	IHD	ESRD or PD
Ampicillin	2g iv q4-6h	2g iv q4-6h	2g iv q4-6h on dialysis days and ESRD dosing on non-dialysis days	2g iv q8-12h, schedule a routine dose after HD	2g iv q8-12h
Cefazolin	1-2g iv q8h	1-2g iv q8h	1-2g iv q8h on dialysis days and ESRD dosing on non-dialysis days	1-2g post HD 3 times per week (none on non-dialysis days)	1g iv q24h
Ceftriaxone	1g iv q24h Meningitis / IE/OM: 2g iv q12h	No dose adjustment			
Ceftazidime	2g iv q8h	2g iv q8h	2g iv q8h on dialysis days and ESRD dosing on non-dialysis days	2g iv q24h dosed after HD on dialysis days	2g iv q24h
Cloxacillin	2g iv q4-6h	No dose adjustment			
Ertapenem	1g iv q24h	1g iv q24h	1g iv q24h on dialysis days and ESRD dosing on non-dialysis days	30% removed with IHD Dose post dialysis on dialysis days 500mg iv q24h	500mg iv q24h
Meropenem	500mg iv q6h / 1g iv q8h Meningitis: 2g iv q8h	500mg iv q6h / 1g iv q8h Meningitis: 2g iv q8h	500mg iv q6h / 1g iv q8h on dialysis days and ESRD dosing on non-dialysis days Meningitis: 2g iv q8h on dialysis days and ESRD dosing on non-dialysis days	500mg iv q8-12h, schedule a routine dose after HD	500mg iv q12h
Piperacillin / Tazobactam	3.375 – 4.5g iv q6h	3.375 – 4.5g iv q6h	3.375 – 4.5g iv q6h on dialysis days and ESRD dosing on non-dialysis days	3.375 – 4.5g iv q12h, schedule a routine dose after HD	3.375 – 4.5g iv q12h

Example 3: Sunnybrook Health Sciences Centre - Antibiotic Dosing Charts in Renal Replacement Therapy (continued)

Antimicrobial	Usual Dose	CRRT	SLED	IHD	ESRD or PD
Daptomycin	6mg/kg iv q24h	6mg/kg iv q24h	Limited data supports extensive elimination via SLED 6mg/kg iv q24h on SLED days and ESRD dosing on non-dialysis days	Only ~15% removed with dialysis Dose 6mg/kg iv q48h	Dose 6mg/kg iv q48h
Fluoroquinolones: Ciprofloxacin	500 mg – 750 mg po q12h 400mg iv q8-12h	500 mg – 750 mg po q12h 400mg iv q8-12h	Insufficient data – usual dosing seems reasonable with an estimated CrCl of ≥ 60mL/min on dialysis days and ESRD dosing on non-dialysis days	400mg iv q12 - 24h or 500mg po q12 - 24h (use q12h regimen in critically ill) (only ~10% removed with HD, but has 50% non-renal clearance)	400mg iv q12 - 24h or 500mg po q12 - 24h (use q12h regimen in critically ill)
Levofloxacin	500mg – 750mg iv / po q24h	500mg – 750mg iv / po q24h	Insufficient data – but usual dosing reasonable when SLED given continuously (CrCl> 60mL/min), and a 250mg post SLED may be used for supplementing when intermittent SLED used since ~25% removed with SLED	750mg iv / po load then 500mg iv/po q48h, dosed after IHD on dialysis days (Not "effectively removed with HD" - ? <10% and has 20% non renal clearance)	750mg iv / po load then 500mg iv/po q48h,
Moxifloxacin	400mg iv / po q24h	400mg iv / po q24h	400mg iv / po q24h	400mg iv / po q24h	400mg iv / po q24h
Linezolid	600mg iv/po q12h	600m iv / po q12h	~30% removed with SLED; Dose post SLED on dialysis days No dose adjustment 600mg iv / po q12h	~30% removed with IHD; Dose post IHD on dialysis days No dose adjustment 600mg iv / po q12h	600mg iv / po q12h

Example 3: Sunnybrook Health Sciences Centre - Antibiotic Dosing Charts in Renal Replacement Therapy (continued)

Antimicrobial	Usual Dose	CRRT	SLED	HD	ESRD or PD
Vancomycin	**Weight <100kg** 1g iv q12h (Trough < 15mg/L) 1g iv q8h (Trough 15 – 20mg/L) **Weight 100 – 150kg** 1.5g iv q12h (Trough <15mg/L) 1.5g iv q8h (Trough 15 – 20mg/L) OR us continuous infusion dosing: 2.5 – 3g iv q24h continuous infusion Monitor levels to individualize dosing	1.25g – 1.5 g iv q24h P/T levels with 3rd or 4th dose and adjust based on levels	8-26% removed during SLED; **Continuous Infusion SLED:** •Usual vancomycin dose •Get P/T with 3rd - 4th dose **Intermittent SLED:** 1g iv followed by 500mg – 1g post dialysis with ESRD dosing **For individualized PK dosing with Intermittent SLED:** Give 1g dose then: •Get Peak level 2h post 1h infusion and random level post intermittent SLED to determine half-life and dose q1 half-life for trough 15 – 20mg/L or q2 half-lives for trough <15mg/L. Use concepts of : i) half-life; ii) at SS the MAF = 2 x concentration following first dose when dose q1 half-life, and iii) P/T will be proportional to dose. •Only give the 500mg – 1g post dialysis dose AFTER you get the post SLED random level •Once you have determined individualized dose for target trough, give this dose following each subsequent SLED	•1g iv post-dialysis initial dose; •30-50% removed with high flux membranes; 0.5 – 1g iv post dialysis (use 0.5g when desired trough <15mg/L; and 1g when desired trough 15 – 20mg/L) Could get levels as per same method as intermittent SLED except need to wait ~3h before getting the post-HD random level to account for rebound seen with HD.	1g iv q5-7days with levels off first dose (peak an 24h level)

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Example 4: Royal Victoria Regional Health Centre - Piperacillin + Tazobactam (Tazocin®): Guidelines for Use 2013

Royal Victoria Regional Health Centre

Piperacillin + Tazobactam (Tazocin®): Guidelines for Use
Royal Victoria Regional Health Centre
June 2013

Background:

Piperacillin-tazobactam is a broad – spectrum antibiotic used to treat a variety of infections including Ventilator Associated Pneumonia, gram-negative sepsis and polymicrobial infections (anaerobes plus gram-negative or gram-positive bacteria).
Due to overuse, susceptibility of *P. aeruginosa* and *E.coli* to this antimicrobial, at our institution, has steadily declined over the last two years.

In general, β-lactam antibiotics exhibit time-dependent bactericidal activity and, with the exception of carbapenems, minimal persistent effects (often termed post-antibiotic effect). As a result, the time for which the free drug concentration (fT) remains above the minimum inhibitory concentration (MIC) of the organism is the pharmacodynamic parameter that predicts clinical and bacteriological outcomes for this drug class.

To maximize the likelihood of achieving desirable pharmacodynamic targets, especially in nosocomial infections caused by less-susceptible bacteria, conventional dosing regimens may need to be modified. Continuous and prolonged infusions increase the probability of target attainment ($fT>MIC$) throughout the dosing interval.

Several studies have evaluated continuous or extended infusions of β-lactam antibiotics but piperacillin-tazobactam is the most widely studied of those. The highest yielded benefits are seen in the more critically ill population. The extended infusion regimen allows for an overall lower total daily dose of piperacillin- tazobactam which will allow for cost savings for the hospital.

In light of the above findings and the education required for uptake, adoption of extended infusions hospital wide may not be the best way to implement. However, currently we use three different doses of piperacillin-tazobactam depending on indication and renal function. This in itself is labour intensive and sets up opportunities for error. After benchmarking with other hospitals, it became evident that we can eliminate some of these choices without compromising efficacy.

Current Practice

Piperacillin – Tazobactam (Tazocin®):

Normal dosing: 3.375g IV q6h as 30 minute infusion

Example 4: Royal Victoria Regional Health Centre - Piperacillin + Tazobactam (Tazocin®): Guidelines for Use 2013 (continued)

Hospital acquired pneumonia (HAP)/Ventilator acquired pneumonia (VAP)/Febrile Neutropenia, documented *Pseudomonas* infection: 4.5 g IV q6h as 30 minute infusion

Adjustment in renal dysfunction:

Creatinine Clearance (mL/min)	Dose and Interval*
> 20	2.25 g IV q6h (3.375g IV q6h for HAP/VAP/Febrile Neutropenia, documented *Pseudomonas* infection)
≤ 20	2.25 g IV q8h (2.25 g IV q6h for HAP/VAP/Febrile Neutropenia, documented *Pseudomonas* infection) with last dose given after HD if applicable

* This is not consistent practice within the institution as we do not have a standardized protocol. Dosing based on best practice with main reference to Lexi-Comp online.

Proposed Practice

1. **Hospital Wide**

Normal dosing (creatinine clearance ≥ 30 mL/min): 3.375 g IV q6h as 30 minute infusion

HAP/VAP/Febrile Neutropenia, documented *Pseudomonas* infection: 4.5 g IV q6h as 30 minute infusion

Adjustment in renal dysfunction:

Creatinine Clearance (mL/min)	Dose and Interval*
10-29	3.375 g IV q8h (4.5 g IV q8h for HAP/VAP/Febrile Neutropenia, documented *Pseudomonas* infection)
< 10, including hemodialysis (HD)	3.375 g IV q12h (4.5 g IV q12h for HAP/VAP/Febrile Neutropenia, documented *Pseudomonas* infection) with last dose given after HD, if applicable

*All given as 30 minute infusion

2. **ICU only (initiation of extended infusions)**

Normal dosing for **creatinine clearance > 20 mL/min**: 3.375g IV **q8h** as **4 hour infusion**

Example 4: Royal Victoria Regional Health Centre - Piperacillin + Tazobactam (Tazocin®): Guidelines for Use 2013 (continued)

HAP/VAP, documented *Pseudomonas* infection, obese patients (≥ 120 kg) with **creatinine clearance > 20 mL/min**: 4.5 g IV **q8h** as **4 hour infusion**

Exclusions to extended infusions:

- Febrile neutropenics, meningitis, cystic fibrosis patients
- Patients with microbiology showing isolates with Minimum Inhibitory Concentrations (MIC) to piperacillin-tazobactam > 16 mcg/mL
- Patients receiving HD, follow hospital wide guidelines
- Patients with creatinine clearance ≤ 20 mL/min., follow hospital wide guidelines

When patients are transferred from ICU to the floor, the ICU pharmacist or the intensivist will reassess the need for extended infusion of piperacillin-tazobactam and decide on one of the following:

1. Continue as extended infusion with very clear orders on transfer to **infuse each dose over 4 hours.** The floor pharmacist will follow up within 48 hours (if transfer happens on a Friday) to ensure that the dose is being administered properly and medication administration record is accurate.
2. Discontinue extended infusion and resume regular dosing schedule with each dose being infused over 30 minutes. Again, transfer orders must be very clear.

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