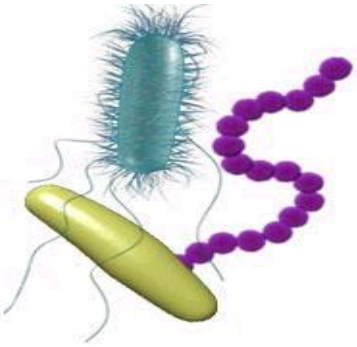
2018-2019 Antimicrobial Stewardship Guidebook



ID Pharmacist:
Matthew Miller, PharmD, BCPS
Pager: 303-266-2383
Office : 720-848-8602

ID Pharmacist Resident:
Pager: 303-266-2182

Antibiotic Approval Pager:
Mon-Fri, 8AM – 8PM
303-266-6966

Inpatient Pharmacy:
720-848-1389

ID Fellow:
See Amion for call schedule

Available online at UCH Source:
Search for stewardship OR Committees → Antimicrobial Stewardship Team

Prepared July 2018

The Antibiogram and Dosing Guidelines Development Team

Information contained was compiled using University of Colorado
2016 susceptibility data

ABX Subcomm. Approved 10/2018

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	% Susceptible																	
Inpatient Gram Negative **(UCHealth Metro - all sources and locations, July 2017 - July 2018)**	**Isolates (n)**	**AMIKACIN**	**TOBRAMYCIN**	**GENTAMICIN**	**AMPICILLIN**	**AMOX-CLAV**	**AMP-SULB**	**CEFAZOLIN (Non-Urine Breakpoint)**	**CEFUROXIME**	**CEFTRIAXONE**	**CEFTAZIDIME**	**CEFEPIME**	**PIPERACILLIN-TAZOBACTAM**	**AZTREONAM**	**MEROPENEM**	**ERTAPENEM**	**CIPRO/LEVOFLOXACIN**	**TETRACYCLINE**	**BACTRIM**
E. coli	1848	99	89	90	50	83	55	71	87	91	93	93	96	92	99	99	77	73	73
Klebsiella spp.	576	100	95	96		90	72	70	86	92	94	95	91	93	98	98	92	87	89
K. pneumoniae	429	100	94	96		92	80	83	87	94	94	95	95	95	99	99	91	84	88
K. oxytoca	127	100	97	97		80	40	20	78	85	94	94	81	85	98	98	94	93	93
Proteus spp.	144	100	89	91	73	94	87	1	89	94	98	96	99	97	100	100	77		81
P. mirabilis	133	100	89	91	78	95	87	2	95	95	98	96	98	98	-	100	76		81
Enterobacter spp.[1]	299	99	98	99						68	71	85	72	72	99	89	98	90	94
Citrobacter spp.[1]	93	100	95	96		31	30	23	30	73	77	94	84	77	99	97	95	88	92
C. freundii[1]	60	100	93	93						63	67	90	77	70	98	95	92	83	93
C. koseri	26	100	100	100		88	84	81	84	84	96	100	96	96	100	100	100	96	100
Serratia spp.[1]	60	98	71	97						90	93	93	96	96	96	96	97	0	-
Pseudomonas aeruginosa	334	97	97	-							93	89	89	76	88		81		
Acinetobacter spp.	30	97	93	97			100[3]				87	93	90	-	97		96	0	90
Stenotrophomonas maltophila	53										-	-					87	[2]	96

Grey boxes indicate organism has intrinsic resistance to the corresponding antimicrobial; boxes w/ hashes indicate organism may be susceptible, but insufficient data/numbers to report

[1] *Citrobacter freundii* (not *koseri*), *Enterobacter*, and *Serratia* have the potential to inducibly produce AmpC beta-lactamase and become resistant to 3rd generation cephalosporins, aztreonam, and piperacillin-tazobactam on therapy. Use these agents with caution. Failure rates appear highest with *Enterobacter* >> *Citrobacter* > *Serratia*. Cefepime and carbapenems appear to be stable in the presence of high-level AmpC production.

[2] Minocycline has good activity against most *Stenotrophomonas* isolates

[3] Sulbactam is the active component against *Acinetobacter spp.* Use of higher doses 18-27g/day total (3g q3-4h or 9g q8h) necessary depending on infection source/severity, and combination usually needed for severe/complicated cases

Inpatient Gram Positive (UCHealth Metro - all sources and locations, July 2017- July 2018)	% Susceptible																	
	Isolates (N)	AMPICILLIN	CEFAZOLIN	CEFTRIAXONE	CLINDAMYCIN	DAPTOMYCIN	GENTAMICIN (Synergy)	LEVOFLOXACIN	LINEZOLID[1]	OXACILLIN[5]	Penicillin G (IV Dosing)	PEN VK (Oral Dosing)	Rifampin	ERYTHROMYCIN	TETRACYCLINE	Bactrim	VANCOMYCIN	Nitrofurantoin (Urine Only)
Enterococcus spp.	674	82				99	90		96						22		86	99
E. faecalis	515	99				100	84		99						21		99	99
E. faecium[3]	117	24				93	100		92						26		40	-
VRE[3]	111	2				92	100		91						25		0	-
Staphylococcus aureus[4]	931		70		78	100	98		100	70			99		91	97	100	100
MSSA[4,5]	656		100		84	100	99		100	100			100		92	98	100	100
MRSA[4]	285		0		64	100	97		100	0			98		89	93	100	100
Coagulase-Negative Staphylococci	313		48		55	100	98		100	48			96		85	-	100	100
Staphylococcus lugdunensis	68		99		88	100	100		100	99			99		97	-	100	100
***S. pneumoniae,* respiratory only**[7]	78	-		94	87			97[6]	-		96	63		63	-	-	100	
***S. pneumoniae,* NOT meningitis**	65	-		97	85			97	-		97	68			-	-	100	
***S. pneumoniae,* Meningitis**	65	-		94							68						100	
Viridans Group Streptococci	77	-		96	-	-		-	-		86						100	
Streptococcus oralis/mitis	32	-		100	-	-		-	-		84						100	
Streptococcus anginosus group	35	-		97	-	-		-	-		97						100	

Grey boxes indicate organism has intrinsic resistance to the corresponding antimicrobial; boxes w/ hashes indicate organism may be susceptible, but insufficient data

[1]Linezolid should not be frequently used in the management of blood stream infections with *Staphylococcus spp.*, it may be used for the management of VRE bacteremia

[2]Enterococci susceptible to ampicillin can be predictably susceptible to ampicillin-sulbactam, amoxicillin, amoxicillin-clavulanate, and piperacillin-tazobactam.

[3]VRE sensitivities to daptomycin are variable and frequently fall at or near the clinical breakpoint for susceptibility (esp. VR-*E. faecium*), Discussion with ID Consult for non-urinary VRE infections is needed prior to daptomycin use to ensure optimal dosing (10-12mg/kg/dose), identified source, and need for combination therapy

[4]*Staphylococcus aureus* blood stream and other moderate to severe infections should **NOT** generally be treated with orals, even if susceptible. Preferred MSSA therapy is IV cefazolin or nafcillin (for CNS infections). Vancomycin, daptomycin, or ceftaroline are preferred for MRSA infections, linezolid may be used for MRSA pneumonia without concurrent bacteremia.

[5]Oxacillin sensitive *Staphylococcus aureus* = MSSA

[6]Susceptibility to moxifloxacin does not always indicate levofloxacin sensitivity, but most respiratory isolates that are sensitivity to moxifloxacin should be susceptible to levofloxacin.

[7]Susceptibility to oral penicillin (MIC ≤ 0.06 / susceptible by oxacillin disc) is predictably susceptible to amoxicillin, cefuroxime, cefpodoxime for non-severe infections

Cumulative Anaerobic and *Candida spp.* Susceptibilities

Cumulative Anaerobic Susceptibilities (UCHealth Metro, 2010-2018)	**% Susceptible**							
	Isolates (n)	**Penicillin**	**Ampicillin-Sulbactam**	**Piperacillin-Tazobactam**	**Cefoxitin**	**Ertapenem**	**Metronidazole**	**Clindamycin**
***Bacteroides fragilis* group**[1]	134	0	88[2]	83[2]	72	97	99	63
Prevotella spp.	40	28	100[2]	95[2]	98	100	98	64
Fusobacterium spp.	55	98	100[2]	95[2]	99	100	95	95
Clostridium perfringens	30	100	100[2]	100[2]	100	100	97	50
***Clostridium spp.* (non-perfrignens/non-difficile)**	34	62	100[2]	95[2]	75	100	100	41

[1] B. fragilis group includes: B. fragilis, B. ovatus, B. vulgatis, B. uniformis, B. thetaiotamicron, B. eggerthii, and Parabacterioides distasonis. According to U.S. cumulative susceptibility data, B. fragilis is relatively susceptible to beta-lactams with the exception of Cefoxitin at 87% (Amp-Sulb, 90%; Pip-Taz, 98%; Ertapenem/Meropenem, 98%). Organisms belonging to the DOT-group (distasonis, ovatus, and thetaiotamicron) have relatively lower rates of susceptibility to amp-sulb and pip-tazo, but are 99-100% susceptible to metronidazole.
[2] In 2018, standard susceptibilities for anaerobes changed from reporting piperacillin-tazobactam to ampicillin-sulbactam. There are only a limited number of anaerobic susceptibilities for ampicillin-sulbactam; interpret percentages with caution.

Cumulative Antifungal Susceptibilities (UCHealth Metro, 2014-2018)	**% Susceptible**				
	Isolates (n)	**Amphotericin-B**	**Anidulafungin**	**Fluconazole**	**Voriconazole**
C. albicans	219	100	100	97	98
C. glabrata	145	99	96	84% SDD[1]	--
C. parapsilosis	48	100	96	100	100
C. krusei	17[3]	100	100	0[2]	94
C. tropicalis	13[3]	92	100	85	54

[1] Fluconazole and other azoles have reduced susceptibility for *C. glabrata* due to efflux. Using fluconazole for these infections requires consideration of infection site and high-dosages. Echinocandin preferred for severe infection.
[2] *C. krusei* is intrinsically fluconazole resistant, but frequently voriconazole sensitive
[3] These species contain fewer than 30 isolates, interpret %Sensitivity with caution
**For *C. dublienensis* similar to *C. albicans* with respect to susceptibility

Antibiograms from Urine Specimens Only (Inpatient and Outpatient)

Inpatient Urine Only Organisms (UCHealth Metro, 2017-2018)	% Susceptibility																			
	Isolates (N)	AMIKACIN	TOBRAMYCIN	GENTAMICIN	AMPICILLIN	AMOX-CLAV	CEFAZOLIN (systemic infx, MIC ≤ 2 mcg/mL)	Cephalexin (cystitis only, MIC ≤ 16 mcg/mL)	CEFUROXIME	CEFTRIAXONE	CEFTAZIDIME	CEFEPIME	PIP-TAZO	MEROPENEM	ERTAPENEM	CIPROFLOXACIN / LEVOFLOXACIN	BACTRIM	Vancomycin	Daptomycin	Linezolid	Nitrofurantoin
Escherichia coli	1545	100	90	91	51	84	73	91	90	93	94	94	97	100	100	79	73				99
Klebsiella spp.	363	100	94	96		90	73	-	86	92	94	96	91	99	99	91	87				43
Klebsiella pneumoniae	294	100	93	95		92	83	94	87	94	94	95	93	99	99	90	86				34
Klebsiella oxytoca	56	100	96	98		79	20	-	74	82	96	98	78	100	100	93	93				84
Proteus spp.	95	100	86	85	71	92	2	89	87	93	98	95	98	100	100	73	78				
Enterobacter spp.	119	98	98	98						67	69	82	71	98	89	99	92				19
Citrobacter spp.	53	100	94	96		34			36	77	79	98	85	100	100	94	91				70
Pseudomonas aeruginosa	119	98	97	-							93	93	90	86		82					
Enterococcus spp.	373				84	-							-			69		88	99	98	99
E. faecalis	306				100	-							-			81		99	100	99	99
E. faecium	74				12	-							-			17		32	99	96	-
VRE	54				2	-							-			2			99	94	-

Outpatient Urine Only Organisms (UCHealth Metro, 2017-2018)	% Susceptibility										
	Isolates (N)	TOBRAMYCIN	Amoxicillin	AMOX-CLAV	Cephalexin (cystitis only)	CEFUROXIME	CEFTRIAXONE	CIPROFLOXACIN / LEVOFLOXACIN	BACTRIM	Nitrofurantoin	Tetracycline
Escherichia coli	936	91	53	87	91	92	95	82	74	98	75
Klebsiella spp.	150	95		95	94	92	95	94	85	46	83
Proteus spp.	32	93		97	88	94	100	90	88	0	0
Enterobacter spp.	39	97					74	100	90	18	95
Pseudomonas aeruginosa	46	93						63			
Enterococcus spp.	95		94	-				78		100	23
E. faecalis	89		100	-				84		100	25

ICU Antibiograms (Non-Urine and Urine Only)

ICU, Non-Urine Organisms (UCHealth Metro, 2017-2018)	% Susceptibility																							
	Isolates (N)	AMIKACIN	TOBRAMYCIN	GENTAMICIN	AMPICILLIN	AMOX-CLAV	AMP-SULB	CEFAZOLIN	Nafcillin	Penicillin (Parenteral)	CEFUROXIME	CEFTRIAXONE	CEFTAZIDIME	CEFEPIME	PIP-TAZO	AZTREONAM	MEROPENEM	ERTAPENEM	CIPROFLOXACIN / LEVOFLOXACIN	COLISTIN	BACTRIM	Vancomycin	Daptomycin	Linezolid	Rifampin
Escherichia coli	67	98	83	85	39	66	42	55			65	74	78	79	88	79	95	95	71	-	76				
Klebsiella spp.	81	99	97	99		88	58	56			81	93	94	94	88	91	94	94	94	-	89				
Enterobacter spp.	79	99	99	99								68	70	80	70	73	97	86	99	-	99				
Serratia spp.	30	97	75	97								90	93	93	93	97	93	93	97	-	-				
Pseudomonas aeruginosa	79	97	91	-									87	78	82	67	82		77	100					
Staphylococcus aureus	234			96		-	-	72	72		-	-		-	-		-	-			95	100	100	100	100
Enterococcus spp.	66			90	71	-	-			-					-							73	98	100	-
E. faecalis	39			-	100	-	-			-					-							100	100	100	-
E. faecium	39			-	13	-	-			-					-							18	89	100	-

ICU, Urine Only Organisms (UCHealth Metro, 2017-2018)	% Susceptibility																						
	Isolates (N)	AMIKACIN	TOBRAMYCIN	GENTAMICIN	AMPICILLIN	AMOX-CLAV	AMP-SULB	CEFAZOLIN	CEFUROXIME	CEFTRIAXONE	CEFTAZIDIME	CEFEPIME	PIP-TAZO	AZTREONAM	MEROPENEM	ERTAPENEM	CIPROFLOXACIN / LEVOFLOXACIN	COLISTIN	BACTRIM	Vancomycin	Daptomycin	Linezolid	Nitrofurantoin
Escherichia coli	136	100	85	89	49	78	50	68	86	90	92	91	96	90	100	99	74	-	79				99
Klebsiella spp.	66	100	94	94		85	62	57	74	86	94	94	85	88	98	98	92	-	92				29
Pseudomonas aeruginosa	46	98	96	-							89	91	85	65	83		85	100					
Enterococcus spp.	95			-	82	-	-						-							82	100	98	100
E. faecalis	78			-	99	-	-						-							97	100	97	100
E. faecium	33			-	6	-	-						-							6	100	100	100

Dual Anti-Pseudomonal Antibiogram (ICU)

Pseudomonas aeruginosa (UCHealth inpatient, 2017)	**% Susceptible**				
	Monotherapy	Plus Amikacin	Plus Tobramycin	Plus Ciprofloxacin	Plus Levofloxacin
Aztreonam (n=161)	71%	100%	98%	88%	87%
Ceftazidime (n=170)	93%	100%	100%	98%	98%
Cefepime (n=162)	88%	100%	98%	93%	94%
Piperacillin-tazobactam (n=170)	89%	100%	99%	95%	96%
Meropenem (n=170)	85%	100%	99%	92%	92%
Imipenem-cilastatin (n=171)	80%	100%	98%	88%	90%

- Information intended to guide initial selection of empiric combination therapy for critically-ill patients at risk for antibiotic-resistant infections, i.e. *Pseudomonas spp.*
- Determining combined susceptibilities is based on choosing a β-Lactam (left column) Plus a non-β-Lactam agent (columns to the right)
- Preferred combination based on results is Cefepime 2g q8h or Ceftazidime 2g q8h + Tobramycin 7-10mg/kg
- Combination therapy should not be used when definitive susceptibilities demonstrate available β-lactam susceptibility
- Aminoglycoside durations ideally ≤ 3 days in most cases, which contributes minimal nephrotoxic/ototoxic risks

Antibiotic Stewardship Tip Sheet for Common Infections

Duration of therapy: Count inpatient antibiotics towards total duration of therapy

- Prolonged antibiotic courses may double C diff risk

Antibiotic Spectrum: Avoid unnecessary class switching if possible (e.g. switching ceftriaxone to levofloxacin at discharge)

- May double C. diff risk

Always check drug-drug interactions and check dose adjustment for renal function.

Skin infections:

- Vancomycin is not needed for non-purulent cellulitis.
- Cefazolin is a better antibiotic against MSSA and strep than vancomycin
- Recommended treatment course is 5 days as long as patients are improving
- Extending treatment duration does not improve outcomes
- Anaerobic and gram negative coverage is not needed for most skin infections (exceptions: immunocompromised host, bites, injection drug use, severe/chronic ulcers or necrotizing infections)
- Mild to moderate diabetic foot infections do not need broader antibiotics, *Pseudomonas* is an infrequent pathogen in diabetic foot infections without significant prior exposure to broad-spectrum antibiotics

UTI/CAUTI:

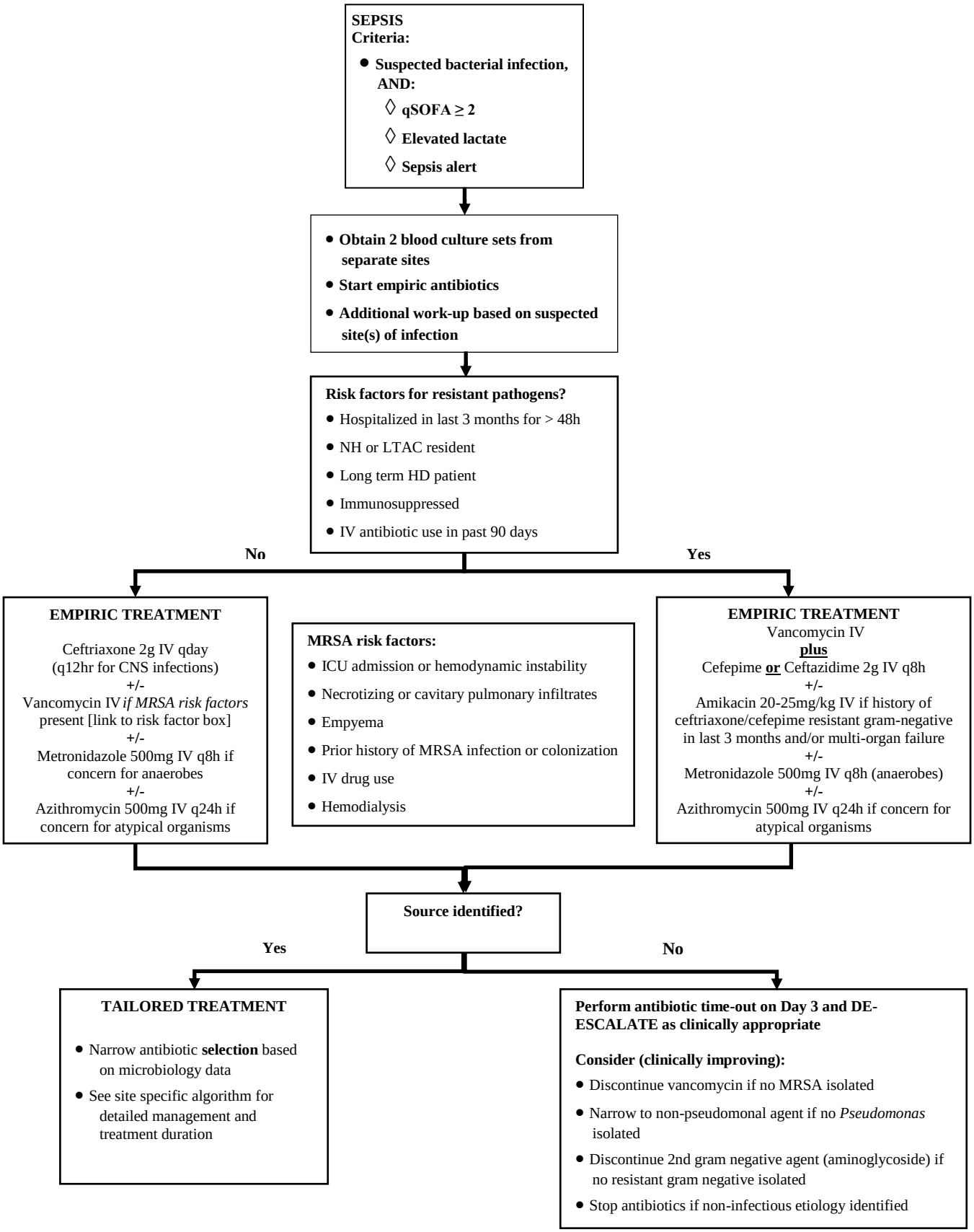
- Delirium alone is not a clear sign for UTI (neither sensitive nor specific)
- UTI typically accompanied by other symptoms (e.g. dysuria)
- Shorter treatment courses recommended w/ appropriate clinical response (see pages 11-12), including those with bacteremic pyelonephritis. Duration in a majority of patients should be ≤ 7 days.
- Avoid class switch at discharge (e.g. switching ceftriaxone to levofloxacin)

Pneumonia:

- CAP
    - Viruses are the most common cause for community-acquired pneumonia. Secondary bacterial infections occur in only ~20% (most common causes of secondary bacterial pneumonia is *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Staphylococcus aureus*, *Streptococcus pyogenes*)
    - The most common cause of hospitalized CAP is rhinovirus
    - Consider d/c antibacterial antibiotics if only viral pathogen found (may consider concurrent assessment of procalcitonin to rule out secondary bacterial pneumonia)
    - Pneumococcal bacteremia presence does not necessitate extended duration of antibiotics, 5 days is usually sufficient if clinically stable and afebrile x 48 hours
- HCAP does not routinely need broad antibiotics (new 2016 guidelines)
    - Treat the same as CAP unless septic shock, immunocompromised, or recent use of broad spectrum antibiotics
- HAP/VAP does not routinely need double-pseudomonal or MRSA coverage (MRSA causing HAP/VAP is < 10% at UCH, only add vancomycin if history of MRSA infection/colonization or critically ill)

Infection	Length of Therapy (Most Cases)
Community Acquired Pneumonia	5 days (clinically stable and afebrile x 2-3 days)
Hospital Acquired/Ventilator Associated Pneumonia	7 days with good initial clinical response
Skin-soft tissue infection (cellulitis)	5-7 days (erythema may not completely resolve by end of treatment, but should regress)
Uncomplicated cystitis	3-5 days (depends on antibiotic choice)
Complicated cystitis	5-7 days (depends on antibiotic choice, complicating feature, and clinical response)
Acute, uncomplicated pyelonephritis	5-7 days (including those with concomitant bacteremia)
Complicated intra-abdominal infections	4 days (adequate source control) ≥ 5-7 days (inadequate source control)
Bacteremia	Depends on source/pathogen/response – usually same duration as indicated for source *Staphylococcus aureus/lugdenensis* usually 4-6 weeks (ID Consult Strongly Encouraged)
**Guideline Based, Usual Durations for "Straight-Forward" Cases	

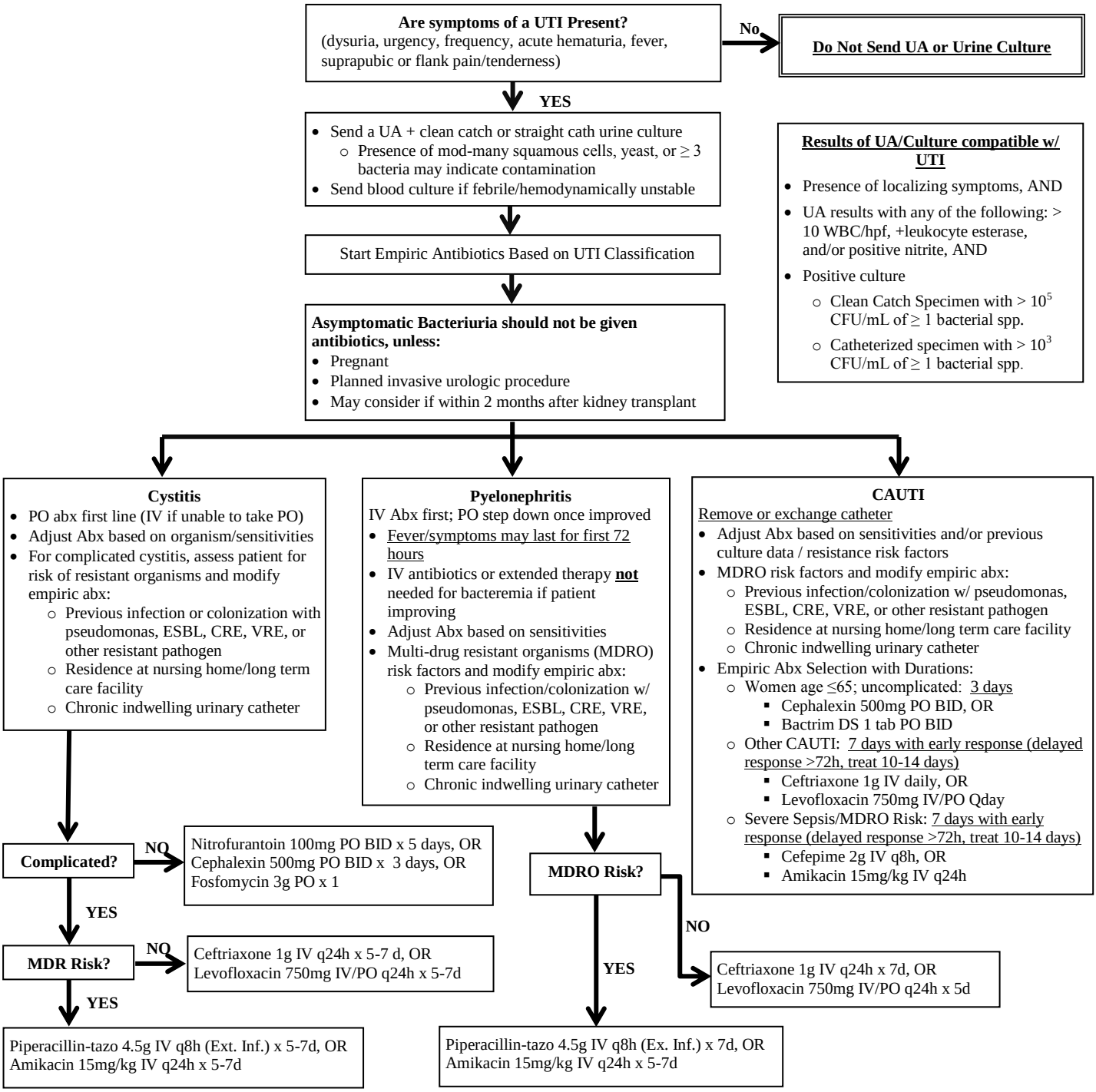
Sepsis Pathway



Notes:

- *Consider prior infection/colonization when selecting empiric antibiotics (e.g., use carbapenem if history of, or concern for, ESBL organisms)*
- *Fluoroquinolones are NOT recommended as a 2nd agent for empiric dual gram-negative coverage (see dual antibiogram)*
- *Alternatives for severe beta-lactam allergy: replace cephalosporin with aztreonam 2g IV q8h OR levofloxacin 750 IV/PO mg daily*

Urinary Tract Infections Algorithm



Predictive value of UA and culture

1. Many cases of positive urine cultures are asymptomatic bacteriuria only
2. Approximately 50% of patients with asymptomatic bacteriuria receive antibiotics unnecessarily
3. A "dirty" UA cannot rule in a UTI, and cannot distinguish asymptomatic bacteriuria from a UTI
   a. You must evaluate for symptoms
4. Catheterized patients almost universally have pyuria and bacteriuria → positive predictive value is only ~25% for UTI
   a. Pyuria and bacteriuria only helpful if negative → negative predictive value of 90-100%
   b.

Table 1: Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of UA for UTI

	Emergency Department		Elderly Patients		Catheterized Patients	
Test	**PPV**	**NPV**	**PPV**	**NPV**	**PPV**	**NPV**
Pyuria (> 5-10 WBCs/HPF)	56	95	--	--	15-28	92-100
Hematuria (> 5 RBCs/HPF)	51	88	---	--	--	--
Nitrite	83	70	74	81	33-38	88-91
Leukocyte Esterase	50	83	46	82	38	91
Nitrite and LE	100	71	77	79	45	88
Bacteria (any amount)	60	74	--	--	25	92

* Values designated as -- have not been studied for predictive value of UA findings for UTI

Table 2: Prevalence of Asymptomatic Bacteriuria

Group	**Prevalence (%)**
Healthy, Premenopausal Women	1 – 5
Pregnant Women	1.9 – 9.5
Postmenopausal Women Aged 50-70yr	2.8 – 8.6
Diabetes Patients	
Women	9 – 27
Men	0.7 – 11
Elderly (Age ≥ 70 Years) in Community	
Women	**10.8 – 16**
Men	**3.6 – 19**
Elderly Person in Long-Term Care	
Women	**25 – 50**
Men	**15 – 40**
Patients with Spinal Cord Injuries	
Intermittent Catheter Use	**23 – 89**
Sphincterotomy and Condom Cath Use	**57**
Patients Undergoing Hemodialysis	**28**
Patients with Indwelling Catheter Use	
Short-Term	**9 – 23**
Long-Term	**100**

Table 3. Treatment Outcomes for UTI

Uncomplicated Cystitis	
Nitrofurantoin [1,2]	No difference in cure for **5 days** vs. 7
SMZ/TMP [1,2]	No difference in cure for **3 days** vs. 7
Fosfomycin [1-2, 5]	Single dose over 90% effective
Fluoroquinolones [1-2, 4]	No difference in cure for **3 days** vs. 7
Beta-lactams [1-3]	No difference in cure for **3-5 days** vs. 7

1. Grigoryan L. *JAMA*. 2014; 312(16): 1677-84.
2. Gupta K. *Clin Infect Dis*. 2011; 52(5): 103-20.
3. Menday AP. *Int J Antimicrob Agents*. 2000; 13(3): 183-7
4. Vachhani AV. *Infez Med*. 2015; 23(2): 155-60.
5. Elhanan G. *Antimicrob Agents Chemother*. 1994; 38(11): 2612-4.

Uncomplicated Pyelonephritis	
Fluoroquinolones[1-3]	**5 days** (Levofloxacin) – **7 days** (cipro) as effective as longer durations
Beta-Lactams (IV first→PO)[4-5]	**10 days** as effective as 14 days. Switch to PO once clinically improved

1. Peterson J. *Urology*. 2008; 71(1): 17-22.
2. Sandberg T. *Lancet*. 2012; 380(9840): 484-90.
3. Talan DA. *JAMA*. 2000; 283(12): 1583-90.
4. Sanchez M. *Emerg Med J*. 2002; 19(1): 19-22.
5. Monmaturapoj T. *Int J Infect Dis*. 2012; 16: 843-9.

Table 4: Microbiological Etiology by UTI Type

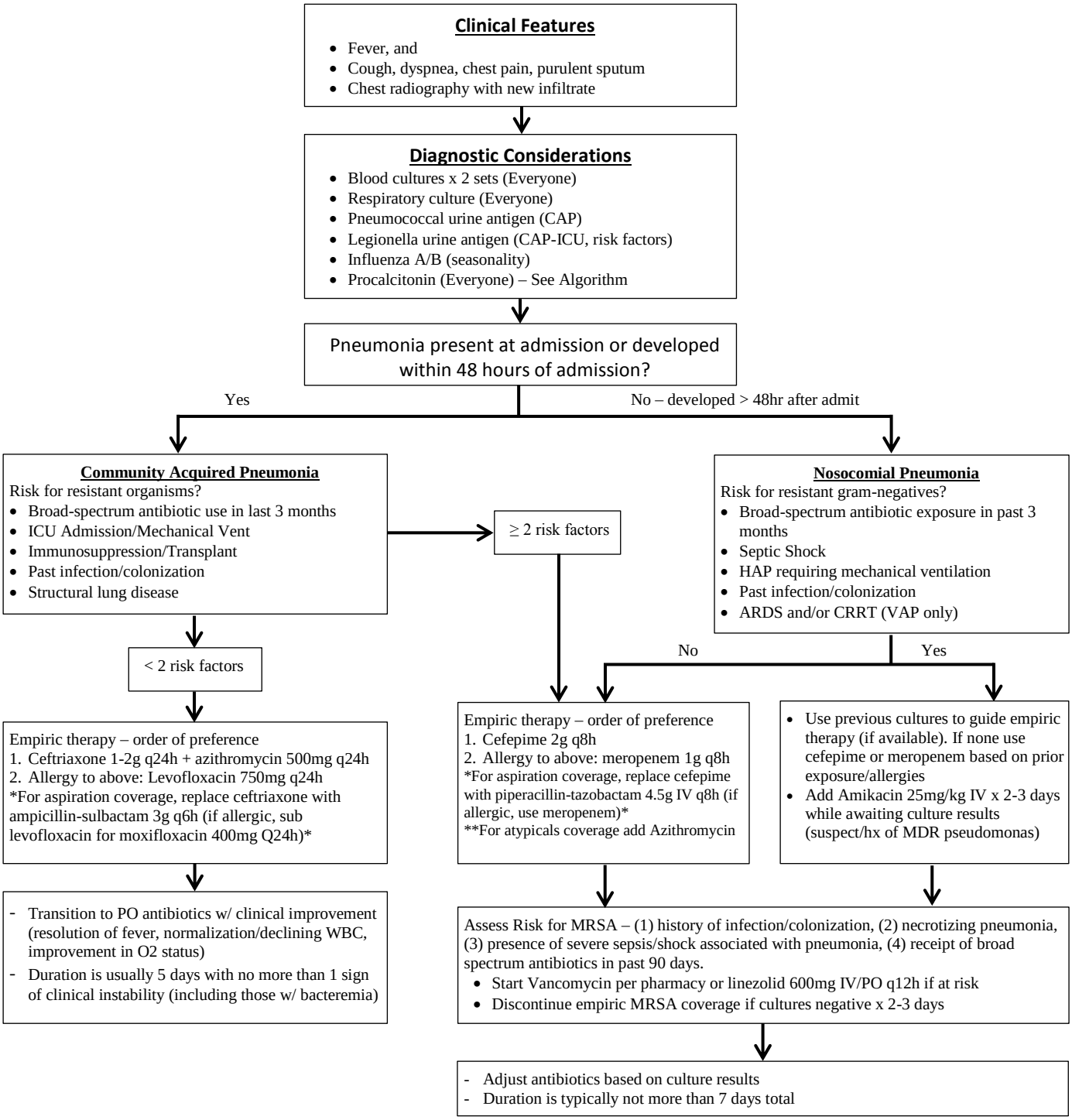
Pathogens	**Uncompl. Cystitis**	**Compl. Cystitis**	**Pyelo**	**CAUTI**
E. coli	81%	56.5%	85%	26.8%
Staphylococcus saprophyticus/CoNS	5%	--	2.3%	-- / 2.2%
Proteus mirabilis	3%	3.9%	1.4%	4.8%
S. agalactiae	2.8%	--	1.9%	--
K. pneumonia	2%	12.9%	4.7%	11.2%
Enterobacter spp.	2%	3.9%	--	4.2%
Enterococcus spp.	1%	7.5%	1.9%	10.3%
Citrobacter spp.	--	4.5%	--	--
S. aureus	--	1.3%	--	2.1%
Pseudomonas a.	--	1.9%	--	11.3%
Candida spp.	--	--	--	12.7%
Serratia spp.	--	--	--	1%
Acinetobacter spp.	--	--	--	0.9%

Short courses of antibiotics (4-7 days) associated with half the C. diff risk of longer courses (8-18 days). Avoid antibiotic class switch if possible (e.g. ceftriaxone to quinolone at discharge).

Characteristic	CDI positive *n* (%)	CDI negative *n* (%)	Adjusted hazard rati (95% CI)
ntibiotic days*	14.0 (23.0)	7.0 (9.0)	—
<4	22 (9)	2208 (22)	Ref
4 to 7	41 (17)	3071 (31)	1.4 (.8, 2.4)
8 to 18	87 (36)	3097 (31)	3.0 (1.9, 5.0)
>18	91 (38)	1537 (16)	7.8 (4.6, 13.4)
of antibiotics*	3.0 (4.0)	2.0 (2.0)	—
1	31 (13)	3744 (38)	Ref
2	54 (22)	2507 (25)	2.5 (1.6, 4.0)
3 or 4	70 (29)	2505 (25)	3.3 (2.2, 5.2)
5 or more	86 (36)	1157 (12)	9.6 (6.1, 15.1)

*median (IQR)

Pneumonia Algorithm



Preferred (Alternate if allergic/intolerant to first choice agent[s]) Agents for Pathogen Directed Therapy (If Susceptible)					
Pathogen	**IV**	**PO Step-Down**	**Pathogen**	**IV**	**PO Step-Down**
***S. pneumoniae*[1]**	Ampicillin or Ceftriaxone (Levofloxacin)	Amox[2] or Cefuroxime (Levofloxacin)	***H. influenzae***	Ampicillin ± Sulbactam[3] or Ceftriaxone (Levofloxacin)	Amox ± Clav[3] or Cefuroxime (Levofloxacin)
MSSA	Cefazolin (Vancomycin)	Bactrim[2] (Linezolid)	**MRSA**	Vancomycin (Linezolid)	Bactrim[2] (Linezolid)
P. aeruginosa	Pip-Tazo or Ceftazidime (Ciprofloxacin)	Ciprofloxacin	**Atypicals (incl. Legionella)**	Azithromycin (Levofloxacin)	Azithromycin (Levofloxacin)
For unknown pathogen – preferred step down is Azithromycin 500mg PO Qday if CAP and Levofloxacin 750mg Qday if HCAP/HAP/VAP					

[1]Penicillin susceptible by disc and isolates w/ MIC ≤ 0.06 mcg/mL (non-meningitis) are predictably sensitive to ampicillin, amoxicillin, cefuroxime, and ceftriaxone. Use of sulbactam or clavulanate does not confer additional susceptibility. Use maximal doses of amp, amox, or cefuroxime.
[2] Preferred dosing of amoxicillin for pneumococcus is 1,000mg PO TID; Bactrim for MSSA/MRSA is 10-15mg/kg/day TMP in 2-3 divided doses
[3]Sulbactam and clavulanate should only be added to treat isolates testing positive for beta-lactamase enzyme

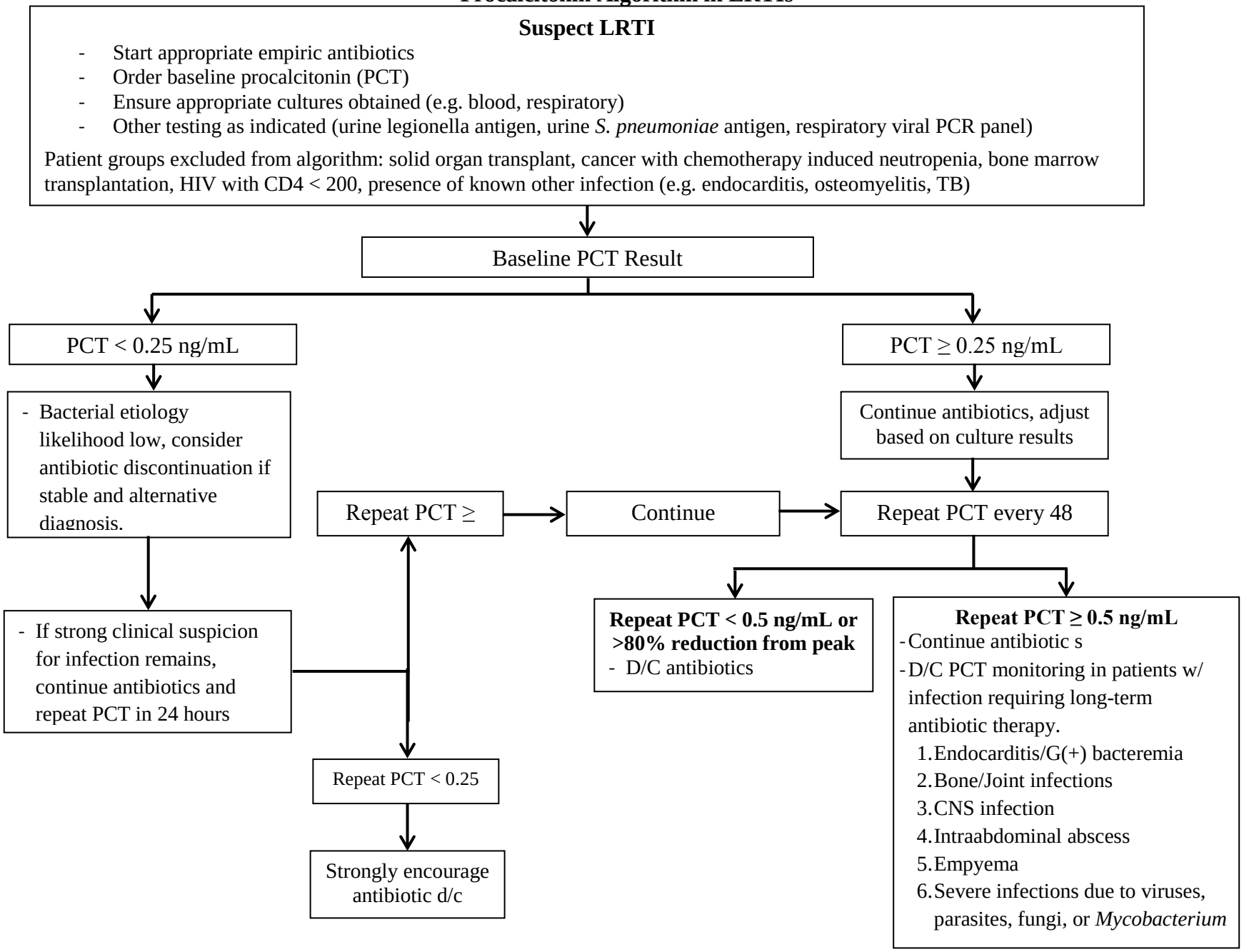
Procalcitonin Algorithm

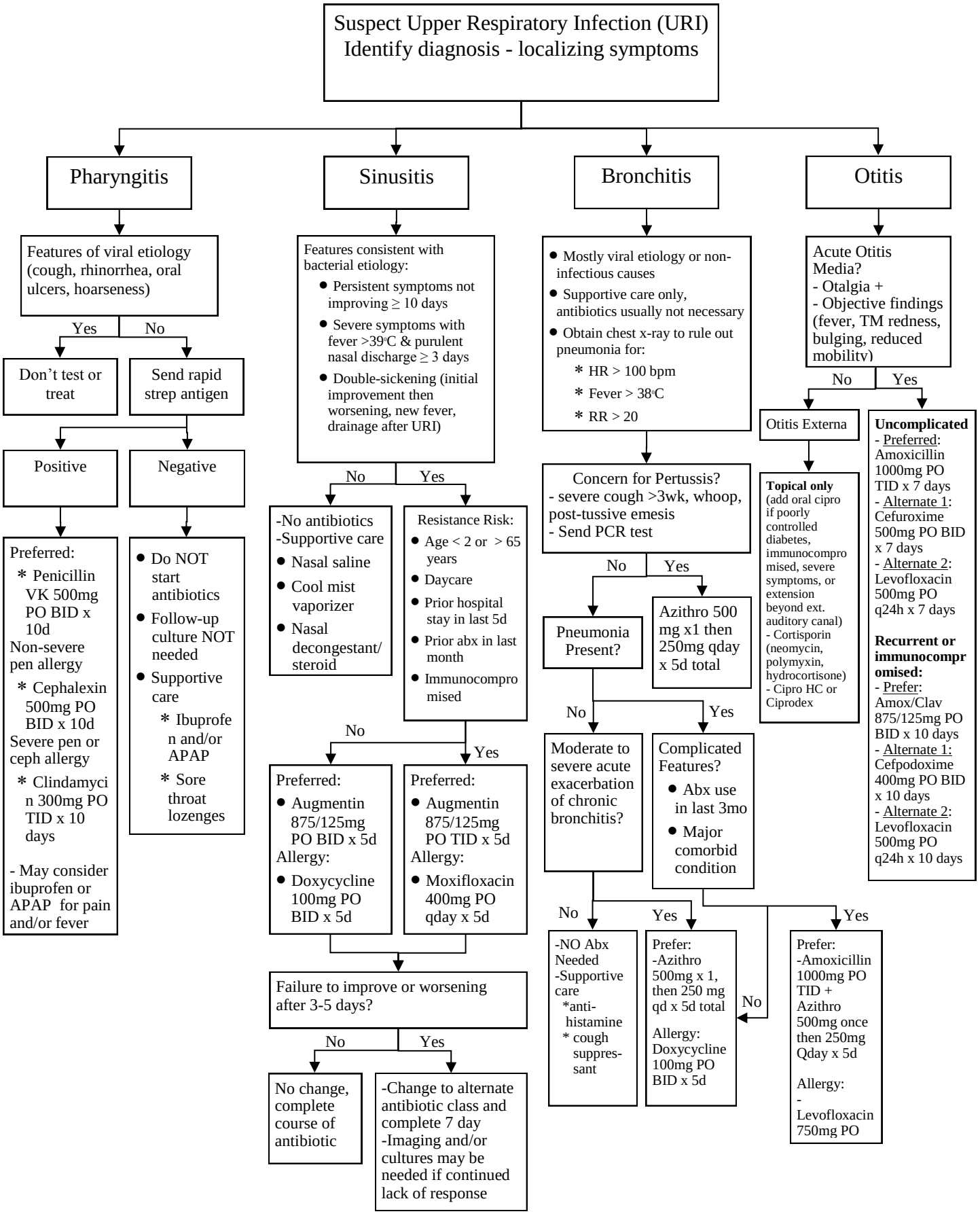
- Indications for Ordering
  - Suspected pneumonia
- Levels to be ordered
  - Baseline (within 24 hours of antibiotics); repeat in 24 hours if initial level < 0.5 ng/mL and strong suspicion for infection persists to detect late peak.
  - If baseline level(s) elevated, repeat PCT every 48 hours until normalized
- PCT levels should be used to guide antibiotic discontinuation when baseline elevated
  - Level decrease to an absolute value of < 0.5 ng/mL, and/or
  - Level decrease to less than ≥80% of peak values (e.g. if peak was 4.0 ng/mL, 80% decline would be a level of 0.8 ng/mL)
- PCT may distinguish between non-infectious causes of acute exacerbation of COPD and heart failure.
  - If clinical suspicion for bacterial pneumonia is high, start appropriate antibiotics based on risk factors and allergy history
  - If baseline and 24 hour PCT levels are <0.25 ng/mL, bacterial etiology is unlikely and antibiotics should be discontinued
    - This excludes those with severe immunosuppression and/or other sources of infection present (endocarditis, musculoskeletal, TB, abscess)
- Pharmacist Consult:
  - Pharmacists will identify patients with new antibiotic orders for suspected pneumonia
  - Pharmacists will ask if provider would like to consult for PCT monitoring, if so consult to pharmacy for PCT monitoring will be placed
  - Baseline PCT will be ordered, and result will be applied to algorithm below to determine appropriate follow-up actions
    - Repeat PCT may be ordered 24 hours after first if the baseline level is < 0.25 ng/mL and suspicion for bacterial infection remains high
    - Subsequent levels will be ordered every 48 hours if one/both of baseline levels elevated ≥ 0.25 ng/mL
  - When levels meet the criteria for antibiotic discontinuation (outlined in the below algorithm), pharmacists will recommend antibiotic discontinuation to the team based on the results of multiple randomized controlled trials documenting safe discontinuation at these levels
  - If at any point a separate infection is recognized that requires prolonged course of antibiotics (endocarditis, osteomyelitis, etc.), PCT monitoring by pharmacist consult will be discontinued and the consult closed

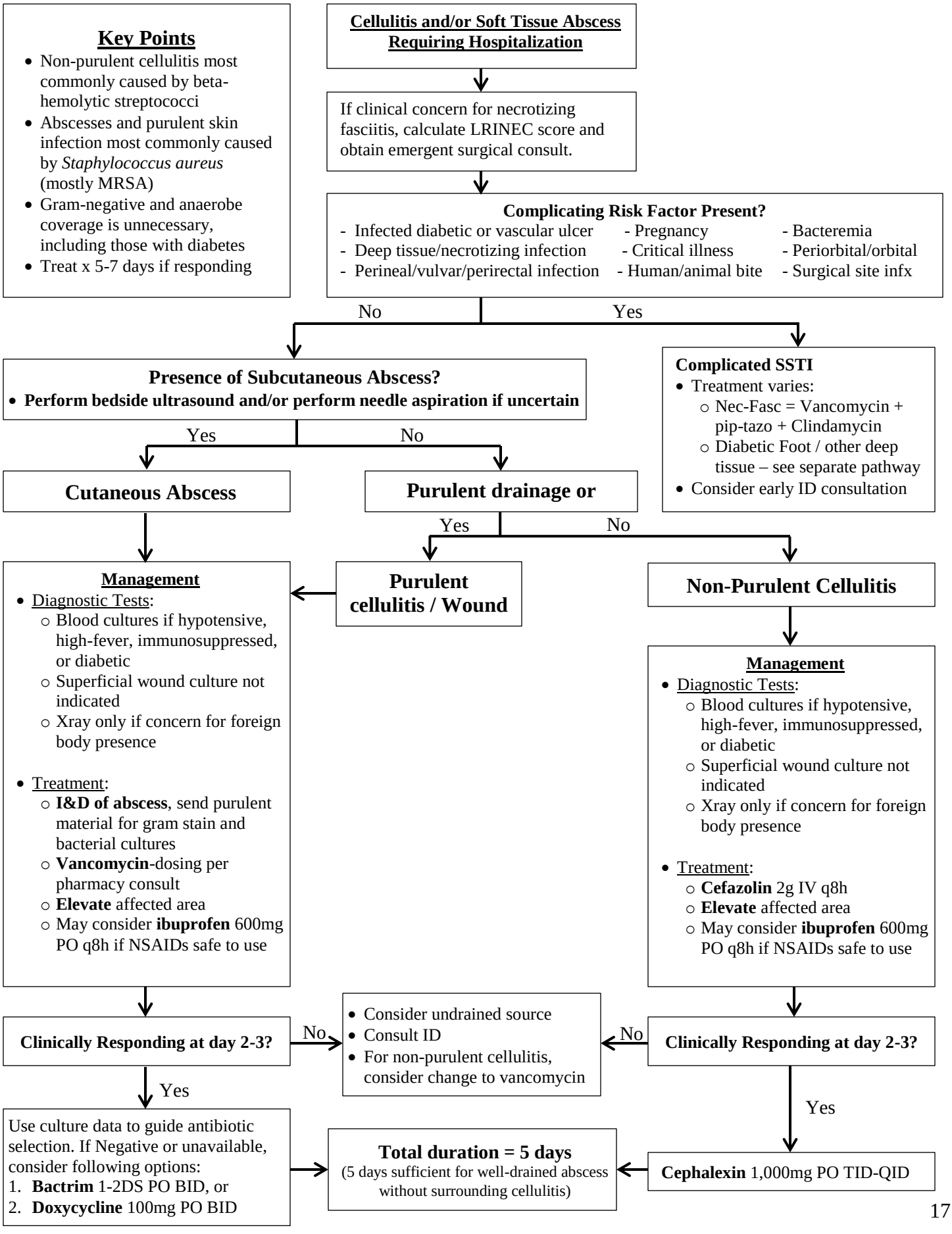
References:

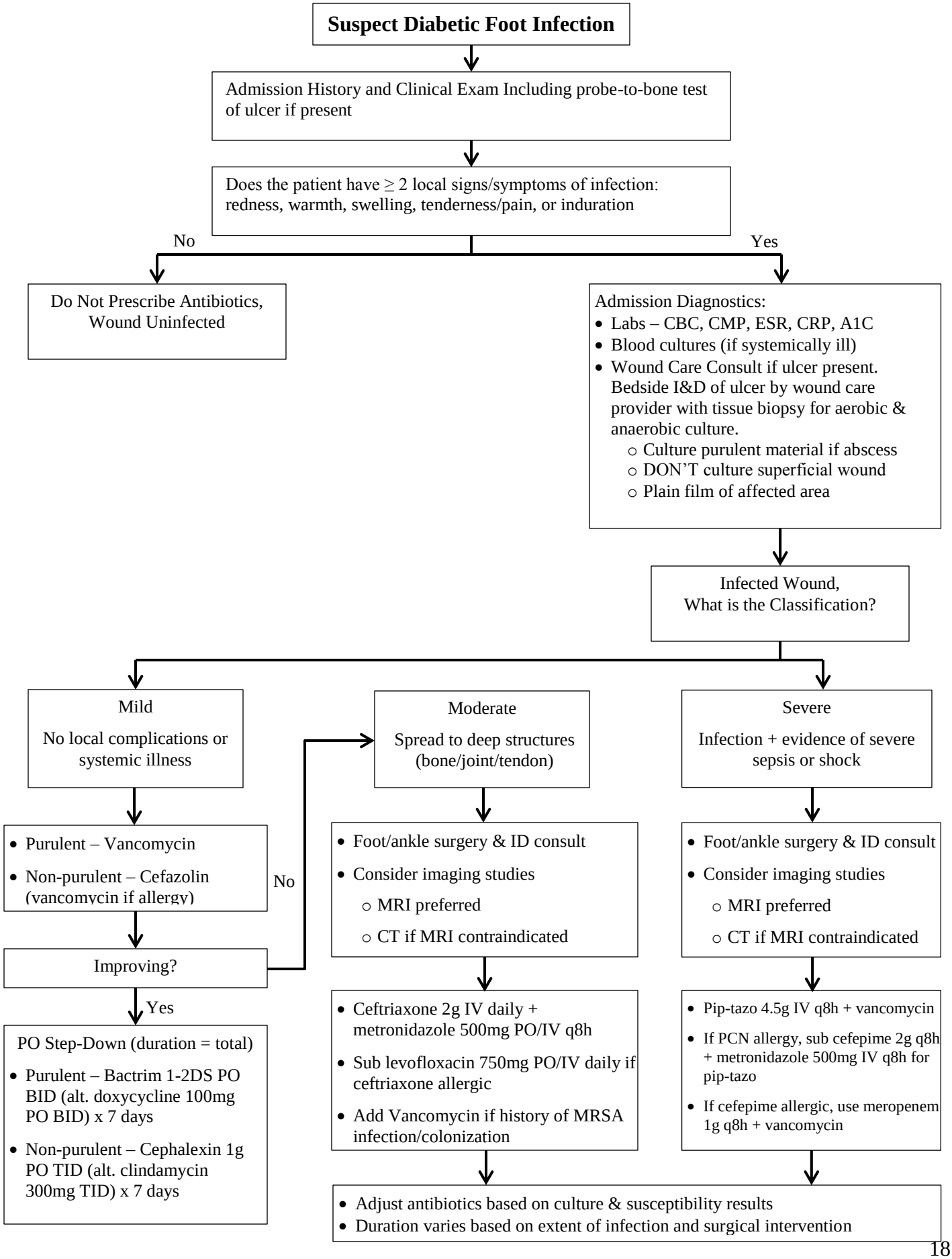
1. De Jong E, et al. Efficacy and safety of procalcitonin guidance in reducing the duration of antibiotic treatment in critically ill patients: a randomized, controlled, open-label trial. *Lancet Infect Dis*. 2016;
2. Bouadma L, et al. Use of procalcitonin to reduce patients' exposure to antibiotics in intensive care units (PRORATA trial): a multicentre randomised controlled trial. *Lancet.* 2010; 375: 463-74.
3. Albrich WC, et al. Effectiveness and Safety of Procalcitonin-Guided Antibiotic Therapy in Lower Respiratory Tract Infections in "Real Life". *Arch Intern Med*. 2012; 172(9): 715-22.
4. Stolz D, Christ-Crain M, Bingisser R, et al. Antibiotic Treatment of Exacerbations of COPD: A Randomized, Controlled Trial Comparing Procalcitonin-Guidance with Standard Therapy. *Chest*. 2007; 131: 9-19.
5. Sager R, Kutz A, Mueller B, et al. Procalcitonin-guided diagnosis and antibiotic stewardship revisited. *BMC Medicine*. 2017; 15 (15): 1-11.

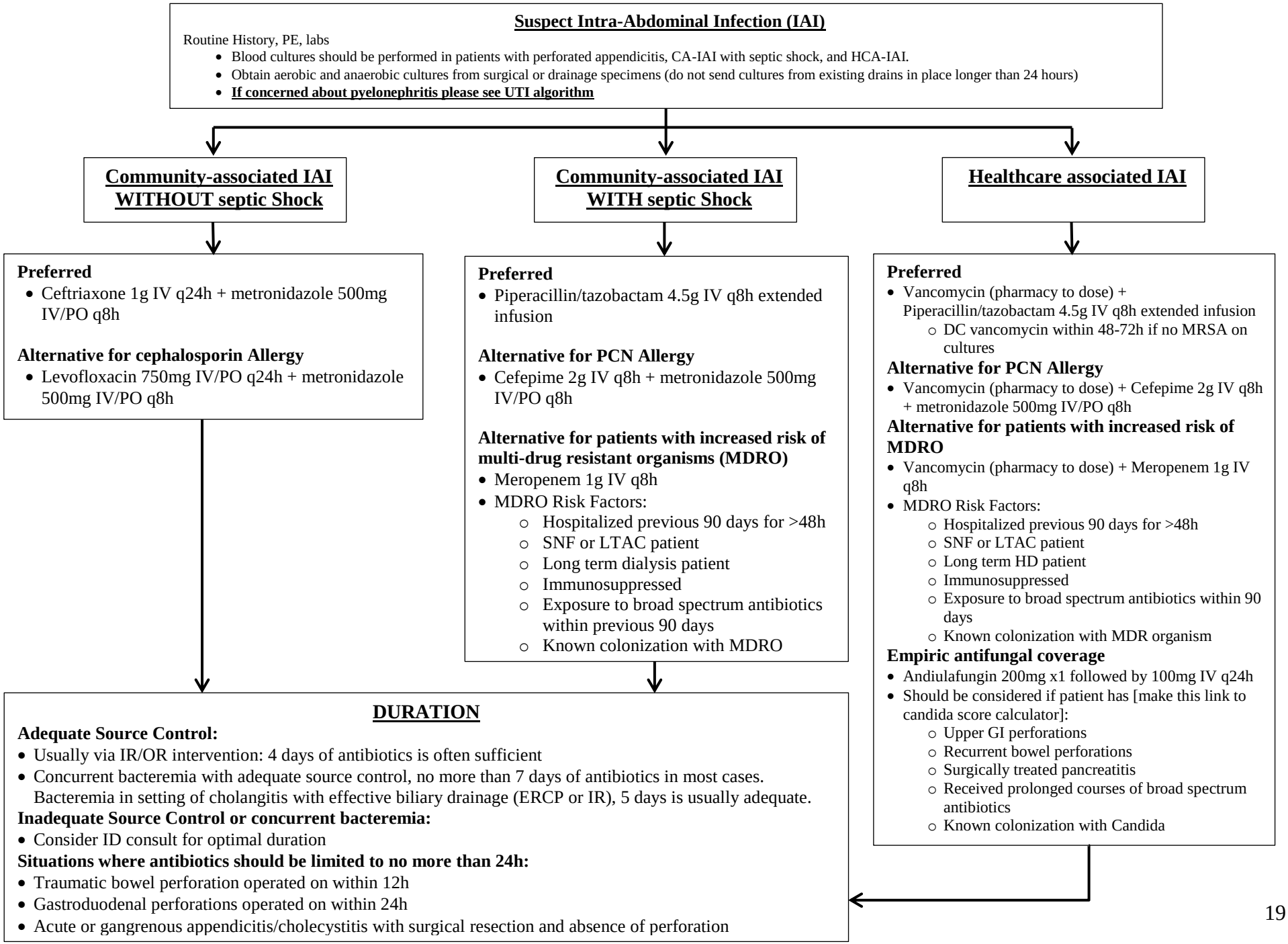
Procalcitonin Algorithm in LRTIs

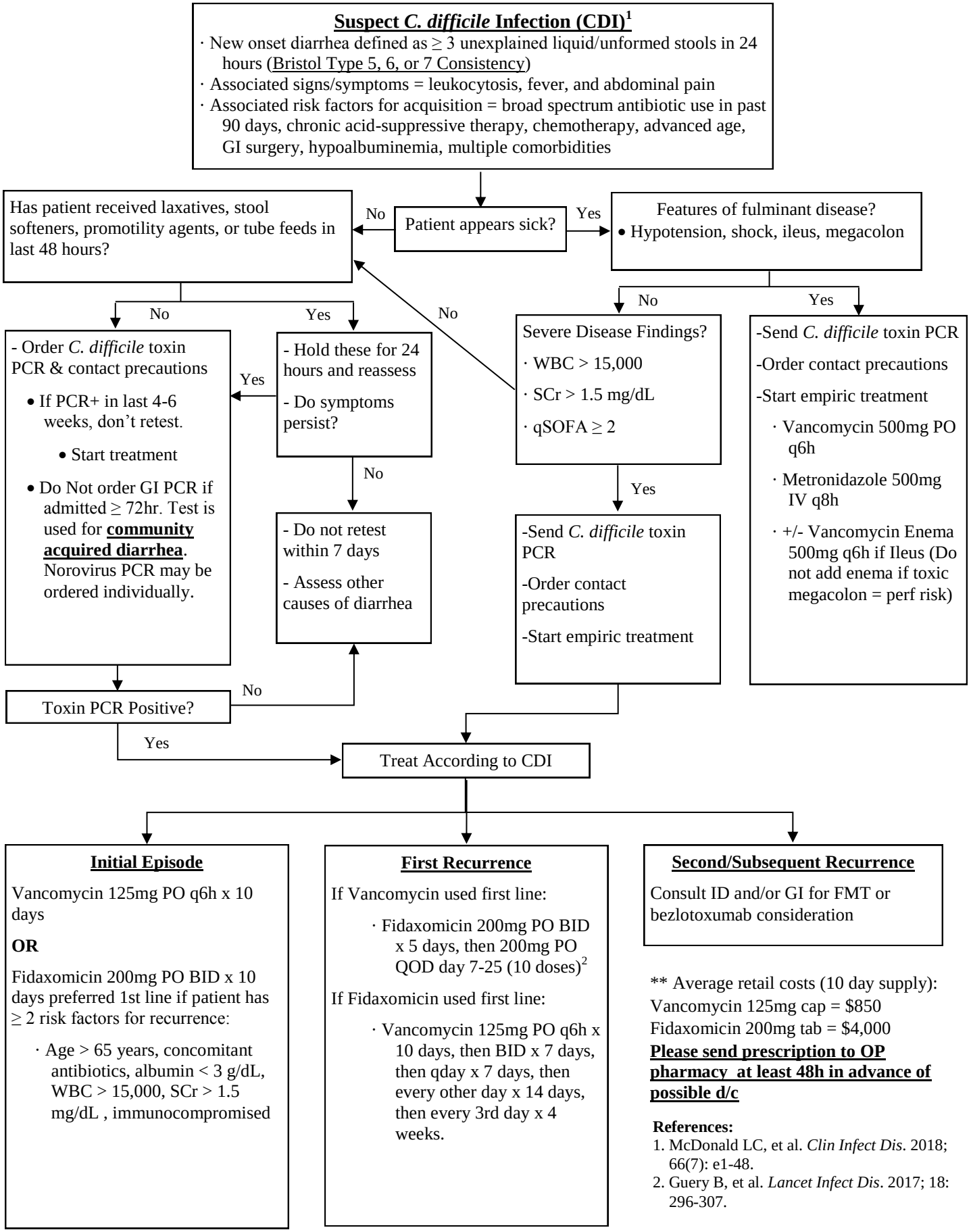



Suspect Upper Respiratory Infection (URI)
Identify diagnosis - localizing symptoms
Pharyngitis
Features of viral etiology (cough, rhinorrhea, oral ulcers, hoarseness)
Yes
No
Don't test or treat
Send rapid strep antigen
Positive
Negative
Preferred:
* Penicillin VK 500mg PO BID x 10d
Non-severe pen allergy
* Cephalexin 500mg PO BID x 10d
Severe pen or ceph allergy
* Clindamycin 300mg PO TID x 10 days
- May consider ibuprofen or APAP for pain and/or fever
• Do NOT start antibiotics
• Follow-up culture NOT needed
• Supportive care
* Ibuprofen and/or APAP
* Sore throat lozenges
Sinusitis
Features consistent with bacterial etiology:
• Persistent symptoms not improving ≥ 10 days
• Severe symptoms with fever >39°C & purulent nasal discharge ≥ 3 days
• Double-sickening (initial improvement then worsening, new fever, drainage after URI)
No
Yes
-No antibiotics
-Supportive care
• Nasal saline
• Cool mist vaporizer
• Nasal decongestant/ steroid
Resistance Risk:
• Age < 2 or > 65 years
• Daycare
• Prior hospital stay in last 5d
• Prior abx in last month
• Immunocompromised
No
Yes
Preferred:
• Augmentin 875/125mg PO BID x 5d
Allergy:
• Doxycycline 100mg PO BID x 5d
Preferred:
• Augmentin 875/125mg PO TID x 5d
Allergy:
• Moxifloxacin 400mg PO qday x 5d
Failure to improve or worsening after 3-5 days?
No
Yes
No change, complete course of antibiotic
-Change to alternate antibiotic class and complete 7 day
-Imaging and/or cultures may be needed if continued lack of response
Bronchitis
• Mostly viral etiology or non-infectious causes
• Supportive care only, antibiotics usually not necessary
• Obtain chest x-ray to rule out pneumonia for:
* HR > 100 bpm
* Fever > 38°C
* RR > 20
Concern for Pertussis?
- severe cough >3wk, whoop, post-tussive emesis
- Send PCR test
No
Yes
Azithro 500 mg x1 then 250mg qday x 5d total
Pneumonia Present?
No
Yes
Moderate to severe acute exacerbation of chronic bronchitis?
Complicated Features?
• Abx use in last 3mo
• Major comorbid condition
No
Yes
Yes
-NO Abx Needed
-Supportive care
*anti-histamine
* cough suppressant
Prefer:
-Azithro 500mg x 1, then 250 mg qd x 5d total
Allergy:
Doxycycline 100mg PO BID x 5d
No
Prefer:
-Amoxicillin 1000mg PO TID + Azithro 500mg once then 250mg Qday x 5d
Allergy:
-
Levofloxacin 750mg PO
Otitis
Acute Otitis Media?
- Otalgia +
- Objective findings (fever, TM redness, bulging, reduced mobility)
No
Yes
Otitis Externa
Topical only (add oral cipro if poorly controlled diabetes, immunocompromised, severe symptoms, or extension beyond ext. auditory canal)
- Cortisporin (neomycin, polymyxin, hydrocortisone)
- Cipro HC or Ciprodex
Uncomplicated
- Preferred: Amoxicillin 1000mg PO TID x 7 days
- Alternate 1: Cefuroxime 500mg PO BID x 7 days
- Alternate 2: Levofloxacin 500mg PO q24h x 7 days
Recurrent or immunocompromised:
- Prefer: Amox/Clav 875/125mg PO BID x 10 days
- Alternate 1: Cefpodoxime 400mg PO BID x 10 days
- Alternate 2: Levofloxacin 500mg PO q24h x 10 days


Key Points
Non-purulent cellulitis most commonly caused by beta-hemolytic streptococci
Abscesses and purulent skin infection most commonly caused by Staphylococcus aureus (mostly MRSA)
Gram-negative and anaerobe coverage is unnecessary, including those with diabetes
Treat x 5-7 days if responding
Cellulitis and/or Soft Tissue Abscess Requiring Hospitalization
If clinical concern for necrotizing fasciitis, calculate LRINEC score and obtain emergent surgical consult.
Complicating Risk Factor Present?
- Infected diabetic or vascular ulcer
- Deep tissue/necrotizing infection
- Perineal/vulvar/perirectal infection
- Pregnancy
- Critical illness
- Human/animal bite
- Bacteremia
- Periorbital/orbital
- Surgical site infx
No
Yes
Presence of Subcutaneous Abscess?
Perform bedside ultrasound and/or perform needle aspiration if uncertain
Yes
No
Cutaneous Abscess
Purulent drainage or
Yes
No
Purulent cellulitis / Wound
Non-Purulent Cellulitis
Complicated SSTI
Treatment varies:
Nec-Fasc = Vancomycin + pip-tazo + Clindamycin
Diabetic Foot / other deep tissue – see separate pathway
Consider early ID consultation
Management
Diagnostic Tests:
Blood cultures if hypotensive, high-fever, immunosuppressed, or diabetic
Superficial wound culture not indicated
Xray only if concern for foreign body presence
Treatment:
I&D of abscess, send purulent material for gram stain and bacterial cultures
Vancomycin-dosing per pharmacy consult
Elevate affected area
May consider ibuprofen 600mg PO q8h if NSAIDs safe to use
Management
Diagnostic Tests:
Blood cultures if hypotensive, high-fever, immunosuppressed, or diabetic
Superficial wound culture not indicated
Xray only if concern for foreign body presence
Treatment:
Cefazolin 2g IV q8h
Elevate affected area
May consider ibuprofen 600mg PO q8h if NSAIDs safe to use
Clinically Responding at day 2-3?
No
Consider undrained source
Consult ID
For non-purulent cellulitis, consider change to vancomycin
No
Clinically Responding at day 2-3?
Yes
Yes
Use culture data to guide antibiotic selection. If Negative or unavailable, consider following options:
1. Bactrim 1-2DS PO BID, or
2. Doxycycline 100mg PO BID
Total duration = 5 days
(5 days sufficient for well-drained abscess without surrounding cellulitis)
Cephalexin 1,000mg PO TID-QID


Suspect Diabetic Foot Infection
Admission History and Clinical Exam Including probe-to-bone test of ulcer if present
Does the patient have ≥ 2 local signs/symptoms of infection: redness, warmth, swelling, tenderness/pain, or induration
No
Yes
Do Not Prescribe Antibiotics, Wound Uninfected
Admission Diagnostics:
• Labs – CBC, CMP, ESR, CRP, A1C
• Blood cultures (if systemically ill)
• Wound Care Consult if ulcer present. Bedside I&D of ulcer by wound care provider with tissue biopsy for aerobic & anaerobic culture.
○ Culture purulent material if abscess
○ DON'T culture superficial wound
○ Plain film of affected area
Infected Wound, What is the Classification?
Mild
No local complications or systemic illness
Moderate
Spread to deep structures (bone/joint/tendon)
Severe
Infection + evidence of severe sepsis or shock
• Purulent – Vancomycin
• Non-purulent – Cefazolin (vancomycin if allergy)
No
• Foot/ankle surgery & ID consult
• Consider imaging studies
○ MRI preferred
○ CT if MRI contraindicated
• Foot/ankle surgery & ID consult
• Consider imaging studies
○ MRI preferred
○ CT if MRI contraindicated
Improving?
Yes
PO Step-Down (duration = total)
• Purulent – Bactrim 1-2DS PO BID (alt. doxycycline 100mg PO BID) x 7 days
• Non-purulent – Cephalexin 1g PO TID (alt. clindamycin 300mg TID) x 7 days
• Ceftriaxone 2g IV daily + metronidazole 500mg PO/IV q8h
• Sub levofloxacin 750mg PO/IV daily if ceftriaxone allergic
• Add Vancomycin if history of MRSA infection/colonization
• Pip-tazo 4.5g IV q8h + vancomycin
• If PCN allergy, sub cefepime 2g q8h + metronidazole 500mg IV q8h for pip-tazo
• If cefepime allergic, use meropenem 1g q8h + vancomycin
• Adjust antibiotics based on culture & susceptibility results
• Duration varies based on extent of infection and surgical intervention


Suspect Intra-Abdominal Infection (IAI)
Routine History, PE, labs
Blood cultures should be performed in patients with perforated appendicitis, CA-IAI with septic shock, and HCA-IAI.
Obtain aerobic and anaerobic cultures from surgical or drainage specimens (do not send cultures from existing drains in place longer than 24 hours)
If concerned about pyelonephritis please see UTI algorithm
Community-associated IAI WITHOUT septic Shock
Community-associated IAI WITH septic Shock
Healthcare associated IAI
Preferred
Ceftriaxone 1g IV q24h + metronidazole 500mg IV/PO q8h
Alternative for cephalosporin Allergy
Levofloxacin 750mg IV/PO q24h + metronidazole 500mg IV/PO q8h
Preferred
Piperacillin/tazobactam 4.5g IV q8h extended infusion
Alternative for PCN Allergy
Cefepime 2g IV q8h + metronidazole 500mg IV/PO q8h
Alternative for patients with increased risk of multi-drug resistant organisms (MDRO)
Meropenem 1g IV q8h
MDRO Risk Factors:
Hospitalized previous 90 days for >48h
SNF or LTAC patient
Long term dialysis patient
Immunosuppressed
Exposure to broad spectrum antibiotics within previous 90 days
Known colonization with MDRO
Preferred
Vancomycin (pharmacy to dose) + Piperacillin/tazobactam 4.5g IV q8h extended infusion
DC vancomycin within 48-72h if no MRSA on cultures
Alternative for PCN Allergy
Vancomycin (pharmacy to dose) + Cefepime 2g IV q8h + metronidazole 500mg IV/PO q8h
Alternative for patients with increased risk of MDRO
Vancomycin (pharmacy to dose) + Meropenem 1g IV q8h
MDRO Risk Factors:
Hospitalized previous 90 days for >48h
SNF or LTAC patient
Long term HD patient
Immunosuppressed
Exposure to broad spectrum antibiotics within 90 days
Known colonization with MDR organism
Empiric antifungal coverage
Andiulafungin 200mg x1 followed by 100mg IV q24h
Should be considered if patient has [make this link to candida score calculator]:
Upper GI perforations
Recurrent bowel perforations
Surgically treated pancreatitis
Received prolonged courses of broad spectrum antibiotics
Known colonization with Candida
DURATION
Adequate Source Control:
Usually via IR/OR intervention: 4 days of antibiotics is often sufficient
Concurrent bacteremia with adequate source control, no more than 7 days of antibiotics in most cases. Bacteremia in setting of cholangitis with effective biliary drainage (ERCP or IR), 5 days is usually adequate.
Inadequate Source Control or concurrent bacteremia:
Consider ID consult for optimal duration
Situations where antibiotics should be limited to no more than 24h:
Traumatic bowel perforation operated on within 12h
Gastroduodenal perforations operated on within 24h
Acute or gangrenous appendicitis/cholecystitis with surgical resection and absence of perforation



** Average retail costs (10 day supply):
Vancomycin 125mg cap = $850
Fidaxomicin 200mg tab = $4,000

Please send prescription to OP pharmacy at least 48h in advance of possible d/c

References:
1. McDonald LC, et al. *Clin Infect Dis*. 2018; 66(7): e1-48.
2. Guery B, et al. *Lancet Infect Dis*. 2017; 18: 296-307.

Probiotics for *C. difficile* (CDI) Prevention Checklist

- ☐ Is the patient starting on broad-spectrum antibiotics posing a moderate to high risk for CDI for an expected duration > 48 hours?
  - ☐ Fluoroquinolone
  - ☐ Carbapenem
  - ☐ Clindamycin
  - ☐ Ampicillin-sulbactam
  - ☐ Amoxicillin-clavulanate
  - ☐ Piperacillin-tazobactam
  - ☐ Ceftolozane-tazobactam
  - ☐ Ceftazidime-avibactam
  - ☐ Cefpodoxime
  - ☐ Cefdinir
  - ☐ Ceftriaxone
  - ☐ Ceftazidime
  - ☐ Cefepime
  - ☐ Ceftaroline
  - ☐ Aztreonam
    - Patients with history of active CDI in last 60 days and starting broad-spectrum antibiotic(s), would consider use of secondary vancomycin 125mg PO BID prophylaxis continued for 5 days after broad spectrum antibiotic(s) discontinue over use of probiotics (avoid use of both PO vancomycin and probiotics).

- ☐ Does the patient have any exclusion criteria (if yes, would not recommend probiotics)
  - ☐ Neutropenia (ANC < 500)
  - ☐ HIV with CD4 < 200
  - ☐ Active CDI
  - ☐ Severe, acute pancreatitis
  - ☐ Active hematological malignancy
  - ☐ History of transplantation (solid or hematologic)
  - ☐ Pregnancy
  - ☐ Active colitis (i.e. Crohn's, UC), active GI bleed, and/or GI perforation, Plus presence of prosthetic heart valve, AICD, and/or vascular grafts (not native fistulas for dialysis)

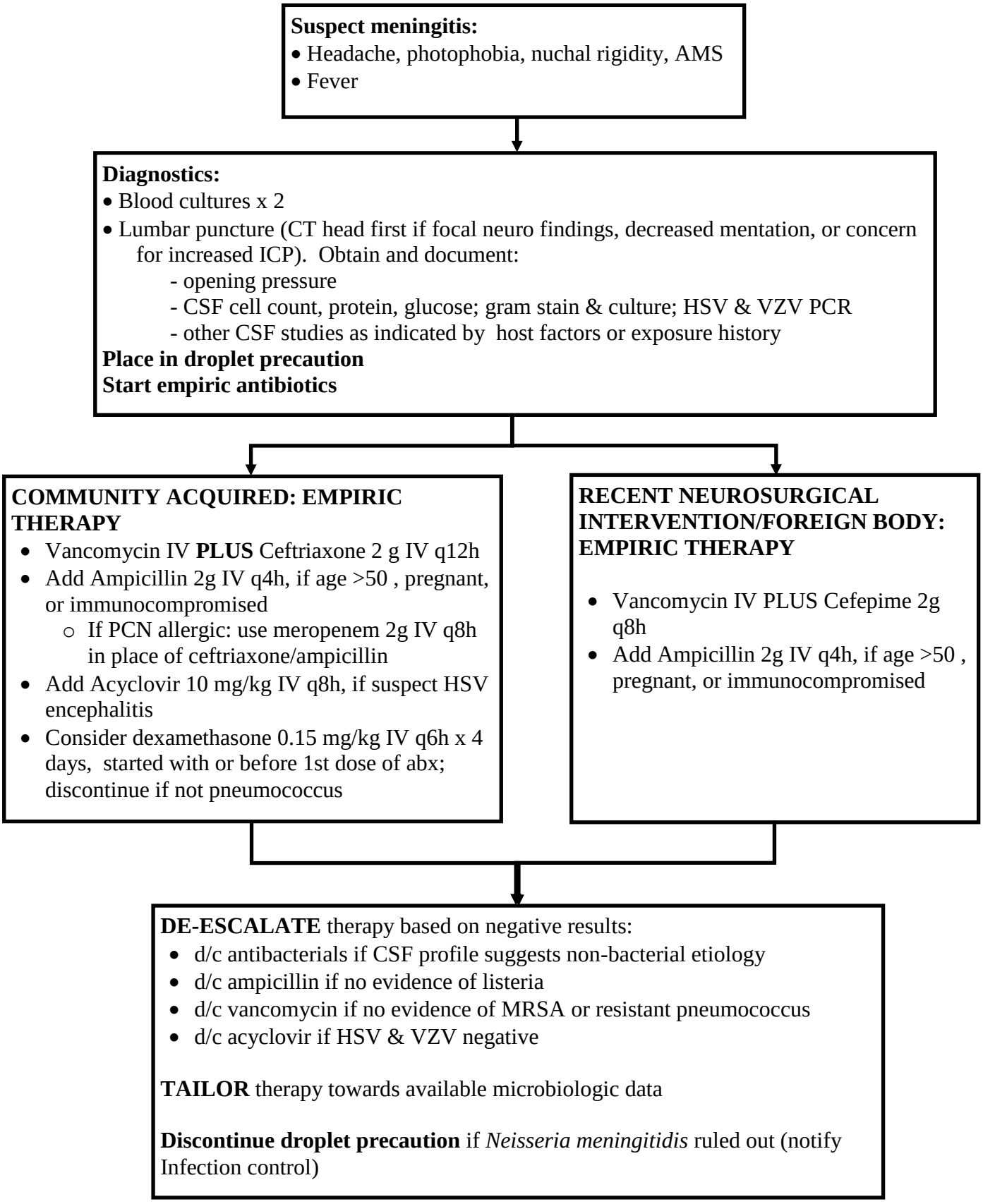
- ☐ If patient is a candidate, order appropriate probiotic (Bio-K Plus) formulation
  - ☐ Start within 24-48 hours of prescribed antibiotic
  - ☐ Continue for 5 days after broad spectrum antibiotic(s) discontinued (available for purchase in Atrium pharmacy if discharging)
  - ☐ Patient able to swallow: Order Bio-K Plus capsules, 2 cap PO once daily
  - ☐ Patient with feeding tube or difficulty swallowing pills: Order Bio-K Plus Fermented Rice Liquid 50 billion CFU (3.5oz) twice daily

Guidelines for Managing Positive GI PCR Results

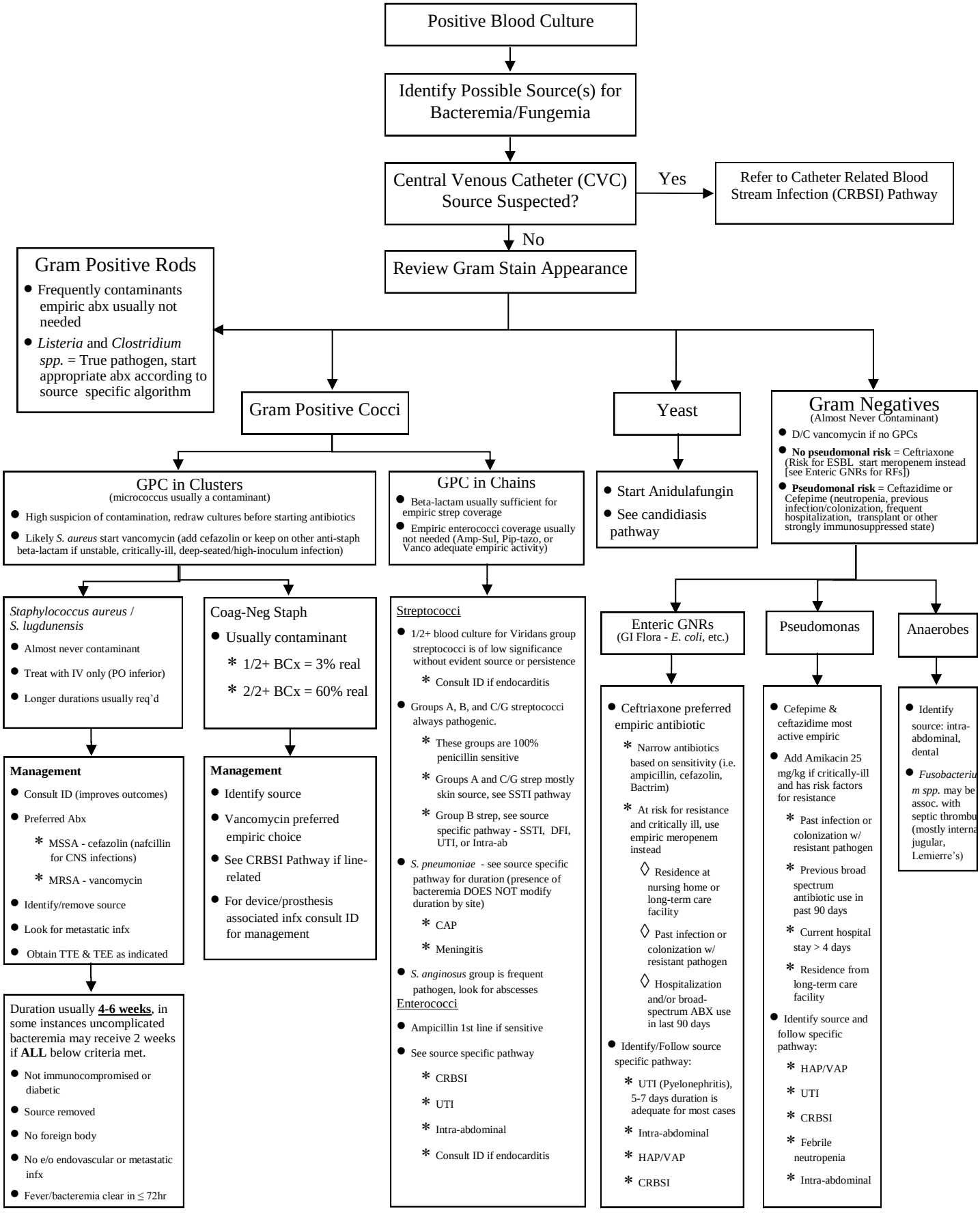
Pathogen/Result	Microbiology	Treatment/notes
Campylobacter	Major cause of dysenteric diarrhea worldwide	Azithromycin 500mg PO QD x 3d (preferred)
C difficile toxin AB	Antibiotic associated; healthcare outbreaks	See treatment pathway (page 20) PO vancomycin or fidaxomicin preferred first line
Salmonella	Typhoid most common in travelers. Non-typhoid common in US. May cause extra-intestinal disease (e.g. endovascular infections) and chronic disease/carriage.	- Non-typhoid, immunocompetent pts (ages 1-50) w/ mild/mod disease **do not** need abx. - Treatment recommended for severe infection, typhoid, immunocompromised, Age > 50yr or < 3mo, joint prosthesis, valvular heart disease/prosthetic valve/endovascular stents/severe artherosclerosis, sickle cell disease, or uremia. 1. Azithromycin 500mg PO QD x 7d (preferred) 2. Bactrim DS 1 tab PO BID x 7d 3. Ciprofloxacin 500mg PO BID x 7d **Immunosuppressed/invasive infection – consult ID **
Y enterocolitica	Associated w/cecitis/terminal ileitis, pseudo-appendicitis and post-transfusion sepsis	Does not usually require treatment. For severe infection or severely immunocompromised states consider: (1) Bactrim 1 DS PO BID, (2) doxycycline 100mg PO BID, or (3) ciprofloxacin 500mg PO BID. Duration = 5 days. (Consult ID for extra-intestinal infections)
Enteroaggregative E coli	Associated w/ chronic diarrhea in immunocompromised patients.	Supportive care. No treatment recommended in most cases.
Enteropathogenic E coli	Gastroenteritis, most often in kids.	
Enterotoxigenic E coli	Common cause for traveler's diarrhea	Mild disease = supportive care. Moderate disease = azithromycin 1g PO x 1, or Cipro 750mg PO x 1; Severe disease = azithromycin 500mg PO daily x 3 days or cipro 500mg PO BID x 3 days
Shiga like toxin producing E coli	Non- O157:H7 E coli that may cause enterohemorrhagic E coli.	Supportive care. Antibiotics may increase risk for HUS in children. *A positive result for both Shiga like toxin and Shigella/EIEC may indicate Shigella dysenteriae presence.*
E coli 0157	Common cause for enterohemorrhagic E coli.	
Shigella/Enteroinvasive E coli[+]	Common cause of diarrhea.	Antibiotics recommended in severe infections and immunocompromised patients. All others – abx may reduce shedding *Abx* – Azithromycin 500mg qday, Cipro 500mg PO BID, or Bactrim 1 DS PO BID x 3d
Cryptosporidium	Diarrhea in AIDS and immunocompromised patients. Associated w/ food/water-borne outbreaks	Self-limited in immune competent pts and do not require abx. *Consider ID consultation for patients with severe immunosuppression (e.g. AIDS, bone marrow transplant, solid organ transplant).*
Giardia lamblia[+]	Associate w/ contaminated water supply; may cause outbreaks	Metronidazole 500mg TID x 5 days
Adenovirus F 40 41	Gasteroenteritis in children and immunocompromised patients.	Supportive care only.
Astrovirus	Gasteroenteritis in children and immunocompromised patients.	Supportive care only.
Norovirus GI GII	Most common cause of acute gastroenteritis in the US	Supportive care for almost all cases. *Consider ID consult for patients with severe immunosuppression (e.g. AIDS, bone marrow transplant, solid organ transplant).*
Rotavirus A	Common cause for gastroenteritis in children	Supportive care only.
Sapovirus	Gasteroenteritis in children; may cause outbreaks in adults.	Supportive care only.

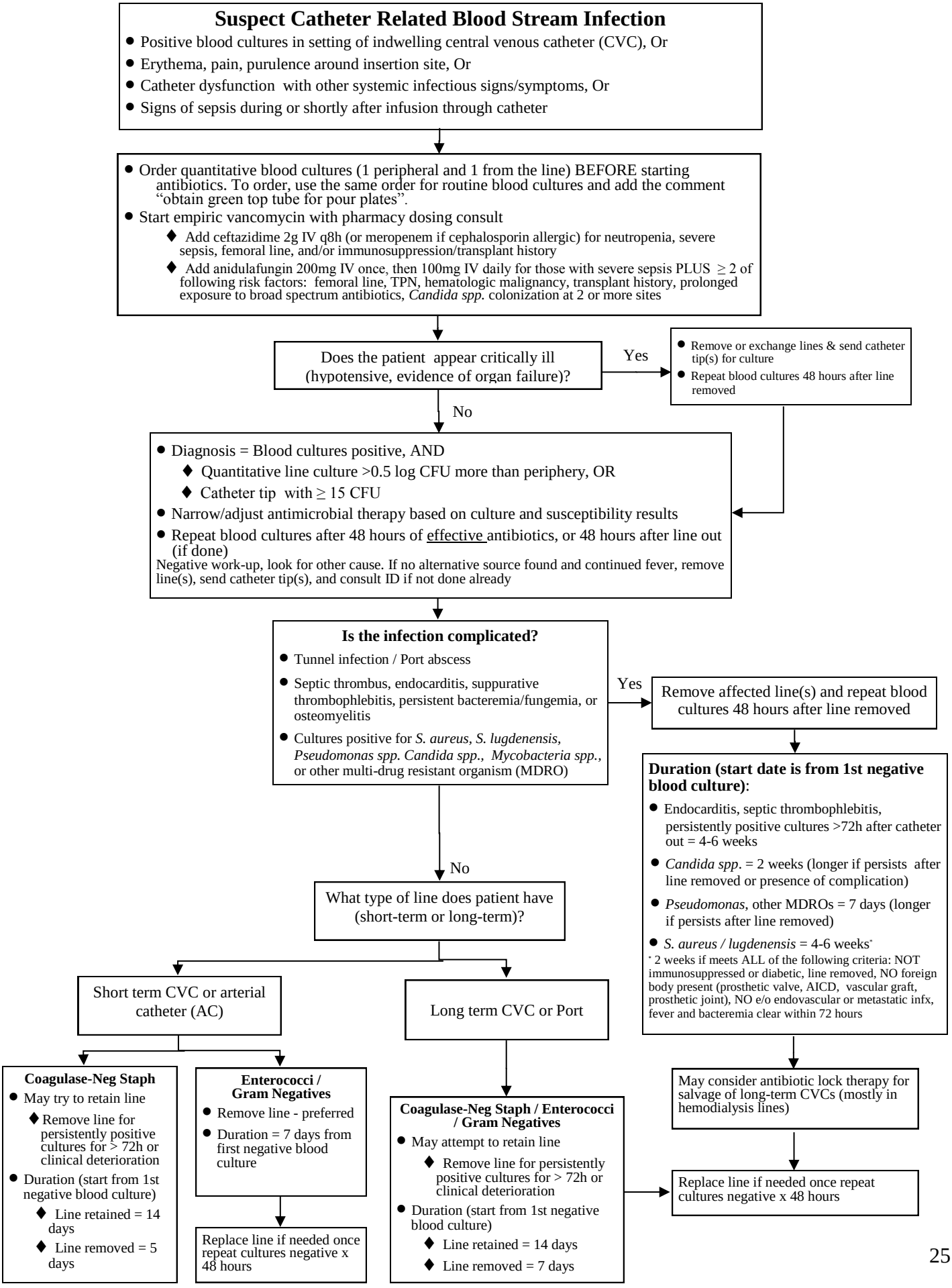
[+] These organisms may be transmitted through certain sexual practices, if this is a concern based on patient history consider work-up for other common sexually transmitted infections (gonorrhea, chlamydia, syphilis, HIV, etc.)
- Entamoeba histolytica is present on the panel, a negative result is not reported, but positives are reported in the results

Meningitis: Evaluation & Empiric Treatment



Management of Positive Blood Cultures / Bacteremia




Suspect Catheter Related Blood Stream Infection
Positive blood cultures in setting of indwelling central venous catheter (CVC), Or
Erythema, pain, purulence around insertion site, Or
Catheter dysfunction with other systemic infectious signs/symptoms, Or
Signs of sepsis during or shortly after infusion through catheter
Order quantitative blood cultures (1 peripheral and 1 from the line) BEFORE starting antibiotics. To order, use the same order for routine blood cultures and add the comment "obtain green top tube for pour plates".
Start empiric vancomycin with pharmacy dosing consult
Add ceftazidime 2g IV q8h (or meropenem if cephalosporin allergic) for neutropenia, severe sepsis, femoral line, and/or immunosuppression/transplant history
Add anidulafungin 200mg IV once, then 100mg IV daily for those with severe sepsis PLUS ≥ 2 of following risk factors: femoral line, TPN, hematologic malignancy, transplant history, prolonged exposure to broad spectrum antibiotics, Candida spp. colonization at 2 or more sites
Does the patient appear critically ill (hypotensive, evidence of organ failure)?
Yes
Remove or exchange lines & send catheter tip(s) for culture
Repeat blood cultures 48 hours after line removed
No
Diagnosis = Blood cultures positive, AND
Quantitative line culture >0.5 log CFU more than periphery, OR
Catheter tip with ≥ 15 CFU
Narrow/adjust antimicrobial therapy based on culture and susceptibility results
Repeat blood cultures after 48 hours of effective antibiotics, or 48 hours after line out (if done)
Negative work-up, look for other cause. If no alternative source found and continued fever, remove line(s), send catheter tip(s), and consult ID if not done already
Is the infection complicated?
Tunnel infection / Port abscess
Septic thrombus, endocarditis, suppurative thrombophlebitis, persistent bacteremia/fungemia, or osteomyelitis
Cultures positive for S. aureus, S. lugdenensis, Pseudomonas spp. Candida spp., Mycobacteria spp., or other multi-drug resistant organism (MDRO)
Yes
Remove affected line(s) and repeat blood cultures 48 hours after line removed
Duration (start date is from 1st negative blood culture):
Endocarditis, septic thrombophlebitis, persistently positive cultures >72h after catheter out = 4-6 weeks
Candida spp. = 2 weeks (longer if persists after line removed or presence of complication)
Pseudomonas, other MDROs = 7 days (longer if persists after line removed)
S. aureus / lugdenensis = 4-6 weeks*
* 2 weeks if meets ALL of the following criteria: NOT immunosuppressed or diabetic, line removed, NO foreign body present (prosthetic valve, AICD, vascular graft, prosthetic joint), NO e/o endovascular or metastatic infx, fever and bacteremia clear within 72 hours
No
What type of line does patient have (short-term or long-term)?
Short term CVC or arterial catheter (AC)
Long term CVC or Port
Coagulase-Neg Staph
May try to retain line
Remove line for persistently positive cultures for > 72h or clinical deterioration
Duration (start from 1st negative blood culture)
Line retained = 14 days
Line removed = 5 days
Enterococci / Gram Negatives
Remove line - preferred
Duration = 7 days from first negative blood culture
Replace line if needed once repeat cultures negative x 48 hours
Coagulase-Neg Staph / Enterococci / Gram Negatives
May attempt to retain line
Remove line for persistently positive cultures for > 72h or clinical deterioration
Duration (start from 1st negative blood culture)
Line retained = 14 days
Line removed = 7 days
May consider antibiotic lock therapy for salvage of long-term CVCs (mostly in hemodialysis lines)
Replace line if needed once repeat cultures negative x 48 hours

Staphylococcus aureus **Bacteremia Management Guide**

Gram Positive Bacteremia, Initial Approach:

- 1 / 2 positive blood culture sets for GPC in clusters and clinically stable
    - Do not start antibiotics, repeat blood cultures, and monitor clinical status
    - These are frequently contamination events
- 2 / 2 positive or 1 / 2 positive with evidence of infection/clinical instability
    - Start vancomycin (target trough 15-20 mg/L) PLUS cefazolin 2g q8h (3g q8h if patient weighs > 119kg) or nafcillin 12g continuous infusion (if CNS involvement)
        - As mentioned, beta-lactams kill MSSA better than vancomycin. Vancomycin monotherapy for MSSA bacteremia is associated with 2-3x the risk of morbidity/mortality when compared to cefazolin, nafcillin, or oxacillin[7-10]. It has also been shown that vancomycin initiation with de-escalation to anti-staphylococcal penicillin when MSSA is identified is associated with increased mortality among critically-ill patients.[11,12]
        - Furthermore, recent data show vancomycin and cefazolin or nafcillin combination are synergistic against vancomycin-susceptible, –intermediate *Staphylococcus aureus*, and heterogenous vancomycin-intermediate *Staphylococcus aureus*[13]; other recent *in vitro* data shows that cefazolin can attenuate the development of vancomycin-intermediate *Staphylococcus aureus* resistance when combined with vancomycin.[14]
- Once *Staphylococcus aureus* has susceptibilities to determine if MRSA or MSSA, discontinue the cefazolin or vancomycin, respectively

Key Points for *Staphylococcus aureus* bacteremia:

1. **Don't ignore it!** *Staphylococcus aureus* in the bloodstream is never a contaminant!
2. **Always get an ID consult!** ID consults with *S. aureus* bacteremia have shown to improve patient outcomes, including fewer relapses, reduced length of stay, and reduced mortality[1,2]
3. **Remove the source** (if applicable)
    a. Prosthetic devices, infected catheters, etc.
4. **Assess for metastatic infection sites**
    a. Osteomyelitis, endocarditis, abscesses, thrombophlebitis, etc.
5. **Blood cultures do not need to be obtained every day!** Repeat blood cultures 48 hours after start of appropriate antibiotics and/or source control intervention, then repeat as needed to document bacteremia clearance.
    a. Remember, subsequent positive blood cultures are a predictor for metastatic infection or intravascular device/foreign body source[3,4]
6. **Consider a TTE** for most *S. aureus* bacteremias, particularly if bacteremia fails to clear within 2-3 days of appropriate antibiotics. TEE may be needed if TTE negative and strong clinical suspicion for infective endocarditis persists.
7. **Use the right drug(s), at the right dose, for the right duration**
    a. Rapid identification of MSSA vs MRSA is possible through use of chromogenic agar (standardly performed by microbiology lab) – If result shows "methicillin-susceptible by screening agar" please direct antibiotics toward MSSA utilizing beta-lactam agent
    b. Remember, beta-lactams kill MSSA better than vancomycin and have also been associated with reduced mortality[5, 7-12]
        i. **MSSA 1st line antibiotic = Cefazolin 2g IV q8h** [3g q8h if patient weighs > 119kg]. Use Nafcillin 2g q4h or 12g continuous infusion for CNS infections
            1. Not all beta-lactams equal for MSSA:
                a. Cefazolin has been associated with improved outcomes when compared to ceftriaxone in MSSA bacteremia (we can extrapolate this data to other beta-lactams, excluding nafcillin/oxacillin)[6]
        ii. MRSA 1st line antibiotic = Vancomycin (target trough 15-20 mg/L)
    c. Duration
        i. 4-6 weeks in most cases
        ii. 14 days if uncomplicated *S. aureus* bacteremia AND if all of the below criteria are met (note up to 15% failure rate using short-course even for uncomplicated infections):
            1. Not immunocompromised/diabetic
            2. Source control obtained
            3. No foreign body
            4. No evidence of endovascular infection
            5. No metastatic infection
            6. Fever/bacteremia clears within 72 hours
8. Patients who have not cleared their blood cultures within 3-7 days may be considered for an alternative agent or combination therapy
    a. Remember, vancomycin pre-treatment increases risk for reduced daptomycin susceptibility
9. Addition of gentamicin 3mg/kg/day synergy only indicated for those with prosthetic valve endocarditis, there is no documented benefit for native valve or persistent bacteremia
10. Addition of rifampin only beneficial in infections with prosthetic devices (prosthetic joints/heart valves, pacemakers)
    a. Consult infectious diseases team if rifampin addition is being considered
    b. Wait for blood culture clearance before initiating rifampin since earlier initiation before bacteremia clears has been associated with increased duration of bacteremia
    c. Do not use rifampin for bacteremia in absence of prosthetic materials, no difference in outcome and increased risk for side effects and drug-drug interactions

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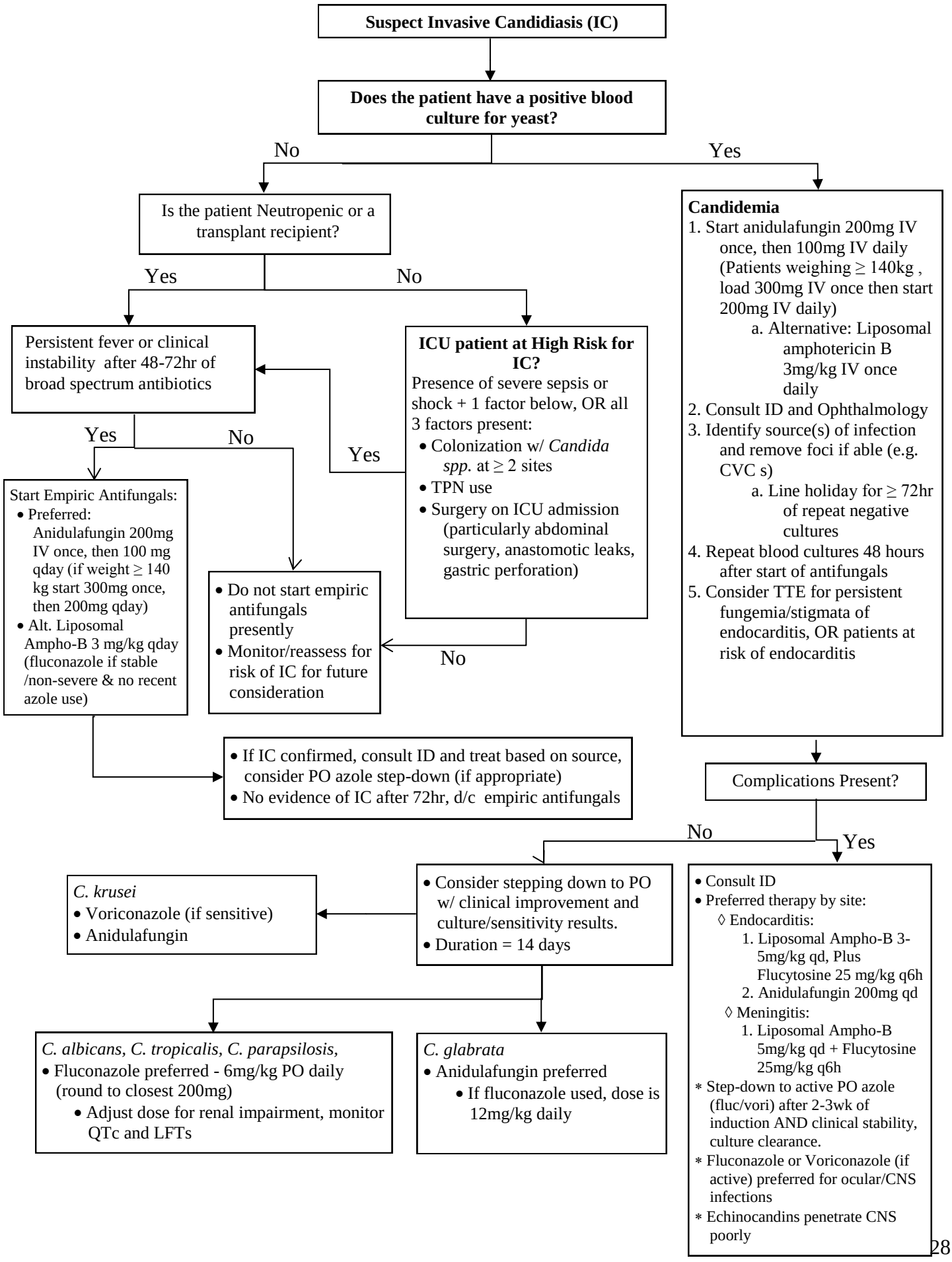

Suspect Invasive Candidiasis (IC)
Does the patient have a positive blood culture for yeast?
No
Yes
Is the patient Neutropenic or a transplant recipient?
Yes
No
Persistent fever or clinical instability after 48-72hr of broad spectrum antibiotics
Yes
No
Start Empiric Antifungals:
• Preferred: Anidulafungin 200mg IV once, then 100 mg qday (if weight ≥ 140 kg start 300mg once, then 200mg qday)
• Alt. Liposomal Ampho-B 3 mg/kg qday (fluconazole if stable /non-severe & no recent azole use)
ICU patient at High Risk for IC?
Presence of severe sepsis or shock + 1 factor below, OR all 3 factors present:
• Colonization w/ Candida spp. at ≥ 2 sites
• TPN use
• Surgery on ICU admission (particularly abdominal surgery, anastomotic leaks, gastric perforation)
Yes
No
• Do not start empiric antifungals presently
• Monitor/reassess for risk of IC for future consideration
• If IC confirmed, consult ID and treat based on source, consider PO azole step-down (if appropriate)
• No evidence of IC after 72hr, d/c empiric antifungals
Candidemia
1. Start anidulafungin 200mg IV once, then 100mg IV daily (Patients weighing ≥ 140kg , load 300mg IV once then start 200mg IV daily)
a. Alternative: Liposomal amphotericin B 3mg/kg IV once daily
2. Consult ID and Ophthalmology
3. Identify source(s) of infection and remove foci if able (e.g. CVC s)
a. Line holiday for ≥ 72hr of repeat negative cultures
4. Repeat blood cultures 48 hours after start of antifungals
5. Consider TTE for persistent fungemia/stigmata of endocarditis, OR patients at risk of endocarditis
Complications Present?
No
Yes
• Consider stepping down to PO w/ clinical improvement and culture/sensitivity results.
• Duration = 14 days
C. krusei
• Voriconazole (if sensitive)
• Anidulafungin
C. albicans, C. tropicalis, C. parapsilosis,
• Fluconazole preferred - 6mg/kg PO daily (round to closest 200mg)
• Adjust dose for renal impairment, monitor QTc and LFTs
C. glabrata
• Anidulafungin preferred
• If fluconazole used, dose is 12mg/kg daily
• Consult ID
• Preferred therapy by site:
◊ Endocarditis:
1. Liposomal Ampho-B 3-5mg/kg qd, Plus Flucytosine 25 mg/kg q6h
2. Anidulafungin 200mg qd
◊ Meningitis:
1. Liposomal Ampho-B 5mg/kg qd + Flucytosine 25mg/kg q6h
∗ Step-down to active PO azole (fluc/vori) after 2-3wk of induction AND clinical stability, culture clearance.
∗ Fluconazole or Voriconazole (if active) preferred for ocular/CNS infections
∗ Echinocandins penetrate CNS poorly

Guide for Managing Candida Infections

Consultation with Infectious Diseases is HIGHLY recommended.

Empiric therapy for candidemia or other invasive candida infections = Anidulafungin (alt. liposomal amphotericin-b)

- For non-invasive infections (oral-pharyngeal or urinary) consider fluconazole as initial empiric therapy

Sources:

- Candidemia (most commonly line-related or intra-abdominal source) = **CONSULT ID**
  - Indwelling central venous catheters will require removal and holiday to document clearance from blood
    - If line cannot be removed, LAmB or echinocandins should be used to penetrate the fungal biofilm
  - Ophthalmology exam to r/o endophthalmitis / chorioretinitis
  - Consider echocardiography to r/o endocarditis
- Candida is an **INFREQUENT cause of UTI and pneumonia**. Presence of candida in the urine and/or sputum/BAL cultures reflects colonization and **SHOULD NOT** be treated (especially in non-neutropenic and non-transplant patients)

Table 1. General patterns of susceptibility of *Candida* species.

Species	Fluconazole	Itraconazole	Voriconazole	Posaconazole	Flucytosine	Amphotericin B	Candins
Candida albicans	S	S	S	S	S	S	S
Candida tropicalis	S	S	S	S	S	S	S
Candida parapsilosis	S	S	S	S	S	S	S to R*
Candida glabrata	S-DD to R	S-DD to R	S-DD to R	S-DD to R	S	S to I	S
Candida krusei	R	S-DD to R	S	S	I to R	S to I	S
Candida lusitaniae	S	S	S	S	S	S to R	S

Note: S, susceptible; I, intermediately susceptible; R, resistant; S-DD, susceptible dose-dependent
***Echinocandin resistance among *C. parapsilosis* isolates is uncommon, though isolates may display elevated MICs**

Step-down therapy should occur once a specific candida species is identified; therapy should be tailored to narrow coverage spectrum Likewise, when a patient is transitioning to oral medications, a "step-down" therapy is required.

Table 2. Management of Candida Infections Based Upon Species

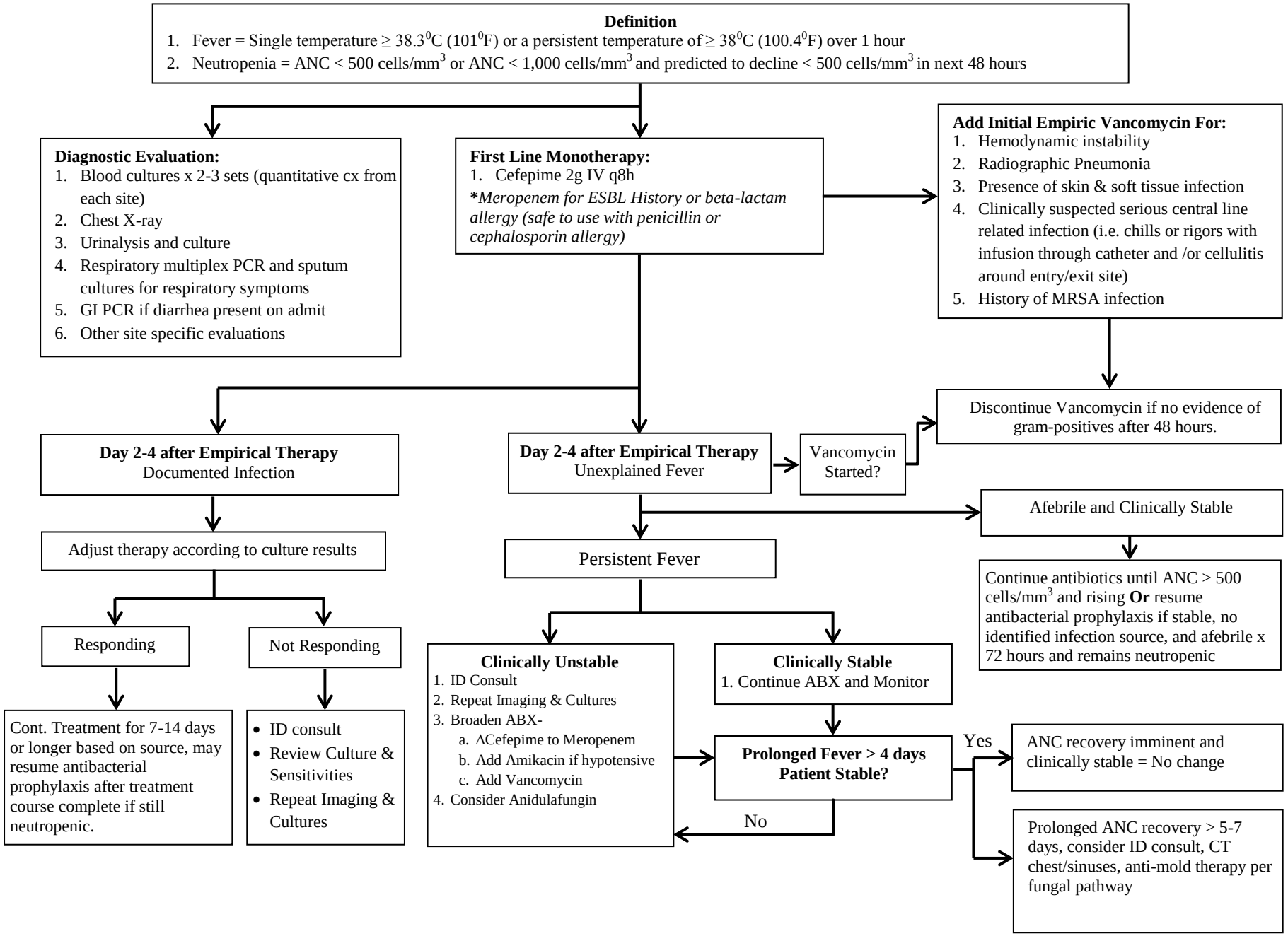
Candida Species	Preferred agent	Alternative options	Step-down options	Should not be used
C. albicans	Fluconazole	Anidulafungin OR LAmB	Fluconazole	
C. glabrata	Anidulafungin	LAmB		Fluconazole OR voriconazole (without susceptibility data)
C. krusei	Anidulafungin	Voriconazole OR LAmB	Voriconazole	Fluconazole OR flucytosine
C. parapsilosis	Fluconazole	Anidulafungin (may have reduced activity) OR LAmB	Fluconazole	Anidulafungin if worsening on treatment

- Azoles
  - Fluconazole has the best CNS and intraocular penetration
  - Voriconazole effective for mucosal and invasive candidiasis; good CNS and intraocular penetration
  - Posaconazole suspension is not preferred due to difficulty attaining adequate drug levels (poor bioavailability)
    - DR tablets (Preferred) have much improved bioavailability and can be taken with or without food.
  - Isavuconazole has limited use for invasive candida infections at present based on Phase 3 study results.
    - This agent may be considered for invasive mold infections (aspergillosis/mucormycosis)
    - IV formulation does not contain cyclodextrin, and thus is not contraindicated in renal impairment.
    - Does not prolong QTc (shortens). Moderate CYP-3A4 inhibitor, consider drug interactions
- Echinocandins
  - Anidulafungin is UCH's formulary echinocandin; Caspofungin and micafungin will be interchanged to anidulafungin
  - Echinocandins have poor CNS, eye, and urine penetration, and should not be used to manage such infections
- Flucytosine: Not used as a single agent (combined with LAmB for endocarditis, meningitis, and endophthalmitis)

Dosing of Antifungals			
Antifungal	**Loading Dose**	**Maintenance Dose**	**Goal Levels (mg/L) – Run T/Th/Sat at ARUP (TAT = 1-6 days)**
Ambisome® (LAmB)	-	3-5 mg/kg daily (7-10mg/kg for CNS Mucor)	-
Flucytosine	-	25 mg/kg q6h	Pk (2hr post): 40-60 candidal and 30-80 cryptococcal (levels >100-125 assoc. w/ higher tox)
Azoles			
Fluconazole*	800 mg (12mg/kg)	400 (6mg/kg) mg daily	-
Itraconazole	200mg TID x 1 day	200 mg (3 mg/kg) q12h	Tr (0.5-1hr pre): > 1 (> 10 toxic)
Posaconazole+ - Suspension - DR Tabs / IV[1-2]	 - 300mg q12h x 1day	 200 mg q6h (alt.400mg q8-12h) 300 mg daily	Tr (0.5-1hr pre): ≥ 0.7 (prophy); and and ≥ 1-2 (treatment)
Voriconazole +[1]	6mg/kg q12h x 1day	4 mg/kg q12h	Tr (0.5-1hr pre): ≥ 0.5-1 (prophy); and 2-4 (treatment); levels >4-5 = tox
Isavuconazole+	372mg q8h x 6 doses (2 days)	372mg q24h	-
Echinocandins			
Anidulafungin+	200 mg	100 mg daily	-

+ = restricted to ID approval pager at UCH; * = Fluconazole Dose/MIC ratio of ≥ 25 for oropharyngeal candidiasis and ≥ 100 for invasive candidiasis have been shown to predict improved clinical response compared to lower ratios; [1] = IV form contains cyclodextrin which may accumulate in renal impairment, caution against use with CrCl < 50 mL/min; [2] = IV should be given via CVC

Febrile Neutropenia Treatment Algorithm



UCHealth Pre-Operative Antibiotic Prophylaxis Recommendations (Select Procedures)

Surgical Category	Procedure*	First Line	Alternative for severe penicillin/cephalosporin allergy
Vascular	Amputation	Cefazolin 2g‡	Vancomycin 15mg/kg
	Hemodialysis Access		
	Open vascular repair		
	Open Vein Procedures		
	Angiography, venography, percutaneous intervention	Antibiotics not routinely indicated	
Colorectal	Colon surgery (open, lap)	Cefazolin 2g‡ + Metronidazole 500mg (+ PO abx and mechanical bowel prep 1 day prior§)	Vancomycin 15mg/kg + Aztreonam 2g + Metronidazole 500mg (+ PO abx and mechanical bowel prep 1 day prior§)
	Rectal procedures		
	APR		
	Ileostomy creation	Cefazolin 2g‡ + Metronidazole 500mg	Vancomycin 15mg/kg + Aztreonam 2g + Metronidazole 500mg
	Anal procedures: I&D, Hemorrhoids	Antibiotics not routinely indicated (if cellulitis present, use cefazolin or vancomycin in PCN/cephalosporin allergy)	
	Pilonidal excision		
TACS/GS	Appendectomy (open, lap)	Cefazolin 2g‡ + Metronidazole 500mg	Levofloxacin 500mg + Metronidazole 500mg
	Cholecystectomy (open, lap)	Cefazolin 2g‡	Vancomycin 15mg/kg + Aztreonam 2g
	Small bowel Procedure	Cefazolin 2g‡ -if obstruction, add Metronidazole 500mg	Levofloxacin 500mg -if obstruction, add Metronidazole 500mg
	Abscess I&D (skin & soft tissue)	Antibiotics not routinely indicated (if cellulitis present, use cefazolin or vancomycin in PCN/cephalosporin allergy)	
	Hernia repair with mesh (inguinal, umbilical, ventral)	Cefazolin 2g‡ (Consider adding single pre-op vancomycin dose if MRSA Hx)	Vancomycin 15mg/kg
	Hernia repair without mesh (inguinal, umbilical, ventral)	Cefazolin 2g‡	Vancomycin 15mg/kg
	Hiatal hernia repair with mesh	Cefazolin 2g‡ (Consider adding single pre-op vancomycin dose if MRSA Hx)	Vancomycin 15mg/kg
	Hiatal hernia repair without mesh	Cefazolin 2g‡	Vancomycin 15mg/kg
	Tracheostomy	Antibiotics not routinely indicated (cefazolin or vancomycin if clean-contaminated, XRT to site, immunosuppression)	
	Enteral feeding access	Cefazolin 2g‡	Vancomycin 15mg/kg + Aztreonam 2g
	Exploratory laparotomy for perforation	Ceftriaxone 2g + Flagyl (piperacillin-tazobactam 4.5g if severe sepsis and/or health-care associated)	Vancomycin 15mg/kg + Aztreonam 2g + Flagyl
	Exploratory laparotomy for trauma (low concern for perforation)	Cefazolin 2g‡	Vancomycin 15mg/kg + Aztreonam 2g
	Laparoscopic lysis of adhesions	Cefazolin 2g‡+ Metronidazole 500mg	Levofloxacin 500mg + Metronidazole 500mg
	Gastrectomy (open, lap, sleeve)	Cefazolin 2g‡	Vancomycin 15mg/kg + Aztreonam 2g
	Gastric Bypass		
Endocrine	Thyroid, parathyroid	Antibiotics not routinely indicated	
	Adrenalectomy (open, lap)	Antibiotics not routinely indicated. If SSI risk factors¥, cefazolin or vancomycin	
Surgical Oncology	Hepatobiliary	Cefazolin 2g‡	Vancomycin 15mg/kg + Aztreonam 2g
	Liver resection (open, lap/robotic)		
	Gastric Procedure (open, lap)		
	Laparoscopic Whipple		
	CRS/HIPEC	Cefazolin 2g‡ + Metronidazole 500mg (+ PO abx and mechanical bowel prep 1 day prior§)	Vancomycin 15mg/kg + Aztreonam 2g + Metronidazole 500mg (+ PO abx and mechanical bowel prep 1 day prior§)
	Esophagectomy (open, lap)	Cefazolin 2g‡ + Metronidazole 500mg	Vancomycin 15mg/kg + Aztreonam 2g + Metronidazole 500mg
	Skin cancer	Antibiotics not routinely indicated for clean procedures	
	Small Bowel resection	Cefazolin 2g‡ -if obstruction, add Metronidazole 500mg	Levofloxacin 500mg -if obstruction, add Metronidazole 500mg
	Retroperitoneal resection (no entry into GU tract)	Antibiotics not routinely indicated. If SSI risk factors¥, cefazolin or vancomycin	
	Colon surgery (open, lap)	Cefazolin 2g‡ + Metronidazole 500mg (+ PO abx and mechanical bowel prep 1 day prior§)	Cefazolin 2g‡ + Metronidazole 500mg (+ PO abx and mechanical bowel prep 1 day prior§)
Cardiac	CABG	Cefazolin 2g‡ + Vancomycin 15mg/kg	Vancomycin 15mg/kg
	Heart transplant		
	Valve replacement or repair		
	TAVR		
	Aortic Surgery		
	ECMO	Cefazolin 2g‡	Vancomycin 15mg/kg
	VAD	Vancomycin 15mg/kg + ceftazidime 2g	Vancomycin 15mg/kg + ciprofloxacin 400mg

Thoracic	Lung procedure (open, VATS)	Cefazolin 2g‡	Vancomycin 15mg/kg
	Tracheal surgery		
	Esophagectomy (open, minimally invasive)	Cefazolin 2g‡ + Metronidazole 500mg	Vancomycin 15mg/kg + Aztreonam 2g + Metronidazole 500mg
	Lung transplant	Cefepime 2g + Vancomycin 15mg/kg	Aztreonam 2g + vancomycin 15mg/kg
	Bronchoscopy	Antibiotics not indicated	
Transplant	Liver transplant: donor resection	Ampicillin-sulbactam 3g	Vancomycin 15mg/kg + Aztreonam 2g + metronidazole 500mg
	Liver transplant: recipient	Ceftriaxone 2g‡, then 1g continuously over 12 hrs +/- Ampicillin-sulbactam 3g +/- Anidulafungin 200mg	Vancomycin 15mg/kg + Aztreonam 2g +/- Metronidazole 500mg +/- Anidulafungin 200mg
	Laparoscopic nephrectomy for donation	Cefazolin 2g‡	Vancomycin 15mg/kg
	Kidney transplant: recipient	Cefazolin 2g‡	Vancomycin 15mg/kg + Aztreonam 2g
	Kidney-Pancreas transplant	Ceftriaxone 2g‡ + fluconazole 400mg IV	Ertapenem 1g IV + Fluconazole 400mg IV
	AV fistula creation	Cefazolin 2g‡	Vancomycin 15 mg/kg
PRS	Reduction mammoplasty	Antibiotics not routinely indicated for clean procedures without additional risk factors If SSI risk factors¥, cefazolin or vancomycin	
	Tendon sheath incision		
	Carpal tunnel release		
	Elective hand surgery without bone involvement		
	Head/neck reconstruction		
	Skin graft	Cefazolin 2g‡	Vancomycin 15mg/kg
	Free flap	Cefazolin 2g‡ -if flap used in head/neck procedure, add metronidazole or use amp/sulbactam 3g	Vancomycin 15mg/kg -if flap used in head/neck procedure, add metronidazole or use clindamycin 900 mg
	Rotational flap		
	Breast Implant/tissue expander placement	Cefazolin 2g‡	Vancomycin 15mg/kg
	ORIF for closed fx	Cefazolin 2g‡	Vancomycin 15mg/kg
	ORIF for open fx Type I/II Type III -Farm-related, fecal contamination, vascular injuries with necrotic tissue	Cefazolin 2g‡ Cefazolin 2-3g‡ + gentamicin 5mg/kg -Add Penicillin-G 4 million units	Clindamycin 900mg Aztreonam 2g + Clindamycin 900mg Aztreonam 2g + Clindamycin 900mg
	Hand surgery with osteomyelitis	Abx choice dependent on known or likely organisms involved with osteomyelitis + skin flora	
	Sacral/infected wound reconstruction	Abx choice dependent on known or likely organisms involved with sacral wound and/or OM	
	Debridement, soft tissue	Abx choice dependent on site and known or likely organisms	
Breast	Lumpectomy	Antibiotics not routinely indicated	
	Mastectomy	Cefazolin 2g‡	Vancomycin 15mg/kg
	Axillary lymph node surgery		
	Breast abscess I&D		

*Pre-op abx not needed for patients already on systemic abx for another infection that would provide protection against expected surgical pathogens (ensure dosing is administered in the appropriate time frame pre-op and re-dose if needed)

‡Use cefazolin 3g if weight ≥120 kg

§PO antibiotics for colorectal procedures: Neomycin 1g and Metronidazole 500mg PO x 3 doses each (at 2pm, 3pm, and 10pm day before procedure)

¥Patient-related factors associated with increased risk of SSI: extremes of age, malnutrition, smoking, DM, obesity, immunosuppression, corticosteroid therapy, prolonged pre-op hospitalization, known colonization, remote body-site infection.

Revised 09/2018

University of Colorado Hospital - Restricted Antimicrobials Criteria for Use

Antimicrobial Restrictions and Exception Criteria: These antibiotics in **Table 1** are restricted and must be approved based on Tier. No approval is needed if meets exception criteria in **Table 1** (enter code as exception -ex. "ICU") or if therapy is recommended by Infectious Diseases Consult (enter code as "ID consult").

Table 1: Restricted Antimicrobials and Exception Criteria		
Drug	**Tier**	**Exceptions**
Anidulafungin	2	Restricted except BMT, SOT, hepatology, CF, and ICUs
Ciprofloxacin	2	Restricted except BMT, lung transplant, and CF
Ertapenem	2	Restricted except BMT
Levofloxacin	2	Restricted except BMT, lung transplant, and CF
Meropenem	2 ICU/ 3 floors	Restricted except BMT, lung transplant, and CF
Moxifloxacin	2	Restricted except BMT, lung transplant, and CF
Piperacillin/tazobactam	2	Restricted except BMT, CF, SOT, and ICUs
Antibiotic lock	3	Restricted except renal
Ceftaroline	3	Restricted to antibiotic approval pager (*ALL services*)
Ceftazidime/avibactam	3	**Non-formulary**; ID only – consideration for MDROs
Ceftolozane/tazobactam	3	Restricted; ID only – consideration for MDROs
Meropenem-vaborbactam	3	**Non-formulary**; ID only – consideration for MDROs
Plazomicin	3	**Non-formulary**; ID only – consideration for MDROs
Eravacycline	3	**Non-formulary**; ID only – consideration for MDROs
Omadacycline	3	**Non-formulary**; ID only – consideration for MDROs
Daptomycin	3	Restricted to antibiotic approval pager (*ALL* services)
Oritavancin (DO NOT GIVE INPATIENT)	3	Restricted to antibiotic approval pager (*ALL* services)
Dalbavancin (DO NOT GIVE INPATIENT)	3	Restricted to antibiotic approval pager (*ALL* services)
Imipenem	3	**Non-formulary**; Ok in non-TB mycobacterial infections
Inhaled amphotericin	3	Restricted except lung transplant
Inhaled colistin, tobramycin, amikacin,	3	Restricted except CF and lung transplant
Isavuconazole	3	Restricted except lung transplant
Linezolid	3	Restricted except BMT, lung transplant, and CF
Polymyxin B (IV)	3	Restricted; ID only
Posaconazole	3	Restricted except BMT, SOT, and hem/onc
Tedizollid	3	**Non-formulary**; ID only
Tigecycline	3	Restricted to antibiotic approval pager except CF
Voriconazole	3	Restricted except BMT, SOT, and hem/onc
CF – Cystic fibrosis patients, SOT- Solid Organ Transplant, ICUs – ICU service or ICU location		

Tier	Definition	Additional Information
Tier 1	Formulary antimicrobials; no restrictions	- If formulary antibiotic not listed on **Table 1**, then considered Tier 1
Tier 2	Verifying pharmacists can approve agents if indication meets criteria listed in **Table 2** or exception criteria in **Table 1**	- If exception criteria met in Table 1, exception criteria written as code - If criteria in Table 2 met, RPh to put code in code box - If criteria not met, RPh will notify clinician of required approval through the antibiotic approval pager
Tier 3	Restricted to antibiotic approval pager only	- These antibiotics are restricted to the antibiotic approval pager *unless* the patient meets the exception criteria in **Table 1**

Antibiotic approval pager (303-266-6966) - **Available 8am to 8pm Monday through Friday**

Outside Operating Hours and Major Holidays:

- The order may be verified with the code "after hours, will follow up"
- It is the responsibility of the primary team to call the antibiotic approval pager within 12 hours after the pager operating hours begin
- The clinician should modify the order with the new approval code
- If urgent Infectious Disease issues arise outside operating hours, the team should page the ID fellow on call

During operating hours:

- Antibiotics should never be withheld if the team cannot get approval within 10-20mins
- Patient's maintained on restricted antibiotics PTA, still require approval according to the tiered criteria above
- If not approved within 10-20mins, pharmacists should verify the order with an ID approval code I-vent left open until the team can discuss the case with the antibiotic approval pager

Table 2: Tier 2 Antimicrobials (Also see empiric treatment guidelines for preferred agents/indications)
Verifying Pharmacists can approve agents if indication meets criteria listed below. If criteria is not met, RPh will notify the that they clinician must get approval through the antibiotic approval pager 266-6966 - 8am to 8pm Mon -Fri

Drug	Criteria	Alternative agent
Levofloxacin Intravenous (IV) .LevoIVRestricted	**Pneumonia (HCAP, HAP, VAP)** - Allergy or contraindication to cefepime or piperacillin/tazobactam	- Cefepime, carbapenems safe in penicillin allergic patients No allergy to β-lactams: cefepime or ceftazidime +/- vancomycin
	Infections other, UTI, wounds, etc. - Allergy or contraindication to recommended beta-lactam - Prostatitis - Documented resistance to other options	- Penicillin allergy:: Ceftriaxone (no *pseudomonas* concern) o *Pseudomonas* concern = cefepime or ceftazidime
	Intra-abdominal infections - Severe β-lactam allergy intolerant to cephalosporins; use with metronidazole	- If no penicillin allergy, use ceftriaxone with metronidazole for community acquired **OR** piperacillin/tazobactam for healthcare associated or complicated
Levofloxacin Oral .LevoPORestricted	**Pneumonia** - Documented HCAP,HAP, or VAP oral step down - CAP with 3rd gen cephalosporin allergy	- If HCAP - levofloxacin - If CAP and no allergy – use amoxicillin, amoxicillin/clavulanate, or cefuroxime + azithromycin, or doxycycline
	Intra-abdominal infections - Oral step down with metronidazole - Diverticulitis with metronidazole	- Oral ciprofloxacin is another option - Consider Augmentin if no risk factors for resistant organisms
	Infections other, UTI, Prostatitis, wounds, etc. - UTI with β-lactam and sulfa allergy and/or documented resistance to other options - Prostatitis - Culture with *Pseudomonas* and PO Abx desired (if sensitive)	- Oral ciprofloxacin is another option - Bactrim has good prostate penetration (if sensitive)
Ciprofloxacin Intravenous (IV) .CiproIVRestricted	**Pneumonia** - Add on as double coverage for Pseudomonas if intolerant to aminoglycosides (400mg q8hrs) – aminoglycoside preferred	- Does not cover Streptococcus pneumoniae, do not use in CAP or as monotherapy empiric therapy for HCAP
	Intra-abdominal infections - Ceftriaxone allergy or contraindication - Add metronidazole to provide anaerobic coverage	- Ceftriaxone with metronidazole safe option for penicillin allergic patients
	Infections other, UTI, wounds, etc. - Ceftriaxone allergy or contraindication - Prostatitis	- Ceftriaxone safe for penicillin allergic patients (no *pseudomonas* concern) o *Pseudomonas* concern = cefepime or ceftazidime or pip-taz
Ciprofloxacin Oral .CiproPORestricted	**Intra-abdominal infections** - Oral step down with metronidazole if cephalosporin allergic - Diverticulitis with metronidazole if cephalosporin allergic - SBP prophylaxis	- Consider Augmentin if no risk factors for resistant organisms , **OR** cefpodoxime + metronidazole - Bactrim alternative for SBP prophylaxis
	Infections other, UTI, wounds, etc. - UTI with cephalosporin and sulfa allergy and/or documented resistance to other options - Prostatitis - Positive culture growing *Pseudomonas* and oral treatment desired	- Bactrim has good prostate penetration - Please see treatment guidance section on UTIs for recommended treatment
Moxifloxacin IV and oral .MoxiRestricted	**Pneumonia IV** - CAP with ceftriaxone allergy **Oral** - CAP with severe β-lactam allergy	**IV** - If no cephalosporin allergy use ceftriaxone plus azithromycin **Oral** - If no allergy use amoxicillin/clavulanate plus azithromycin

Meropenem ICU status patient .MeropenemICURestricted	**Empiric coverage for resistant gram negatives including *Pseudomonas*** - Documented exposure to and/or worsening on broad spectrum antibiotics such as cefepime, piperacillin/tazobactam, or ceftazidime (Higher resistance with *Pseudomonas* vs. cefepime/ceftazidime) - Serious infection suspected of being polymicrobial and/or involving anaerobic bacteria in patients intolerant of /or resistant to piperacillin/tazobactam or cefepime/metronidazole - Penicillin and 3rd/4th generation cephalosporin allergy **Documented infection due to a resistant gram negative organism** - Amp C or ESBL producing gram negative severe infection and resistant to ertapenem and/or concurrent *Pseudomonas* infection - Piperacillin/tazo, cefepime, ceftazidime, and ertapenem resistant gram negative infection	<u>For anti-pseudomonal empiric coverage</u> - Cefepime, ceftazidime, or piperacillin/tazobactam (alone) - If anaerobic coverage needed, can add metronidazole to for intra-abd source or clindamycin if aspiration/lung source - Ceftolozane-tazobactam may have expanded coverage for MDR-Pseudo <u>If allergic to penicillins, cephalosporins, and carbapenems and need empiric anti-pseudomonal coverage: (intolerant to any β-lactam)</u> - Aztreonam 2g IV q8hrs + Tobramycin - If anaerobic coverage needed, can add metronidazole for intra-abd source or clindamycin if aspiration/lung source
Ertapenem .ErtapenemRestriction	**Empiric Coverage** - Intra-abdominal infection with penicillin and 3rd/4th generation cephalosporin allergy - Wound or diabetic foot infection with penicillin and 3rd/4th generation cephalosporin allergy - Switched for ease of outpatient antibiotic use (24-48hrs prior to dc only) **Documented infection due to a resistant gram negative organism** - ESBL infection - History of or current Enterobacter spp., Citrobacter freundii, or Serratia spp. infection with the potential of producing Amp C beta-lactamases. Cefepime can often be used if sensitive	For community acquired intra-abdominal: - Ceftriaxone 1g qday and metronidazole 500mg PO/IV q8hrs For healthcare associated intra-abdominal - Ceftazidime 2g IV q8hrs + metronidazole 500mg PO/IV q8hrs, or pip-tazo **Not recommended** - CNS infection - Pneumonia unless targeting documented ESBL or Amp C organisms - Treatment of confirmed or suspected *Pseudomonas spp.* or *Enterococcus spp.* infection
Piperacillin/ Tazobactam .ZosynRestricted	**Pneumonia** - HCAP/VAP/HAP plus suspected aspiration **Intra-abdominal** - Healthcare associated intra-abdominal infections **Empiric sepsis** - Documented or suspected infection due to a resistant gram negative organism (resistant or intolerant to cephalosporins) **Skin and soft tissue** - Limb threatening diabetic foot or necrotizing fasciitis - Polymicrobial and/or involving anaerobic bacteria in patients intolerant or resistant to amp/sul or a cephalosporin + metronidazole	- Use cefepime or ceftazidime if no aspiration - Community onset intra-abdominal infections – use ceftriaxone/metronidazole or ciprofloxacin/metronidazole (if allergy to ceftriaxone); health-care associated utilize ceftazidime + metronidazole - Ceftazidime + /- metronidazole + vancomycin is an additional option for empiric septic pts with risk factors for resistance
Anidulafungin .AnidulafunginRestriction	**Empiric therapy for candidemia or invasive candidiasis** - Moderate to severe illness or recent exposure to Azoles - Positive blood culture for Yeast **Documented fungal infection** - Documented C. krusei, or C. glabrata - C. albicans infection but intolerance to azoles	- Azole naïve and less critically ill - Use fluconazole - Narrow with identification/sensitivities **Not recommended** - Urinary, eye, or CNS infections. Caution in C. parapsilosis infections.

*Risk factors for resistant organisms: hospitalized prev 3 months, NH or LTC pt, long term HD patient, immunosuppressed, or recent expo to broad spectrum antibiotics; See penicillin allergy section for more detail

RENAL DOSING

Renal Dose Adjustment per Pharmacy Protocol will be available for the following agents:

Antimicrobials	Anticoagulants	Other
Acyclovir	Apixaban*	Allopurinol
Amoxicillin/Clav	Dabigatran*	Famotidine
Ampicillin	Dalteparin*	Gabapentin
Ampicillin/Sulb	Enoxaparin	Ketorolac
Aztreonam	Fondaparinux*	Metoclopramide
Cefazolin	Rivaroxaban*	Ranitidine
Cefepime		
Ceftazidime		
Cephalexin		
Ciprofloxacin		
Daptomycin		
Ertapenem		
Fluconazole		
Levofloxacin		
Meropenem		
Piperacillin/Taz		
TMP/Sulfa		
Valacyclovir		
Vancomycin		

*Per the University of Colorado Hospital policy, these agents are not recommended for patients with a CrCl < 30 ml/min since this population was not studied in the clinical trials.

- All medications on this protocol will be evaluated for appropriateness of dosing by a pharmacist on initial verification and at least every 72 hours.
- Cockcroft-Gault equation will be used to determine CrCl, using adjusted body weight in obese individuals, and the UCH Antimicrobial Stewardship Handbook and/or Lexi comp® Drug Information Handbook will be utilized for medication dosing.
- Progress notes will be written when medication doses are renally adjusted
- Provider will be contacted in the following situations: (1) medication is contraindicated based on renal function, (2) medication is not on the renal dose protocol, or (3) original ordered dose is not appropriate for the indication.

Antimicrobial dosing during continuous renal replacement therapy (CRRT)

CRRT therapy fluid/dialysate fluid rates vary from 2-10 L/hr and can change on a daily basis. Recommendations within this book are for patients receiving CRRT flow at rates of 2-3 L/hour. If a patient's CRRT flow rates are > 3 L/hr, their actual flow rates should be considered when applying the drug dosing regimens for CRRT in this booklet to avoid under-dosing. For antimicrobials with dosing adjustments for CRRT, the drug clearance can be estimated by multiplying the total ultrafiltration rate (therapy fluid and/or dialysis fluid rates plus any additional fluid removal) by the drug's sieving coefficient (the sieving coefficient can be estimated as the free fraction of drug in the plasma). The result can be applied to the CrCl cut-offs for drug dosing decisions listed within this book.

Example for meropenem with a CVVH ultrafiltration rate of 6 L/hr:

1. Ultrafiltration rate = 6 L/hr, (convert to ml/min = 100 ml/min)
2. Meropenem is 2% protein bound: free fraction is 98% (0.98 ~ sieving coefficient)
3. Meropenem clearance by CRRT = 0.98 x 100 ml/min = 98 ml/min
4. Therefore, in this patient apply 98 ml/min to meropenem CrCl dosing cut offs within this book when making dosing decisions

Antimicrobial dosing during intermittent hemodialysis (HD)

Drug dosing recommendations for HD within this booklet are based upon 3 times weekly HD with a standard 4 hour HD treatment. Dosing modifications may be necessary if HD is prescribed outside of these assumptions.

ANTIBACTERIALS

Amikacin (IV)

Monitor concentrations. Recommend Pharmacy Consult. Refer to dosing guidelines

Amoxicillin (PO)

≥30: 250-500mg TID or 875mg BID (1,000mg TID for pneumococcal infections)
11-29: 250-500mg BID
≤ 10: 250-500mg daily
HD: 250-500mg daily dosed after hemodialysis
CRRT: 500 mg BID

Amoxicillin/clavulanate (Augmentin) (PO)

≥30: 250-500mg TID or 875mg BID (XR formulation – 2000/125mg PO BID [for pneumococcal infections])
11-29: 250-500mg BID
≤ 10: 250-500mg daily
HD: 250-500mg daily dosed after hemodialysis

Ampicillin (IV)

≥50: 2g q4-6h or 6g continuous infusion q12h. Max dose 12g/day-use for meningitis, endocarditis
30-49: 2g q6-8h
11-29: 2g q8-12h
≤ 10: 2g q12h
HD: 2g q12h dosed after hemodialysis
CRRT: 2 gram load, then 1-2g q6h

Ampicillin/Sulbactam (Unasyn®) (IV)
≥50: 3g q6h (higher doses than normal should be used if treating *Acinetobacter spp.*)
30-49: 3g 8h
15-29: 3g q12h
≤ 14: 3g q24h
HD: 3g q12-24h dosed after hemodialysis
CRRT: 3g q6-8h

Azithromycin (PO/IV)
≥10: 250-500mg q24h (One-time doses of 1-2g PO may be used for some STDs; MAC prophylaxis 1,200mg qwk)
< 10: Use with caution
HD: Hemodialysis removal unknown; no supplemental dose needed post HD
CRRT: No change recommended

Aztreonam (IV/IM)
Mild to Moderate Infections **(UTIs, SSTIs)**
≥30: 1g q8h
11-29: Load 1g, then 500mg q8h
≤ 10: Load 1g, then 250mg q8h
HD: Load 1g, then 250mg q8h after hemodialysis
CRRT: 2g load, then 1g q12h
Severe Infections **(Pseudomonas, Sepsis, Pneumonia, CF, Obese, Febrile Neutropenia)**
≥30: 2g q8h, consider 2g q6h (max 8g/day)
11-29: Load 2g, then 1g q8h
≤ 10: Load 2g, then 500mg q8h
HD: Load 2g, then 500mg q8h after hemodialysis
CRRT: 2g load, then 1g q8h

Bezlotoxumab (IV) – Restricted/Non-Formulary, not for routine IP use, contact ID Pharm for use
Prevention of *C. difficile* infection recurrence: 10mg/kg IV once (Use adjusted body weight in obese)
No dose adjustment in renal/hepatic impairment

Cefazolin (IV) – Preferred for all MSSA Infections (excluding infections involving CNS)
Mild to Moderate Infections **(SSTIs, UTI)**
≥50: 1g q8h; 2g for surgical prophylaxis (3 grams for patients weighing ≥ 120kg)
11-49: 1g q12h
≤ 10: 1g q24h
HD: 1g x 1 load, then 500mg daily *Preferred Inpatient* (1g 3x/week after HD alternative for discharge)
CRRT: 1g q12h
Severe Infections **(Endocarditis, Bacteremia, Pneumonia, Osteomyelitis)**
≥50: 2g q8h; up to 12g/day has been used for endocarditis, consider 3g IV q8h for those ≥ 120kg)
11-49: 2g q12h (3g q12h)
≤ 10: 2g q24h (3g q24h)
HD: 2g x 1 load, then start 1g daily *Preferred Inpatient* (2g 3x/week after HD alternative for discharge)
CRRT: 2g q12h

Cefpodoxime (PO) – Formulary oral 3rd generation cephalosporin
≥ 30: 200-400mg BID
< 30: 200-400mg daily
HD: 100-200mg qday after HD *Preferred Inpatient* (200-400mg 3 times/week after HD alternative)

Cefepime (IV)
Mild to Moderate Infections **(UTI, SSTIs)**
≥60: 1-2g q12h
30-59: 1-2g q24h
11-29: 1-2g load, then 0.5-1g q24h
≤ 10: 1-2g load, then 0.5g q24h
HD: 1g x 1 load, then 500mg q24h *Preferred Inpatient* (1g 3x/week after HD alternative for discharge)
CRRT: 1g q12h
Severe Infections **(Febrile Neutropenia, Pseudomonal, Pneumonia, Meningitis)**
≥60: 2g q8h
30-59: 2g q12h
11-29: 2g q24h
≤ 10: 2g load, then 1g q24h
HD: 2g load, then 1g q24h *Preferred Inpatient* (2g 3x/week after HD alternative for discharge)
CRRT: 2g q12h

Cefotaxime (IV/IM)
Mild to Moderate Infections
≥ 50: 2g q8h
11-49: 2g q12h
≤ 10: 2g q24h
HD: 1g q24h dosed after HD
CRRT: 1g q8h
Severe Infections **(Septicemia, meningitis)**
≥50: 2g q4-6h; for life threatening infections (meningitis) dose q4h
11-49: 2g q8h
≤ 10: 2g q12h
HD: 2g q24h dosed after HD
CRRT: 1-2g q8h, consider 2g if UF rate exceeds 3L/hour

Cefoxitin (IV)
≥50: 1-2g q6h (PID dosing: 2g IVq6h, *mycobacterium abscessus* 2g q4h max: 12g/day)
30-49: 1-2g q8h
10-29: 1-2g q12h
< 10: 2g load, then 1g q24h
HD: 1-2g load, then 1g q24h dosed after hemodialysis
CRRT: 1-2g q8h

Ceftaroline (IV) Restricted (see antimicrobial restrictions on page 33)
Mild to Moderate Infections **(CAP or cSSSI)**
≥50: 600mg q12h
31-49: 400mg q12h
16-30: 300mg q12h
≤ 15: 200mg q12h
HD: 400mg q24h dosed after hemodialysis
CRRT: 400mg q12h
Severe Infections **(MRSA bacteremia/persistent disease, Endocarditis, Osteomyelitis)**
≥50: 600mg q8h
31-49: 600mg q12h
≤ 30: 600mg q24h
HD: 600mg q24h dosed after hemodialysis
CRRT: 600mg q8-12h

Ceftazidime (IV)
Mild to Moderate Infection **(SSTI, UTI)**
≥50: 1g q8h
31-49: 1g q12h
10-30: 1g q24h
< 10: 1g load then 0.5g q24h
HD: 1g x 1 load, then 500mg q24h *Preferred Inpatient* (1g 3x/week after HD alternative for discharge)
CRRT: 1-2g q12h
Severe Infection: **(Gyn, Intra-ab, Meningitis, Nosocomial pneumonia, Septicemia, CF)**
≥50:2g q8h (in CF patients, dose 2g q6h or 8g continuous infusion; 8g/day max)
31-49: 2g q12h
10-30: 2g q24h
< 10: 2g load then 1g q24h
HD: 2g load, then 1g q24h *Preferred Inpatient* (2g 3x/week after HD alternative for discharge)
CRRT: 2g q8-12h, consider q8h if 2.5L/hour or greater UF rate

Ceftazidime/Avibactam (IV) Non-Formulary (see restrictions to use on page 33)
> 50: 2.5g (2g ceftazidime / 500mg avibactam) q8h
31-50: 2.5g x 1, then 1.25g (1g ceftazidime / 250mg avibactam) q8h
16-30: 2.5g x 1, then 0.94g (750mg ceftazidime / 190mg avibactam) q12h
6-15: 2.5g x 1, then 0.94g (750mg ceftazidime / 190mg avibactam) q24h
HD: 2.5g x 1, then 0.94g (750mg ceftazidime / 190mg avibactam) q24h
CRRT: 2.5g x 1, then 1.25g (1g ceftazidime / 250mg avibactam) q8h (Sieving Coeff = 0.96 / 0.93)

Ceftolozane/Tazobactam (IV) Restricted Use (see restrictions to use on page 33)
> 50: 1.5g (1g ceftolozane / 500mg tazobactam) q8h (3g q8h for severe/respiratory infections)
30-50: 750mg (500mg ceftolozane / 250mg tazobactam) q8h (3g x 1, then 1.5g q8h)
15-29: 375mg (250mg ceftolozane / 125mg tazobactam) q8h (3g x 1, then 750mg q8h)
HD: 750mg once, then 150mg (100mg ceftolozane / 50mg tazobactam) q8h (3g x 1, then 300mg q8h)
CRRT: 3g x 1, then 1.5g (1g ceftolozane / 500mg tazobactam) q8h (consider 3g q8h at higher UF rates)
***For severe/respiratory infections consider doubling above doses for improved target attainment

Ceftriaxone (IV)
No adjustment necessary: 1g q24h; 2g q24h (endocarditis, osteomyelitis); 2g q12h (meningitis/enterococcal endocarditis synergy with ampicillin)
HD: Not removed by conventional dialysis, no data for high permeability. Patients with concomitant liver and renal insufficiency daily dosing should not exceed 2g daily.

Cefuroxime (PO)
≥ 30: 250mg (cystitis only) – 500mg PO BID
< 30: 250-500mg PO q24h
HD: 250-500mg PO q24h (dosed after HD on those days)

Cephalexin (PO) – Not to be used for cSSTI, blood stream infections, or complicated pyelonephritis
≥ 50: 500-1,000mg TID-4x/day
31-49: 500mg TID
≤ 30: 500mg BID
HD: 250mg BID (second dose after hemodialysis)

Ciprofloxacin (IV) - Restricted (see antimicrobial restrictions on page 33)
***Mild to Moderate Infections* (UTI, intra-abdominal, SSTI)**
≥30: 200-400mg q12h
<30: 200-400mg q24h
HD: Not removed by conventional hemodialysis; 200mg q24h.
CRRT: 200mg q12-24h
***Severe Infections* (Nosocomial pneumonia, Neutropenic fever, Osteomyelitis)**
≥50: 400mg q8h
30-49: 400mg q12h
< 30: 400mg q24h
HD: Not removed by conventional hemodialysis; 400mg q24h
CRRT: 400 mg q12-24h

Ciprofloxacin (PO) - Restricted (see antimicrobial restrictions on page 33)
***Mild to Moderate Infections* (UTI, intra-abdominal, SSTI)**
≥ 30: 250-500mg BID
< 30: 250-500mg daily
HD: 250-500mg daily after HD. Not removed by conventional hemodialysis; no data for high permeability.
CRRT: 500mg q12-24h
***Severe Infections* (Nosocomial pneumonia, Neutropenic fever, Osteomyelitis)**
≥ 50: 750mg BID
30-49: 500mg BID
< 30: 500mg daily
HD: 500mg daily after HD. Not removed by conventional hemodialysis; no data for high permeability.
CRRT: 750 mg q12-24h

Clarithromycin (PO) - Indicated for *H. pylori* or MAC infections
≥30: 250-500mg BID
<30: 125-250mg BID or 250-500mg daily
HD: 500mg q24h (dosed after dialysis) / CRRT: 500mg q12-24h

Clindamycin (PO/IV) - No adjustment necessary for renal or hepatic insufficiency (not removed by RRTs)
IV dose: 600-900mg q8h, max dose 4800mg/day (PCP & CNS toxoplasmosis, 600mg q6h)
Oral dose: 300-450mg TID to 4x/day (CNS toxoplasmosis, 450-600mg 4x/day)

Colistimethate (IV) - Ideal body weight should be used (Doses provided assume Goal C_{ss} = 2mg/L)

<table>
<tr><th rowspan="2">Dosing Strategy (Dosing given as mg of colistin base activity)</th><th rowspan="2">Loading Dose All Patients (Max 300mg)</th><th colspan="7">Maintenance Dosing by CrCl (mL/min) / Dialysis Modality</th></tr>
<tr><th>≥ 80</th><th>50-79</th><th>30-49</th><th>10-29</th><th>HD</th><th>CRRT</th><th>SLED</th></tr>
<tr><td>Inhaled</td><td>N/A</td><td colspan="7">150mg nebulized q8-12h – no dose adjustment necessary, minimal systemic absorption</td></tr>
<tr><td>Preferred Systemic (Equation)
Goal Css = 2 mg/L</td><td>4mg/kg x IBW
(Dose=$C_{ss\text{-}goal}$ x 2 x IBW)</td><td colspan="4">Colistin Base (mg/day) = 2 x $10^{(0.0048 \times CrCl + 1.825)}$
[In 1-2 divided doses]</td><td>3h=170mg qd
4h=180mg qd</td><td rowspan="2">150mg q8h</td><td rowspan="2">Base 130mg/d + 10%/hr of SLED (10h=260mg/d)</td></tr>
<tr><td>Alternative</td><td>5mg/kg x IBW</td><td>2.5mg/kg q12h</td><td>1.9mg/kg q12h</td><td>1.25mg/kg q12h</td><td>1mg/kg qd</td><td>1.5mg/kg qd</td></tr>
</table>

Dalbavancin – Restricted, do not give inpatient without explicit approval (see restrictions pg 33)
≥ 30 or receiving dialysis: 1500mg IV once over 30 minutes
< 30 not receiving dialysis: 1125mg IV once over 30 minutes

Daptomycin (IV) - Restricted (see antimicrobial restrictions on page 33)
Do not use in pneumonia

Indication	CrCl ≥ 30 mL/min	CrCl < 30 mL/min	Hemodialysis[1]	CRRT
Cystitis (including VRE)	250 mg IV Qday	250 mg IV Q48h	Same dose as < 30 mL/min	250 mg IV Qday
Pyelonephritis/Cellulitis	4 mg/kg IV Qday	4 mg/kg IV Q48h	Same dose as < 30 mL/min	4 mg/kg IV Qday
Uncomplicated Bacteremia/Right-Sided Endocarditis (NOT VRE)	6 mg/kg IV Qday	6 mg/kg IV Q48h	Same dose as < 30 mL/min	8 mg/kg IV Q48h
Osteomyelitis, Prosthetic Joint Infection, VRE[2] Bacteremia (source control adequate)	8 mg/kg IV Qday	8 mg/kg IV Q48h	Same dose as < 30 mL/min	Administer usual dose daily for 2-3 days, then reduce frequency to q48h
Refractory MRSA bacteremia, left-sided endocarditis, VRE[2] infection/bacteremia (inadequate source control and/or BMT)	10-12 mg/kg IV Qday	10-12 mg/kg IV q48h	Same dose as < 30 mL/min	

For **Obese patients, defined as actual body weight (ABW) > 120 kg, dose based on **Adjusted Body Weight = [0.4*(ABW – IBW) + IBW]****
[1] Alternative HD dosing, administer usual recommended dose during 48 hour intradialytic days and on 72 hour intradialytic day increase usual dose by 2mg/kg (i.e. Patient with M-W-F HD schedule, administer 6mg/kg on Mon. and Wed., then 8mg/kg on Fri.; or 8-8-10mg/kg, or 10-10-12mg/kg)
[2] *Enterococcus spp.* with daptomycin MIC's ≥ 2 mcg/mL should receive higher doses due to potential for resistance development. Less complicated patients (non-transplant, line-related infections, and adequate source control) can likely be managed with doses of 8mg/kg. Others with more complex infections should receive higher doses of 10-12 mg/kg. Those with MIC's ≤ 1 mcg/mL may be managed similarly to S*taphylococcus aureus*.

Dicloxacillin (PO)
Renal Dysfunction: No adjustment necessary: 250-500mg 4x/day
CRRT: No adjustment necessary

Doxycycline (PO/IV)
No dose adjustment for sever hepatic or renal insufficiency (not removed by RRTs)
PO/IV: 100mg q12h

Ethambutol (PO)
Tuberculosis, Non-Tuberculous Mycobacterium *(M. avium* and *M. kansasii)*
> 10: 15-20 mg/kg q24h (max: 1.6g/day)
≤ 10: 15 mg/kg q48h
HD: 15-20mg/kg post-HD 3x/week
CRRT: 15-25mg/kg q24-36h

Fidaxomicin (PO)
C. difficile infection treatment: 200mg PO BID x 10 days
(alt. dosing in recurrent disease 200mg PO BID x 5 days, then 200mg PO QOD x 10 doses)
No adjustment necessarry in renal/hepatic impairment

Fosfomycin (PO) - Should NOT be used for pyelonephritis
Uncomplicated cystitis: 3g sachet x1
Complicated UTI (cystitis-only): 3g sachet q48h for 3 total doses **(requires ID approval)**
No adjustment necessary (HD: No data)

Ertapenem (IV) Restricted (see antimicrobial restrictions on page 33)
≥30: 1g q24h (2g qday may be appropriate in morbidly obese patients)
< 30: 500mg q24h
HD: 500mg q24h dosed after hemodialysis-preferred (alternate: 1g three times weekly after HD)
CRRT: 1g q24h

Gentamicin (IV)
Monitor concentrations. Recommend Pharmacy Consult. Refer to dosing guidelines

Imipenem/Cilastatin (IV) - Nonformulary (see antimicrobial restrictions on page 33)
***Mild to moderate infections* (Severe, resistant, CNS, and/or mycobacterial infections)**
≥ 90: 1g IV q8h (1g IV q6h)
60-89: 500mg q6h (1g IV once for load, then 750mg IV q8h)
30-59: 500mg IV q8h (1g IV once for load, then 500mg IV q6h)
20-29: 1g x 1, then 500mg IV q12h (1g IV once for load, then 500mg IV q8h)
< 20: 1g x 1, then 250mg IV q12h (1g IV once for load, then 500mg IV q12h)
HD: 500mg load, then 250mg q12h dosed after HD (1g load, then 500mg q12h dosed after HD)
CRRT: 1g load, then 500mg q8h (for organisms with elevated MIC ≥ 4mcg/mL, dose q6h)

Levofloxacin (IV/PO) Restricted (see antimicrobial restrictions on page 33)
***Mild-Moderate Infections* (CAP-attention to duration/dose, sinusitis, UTI, prostatitis)**
≥50: 500mg q24h
21-49: 500mg load, then 250mg q24h
≤ 20: 500mg load, then 250mg q48h
HD: 500mg load, then 250mg q48h.
CRRT: 500-750 mg load, then 250-500 mg q24h
***Severe Infections* (Nosocomial pneumonia, cSSTI, bacteremia/sepsis)**
≥50: 750mg q24h (consider higher dosing in obese patients w/ CrCl >90ml/min: 1,000-1,500mg/day)
21-49: 750mg load, then 750mg q48h
≤ 20: 750mg load, then 500mg q48h
HD: 750mg load, then 500mg q48h.
CRRT: 750 mg load, then 500 mg q24h

Linezolid (PO/IV) Restricted (see antimicrobial restrictions on page 33)
No adjustment necessary: 600mg q12h
HD: Removed by conventional and high permeability dialysis. Dose after hemodialysis
CRRT**:** No change recommended

Meropenem (IV) Restricted (see antimicrobial restrictions on page 33)
Extended infusion dosing: Pneumonia, sepsis, empiric therapy
>50: 1g q8h over 3 hours
26-50: 1g q12h over 3 hours
10-25: 1g x1 then, 500mg q12h over 3 hours
<10: 1g x1 then, 500mg q24h over 30mins
HD: 1g x1 then, 500mg q24h dosed after hemodialysis
CRRT: 1g q12h over 3 hours
Bacterial meningitis, Cystic Fibrosis
>50: 2g q8h over 3 hours
26-50: 2g q12h over 3 hours
10-25: 2g x1 then, 1g q12h over 3 hours
<10: 2g x1 then, 1g q24h over 30 mins
HD: 2g x1 then, 1g q24h over 30 mins dosed after hemodialysis
CRRT: 2g x1 then, 1g IV q8h over 3 hours

Metronidazole (PO/IV)
≥10: 500mg q8h, max dose 4g/day
<10: 500mg q12h, max dose 2g/day
HD/CRRT: Metabolites are rapidly removed by dialysis; no dose reduction necessary

Minocycline (PO/IV) – ID approval needed for IV minocycline
No dose adjustment for severe hepatic or renal insufficiency (not removed by RRTs)
Loading dose 200mg once, then 100mg BID (200mg BID may be necessary for some resistant infections)

Moxifloxacin (IV/PO) Restricted (see antimicrobial restrictions on page 33)
No adjustment required: 400mg q24h

Nafcillin (IV) – Preferred Only in Cases of MSSA Infection with CNS Involvement
No adjustment necessary: 2g q4h or 12g continuous infusion over 24 hours

Nitrofurantoin (*Macrobid*) (PO) – Do NOT use for pyelonephritis
≥40: 100mg BID x 5 days for UTI treatment; 50-100mg qhs for UTI prophylaxis
<40: Avoid use; increased risk of toxic serum levels and lack of efficacy
HD/CRRT: Avoid use

Oritavancin – Restricted, do not give inpatient without explicit approval (see restrictions pg 33)
1200mg IV once over 3 hours (no dose adjustment for renal impairment)

Penicillin G (IV)
Avoid potassium salt in renal failure, may give total daily dose as continuous infusion
≥50: 2-4 million units q4-6h, max dose 24 million units/day
11-49: 2-3 million units q4h, max dose 18 million units/day
≤ 10: 2 million units q4-6h, max dose 12 million units/day
HD: 2 million units q4-6h (dosed after hemodialysis)
CRRT: 2-3 million units q4-6h

Penicillin V Potassium (PO)
≥10: 250-500mg 4x/day
< 10: 250-500mg TID
HD: 250-500mg TID dosed after hemodialysis

Piperacillin/Tazobactam (Zosyn®) (IV) Restricted (see antimicrobial restrictions on page 33)
ALL doses infused over 4 hours standard, maintenance dosing starts 3 hours after loading dose
Mild to Moderate infections
≥20: Load 3.375g x 1 over 30min, then 3.375g q8h over 4 hours (continuous infusion, 9g daily over 24h)
< 20: Load 3.375g x 1 over 30min, then 3.375g q12h over 4 hours
HD: Load 3.375g x 1 over 30min, then 3.375g q12h over 4 hours
CRRT: Load 3.375g x 1 over 30min, then 3.375g q8h over 4 hours
Severe infections, Nosocomial pneumonia, obesity
≥20: Load 4.5g x 1 over 30min, then 4.5g q8h over 4 hours (continuous infusion, 13.5-18g daily over 24h)
< 20: Load 4.5g x 1 over 30min, then 4.5g q12h over 4
HD: Load 4.5g x 1 over 30min, then 4.5g q12h over 4
CRRT: Load 4.5g x 1 over 30min, then 4.5g q8h over 4

Polymyxin B – Use Actual Body Weight (1mg = 10,000 units)
Loading Dose: 2.5mg/kg IV x 1
Maintenance Dose: 1.25mg/kg q12h (start 12 hours after loading dose)
No dosing adjustment necessary for renal impairment, limited evidence indicates < 10% removal by CRRT

Rifampin (PO/IV)
>10: Mycobacterium 450-600mg q24h; Prosthetic valve endocarditis 300mg q8h;
Prosthetic join infection, 300-450mg q12h
≤ 10: Dose adjustment likely not necessary
HD: Not removed by conventional hemodialysis; not removed by high permeability.
CRRT: No change in dosing necessary

Tigecycline (IV) – Restricted (see antimicrobial restrictions on page 33)
No renal adjustment necessary: 100mg load, then 50mg q12h (not removed by HD)
Hepatic Impairment (Child-Pugh score C): 100mg load, then 25mg q12h
*****Warning, FDA precautions use due to risk of increased overall mortality*****

TMP/Sulfa (IV/PO) Dose based on TMP component
Mild to Moderate infections
≥30: 5 mg/kg/day divided q12h OR (1) DS tablet BID
<30: 2.5 mg/kg/day OR (1) SS tablet BID OR (1) DS tablet daily
HD: 5 mg/kg TIW after dialysis on HD days OR (2) DS tablets TIW after dialysis on HD days.
CRRT: 2.5 mg/kg TMP q8-12h
Moderate to Severe infections
≥30: 8-15 mg/kg/day divided q6-12h
<30: 8-15 mg/kg/day divided q6-12h for 48 hours, then 4-7 mg/kg/day divided q12h
HD: 8-15 mg/kg TIW after dialysis on HD days
CVVH: 2.5 mg/kg TMP q8-12h
Pneumocystis jirovecii pneumonia, Nocardia CNS infections, Toxoplasma Encephalitis
≥30: 15-20 mg/kg/day divided q6-8h
16-29: 15-20 mg/kg/day divided q6-8h for 48 hours, then 7-10 mg/kg/day divided q12h
≤ 15: 7-10 mg/kg/day divided q12-24h
HD: 15-20 mg/kg TIW after dialysis on HD days
CRRT: 5mg/kg TMP every 8-12h
Pneumocystis jirovecii / Toxoplasmosis Prophylaxis
≥30: 1 DS PO Q24h (preferred HIV) or 1 SS PO Q24h or 1 DS PO TIW or 1 DS PO BID on Mo/Th
15-29: 1 SS PO Q24h or 1 DS PO TIW or 1DS PO daily on Mo/Th
< 15: 1 SS PO TIW
HD: 1 SS PO TIW after HD
CRRT: 1 SS PO Q24h or 1 DS PO TIW or 1DS PO daily on Mo/Th

Tobramycin (IV)
Monitor concentrations. Recommend Pharmacy Consult. Refer to dosing guideline

Vancomycin (IV)
Refer to Vancomycin Dosing Nomogram. Recommend Pharmacy Consult

ANTIFUNGALS

Amphotericin B Liposomal (Ambisome) (IV)
≥10: 3-5mg/kg q24h No adjustment needed; dose by indication
<10: Not studied; consider dosage reduction for SCr increases to 2.5-3 mg/dL during treatment.
HD**:** Not removed by conventional dialysis; no data for high permeability.
CRRT**:** No significant influence on dosing; 3-5mg/kg every 24 hours
Ensure patients receive hydration with each dose and monitor/replete electrolytes-K/Mg

Anidulafungin (IV) Restricted (see antimicrobial restrictions on page 33)
No adjustment needed; dose by indication
HD/ESLD: No dosage adjustment needed
Candidemia, empiric treatment*:* 200mg load, then 100mg q24h (max 200mg/day)
Esophageal candidiasis: 100mg load, then 50mg q24h
Candida Endocarditis: 200mg IV q24h

Fluconazole (IV/PO)
***Severe Infections* – Use 12mg/kg daily for Susceptible-Dose Dependent (S-DD) Isolates**
≥ 50: 800mg (12mg/kg) Load, then 400mg (6mg/kg) daily
< 50: 400 load, then 200mg daily (50% of recommended dose in normal renal fxn)
< 10: 400mg load, then 100mg daily (25% of recommended dose in normal renal fxn)
HD: 400mg load, then 200mg daily *Preferred Inpatient* (Alternate dosing 400mg 3x/week post HD)
CRRT: 400 mg q24h; Consider 800mg q24h in life-threatening or higher UF rates (>2L/hour)
Urogenital, recurrent esophageal/oropharyngeal candidiasis/HIV prophylaxis
≥ 50: 200mg daily
< 50: 100mg daily
HD: 200mg load, then 100mg daily *Preferred Inpatient* (Alternate dosing 200mg 3x/week post HD)
CRRT: 200mg q24h

Flucytosine (PO)
Monitor levels/CBC closely. Use with caution in renal failure. Dose based on IBW in obese
≥40: 25 - 37.5 mg/kg q6h
21-39: 25 - 37.5 mg/kg q12h
11-20: 25 - 37.5 mg/kg q24h
≤ 10: 25 - 37.5 mg/kg q48h
HD: 25 - 50 mg/kg 3x/week post hemodialysis
PD: 0.5 - 1g q24h
CRRT: 25mg/kg q 12 – 24 hours Therapeutic drug monitoring recommended
TDM: Goal peak 30-80mg/L (Cryptococcal, 70-80mg/L in HIV); 40-60mg/L (Candida meningitis)
Draw levels 2h after dose on day 3-4. Toxicity at Peaks ≥100mg/L (hepatotoxicity, thrombocytopenia, leukopenia)

Isavuconazonium (Cresemba) IV/PO Restricted (see antimicrobial restrictions on page 33)
Dosing (IV/PO): load 372 mg q8h x 6 doses, then start 372mg q24h starting 12-24h after last LD
Swallow capsules whole; don't crush, chew, dissolve, or open. Administer with or without food.
No renal adjustment needed; Use with caution in severe hepatic impairment (Child-Pugh class C)
Therapeutic drug monitoring has not been established for this agent, and is not necessary at this time.

Itraconazole (PO)
No renal adjustment needed; dose by indication
HD: Not removed by conventional hemodialysis or high permeability filters
Histoplasmosis: 200mg capsule PO TID x3 days, then 200mg capsule PO BID
Aspergillus Prophylaxis in Transplant: 100mg capsule PO BID
TDM: goal trough > 1 mg/L (levels > 10 associated with increased toxicity), check level after day 5
*Capsules should be taken with food/acidic beverage, avoid use of gastric acid suppressants
*Suspension taken on empty stomach (food decreases absorption ~30%)
*Suspension has improved bioavailability compared to capsules, consider if difficulty obtaining therapeutic levels (Conversion: 200mg capsule is approximately 100mg liquid)

Posaconazole (IV/PO) Restricted (see antimicrobial restrictions on page 33)
No renal adjustment needed; dose by indication (not removed by HD)
ESLD**:** No adjustment needed
Suspension: reserved for severe mucositis, inability to swallow tablets, gastric tube; must be administered with high fat meal and/or acidic beverage to ensure improved absorption

- Invasive molds (mucor, aspergillosis), 200mg q6h until stabilization, then 400mg BID-TID
- Aspergillosis prophylaxis, disseminated candidiasis in immunocompromised: 200mg TID

Delayed Release Tablets / IV Formulation: DR tabs preferred use at UCH; take with food; swallow whole-don't crush, chew, divide, or dissolve

- Treatment/Prophylaxis Invasive Fungal Infection: 300mg q12h x 2 doses, then 300mg qday
- < 50: avoid use of IV formulation due to accumulating cyclodextrin vehicle
- CRRT: IV formulation- No dosage change necessary; cyclodextrin adequately removed by CRRT

TDM: Goal trough, > 0.7-1 (prophylaxis) and >1-2 mg/L (treatment), check level on/after day 6

Voriconazole (IV) Restricted (see antimicrobial restrictions on page 33)
≥50: Load 6mg/kg q12h x2 doses, then 4mg/kg q12h (Use Adjusted body weight in obese)
<50: Avoid due to accumulating cyclodextrin vehicle.
HD: Not removed by conventional hemodialysis; removal by high permeability unlikely.
CRRT: No dosage change necessary; cyclodextrin adequately removed by CRRT
Hepatic impairment (Child-Pugh A, B): Standard load, then reduce maintenance dose by 50%
TDM: Goal trough, >0.5-1 (prophylaxis) and 2-4 mg/L (treatment), levels >4-5.5 associated with increased toxicity risk, may obtain level on day 3-4 (if LD given) or day 5-6 (if no LD given)

Voriconazole (PO) Restricted (see antimicrobial restrictions on page 33)
No renal adjustment needed; dose by indication
HD: Not removed by conventional hemodialysis; no data for high permeability
Hepatic impairment (Child-Pugh A, B): Standard load, then reduce maintenance dose by 50%
Aspergillosis, Blastomycosis: Load 6mg/kg q12h x2 doses, then 4mg/kg q12h; round to nearest 50mg
Candidiasis: ≥ 40kg: 200mg BID (max dose 600mg/day)
< 40kg: 100mg BID (max dose 300mg/day)
Febrile neutropenia, empiric coverage for candida/mold: Load 6mg/kg q12h x2 doses, then 4mg/kg q12h (Use Adjusted body weight in obese) – round doses to nearest 50mg
TDM: Same as listed for IV above

ANTIVIRALS

Acyclovir (IV)
Use adjusted body weight in obese (>120% of IBW) otherwise use actual body weight
HSV encephalitis, severe Herpes Zoster-dermatomal/visceral, Varicella Zoster
≥50: 10 mg/kg q8h**, max 15 mg/kg/dose**
25-49: 10 mg/kg q12h
11-24: 10mg/kg q24h
≤ 10: 10mg/kg x 1, then 5mg/kg q24h
HD: 10mg/kg x 1, then 5mg/kg q24h dosed after HD (alt. 7.5 mg/kg 3x/week post hemodialysis)
CRRT: 10mg/kg q24h (for CVVHD/CVVHDF may dose 10mg/kg q12h in severe disease)
Genital Herpes Simplex, mucocutaneous HSV
≥50: 5mg/kg q8h
25-49: 5 mg/kg q12h
11-24: 5 mg/kg q24h
≤ 10: 5 mg/kg load, then 2.5mg/kg q24h
HD: 5mg/kg load, then 2.5mg/kg q24h dosed after HD (alt. 5mg/kg 3x/week post hemodialysis)
CRRT: 5mg/kg q24h

Acyclovir (PO)
Herpes Simplex
≥10: 400mg TID (genital/oral mucocutaneous)
400mg BID (chronic suppression or HSV prophylaxis in non-HSCT hematologic malignancy)
800mg BID (Prophylaxis of HSV/VZV in HSCT recipients)
< 10: 200mg BID (400mg BID for HSCT recipients)
HD: 200mg BID post hemodialysis (400mg BID for HSCT recipients)
CRRT: 200-400mg q24h
Herpes Zoster
≥25: 800mg 5X/day (spaced q4h)
10-25: 800mg TID
<10: 800mg BID
HD: 800mg BID with one dose after HD on HD days (PD: 600-800mg daily)
CRRT: 600- 800mg q24h

Ganciclovir (IV)
CMV Induction duration usually 2-3 weeks (ideally CMV blood PCR negative x 2-3)

CrCl	Induction (requires loading dose)	Maintenance/Prophylaxis
≥70	5 mg/kg q12h	5 mg/kg q24h OR 6 mg/kg q24h (5 days/wk)
50-69	5 mg/kg Load; 2.5 mg/kg q12h	2.5 mg/kg q24h
25-49	5 mg/kg Load; 2.5 mg/kg q24h	1.25 mg/kg q24h
10-24	5 mg/kg Load; 1.25 mg/kg q24h	0.625 mg/kg q24h
HD	5 mg/kg Load; 1.25 mg/kg 3x/wk post HD	0.625 mg/kg 3x/wk post HD
CRRT	2.5-5 mg/kg q24h	1.25-2.5 mg/kg q24h

Oseltamivir (PO) - ***Treatment (Prophylaxis) of Influenza***
> 60: 75mg BID x 5d, may continue > 5d for severe disease (Prophylaxis: 75mg daily x 7d)
30-60: 30mg BID (Prophylaxis: 30mg daily)
11-29: 30mg daily (Prophylaxis: 30mg every other day)
HD: Removed by conventional dialysis, 30mg (low-flux/prophylaxis) – 75mg (high-flux) post HD
CRRT: 75 mg daily-BID, consider 150mg BID if patient is receiving ECMO and CVVH.

Ribavirin (PO) – Treatment of RSV, PIV, HMPV Pneumonia (round to closest 200mg interval
> 50: Load 10mg/kg (max 2g) PO once, then start 400mg (40-60kg), 600mg (61-90kg), 800mg (91-120kg), or 1000mg (> 120kg) PO TID.
30-50: Load 10mg/kg (max 2g) PO once, then start 200mg PO TID
< 30/HD: Load 10mg/kg (max 2g) PO once, then 200mg PO qday (limited data)
For lung transplant, omit loading dose and start 15-20mg/kg/day in 3 divided doses

Valacyclovir (Valtrex®) (PO)

Herpes Zoster (Shingles), 7 day course of therapy (step down HSV meningitis)

≥50: 1g TID (use 2g PO TID for VZV meningitis step-down)
30-49: 1g BID
10-29: 1g daily
<10: 1g load, then 500mg daily
HD: 1g load, then 500mg daily post hemodialysis

Herpes Labialis (cold sore)

≥50: 2g BID x 2 doses
30-49: 1g BID x 2 doses
10-29: 500mg BID x 2 doses
<10/HD: 500mg x 1 dose

Genital Herpes, Initial Episode, 7-10 day course of therapy

≥30: 1g BID
10-29: 1g daily
<10: 500mg daily
HD: 500mg daily post hemodialysis

Genital Herpes, Recurrent Episode, 3 day course of therapy

≥30: 500mg BID
<30: 500mg daily
HD: 500mg daily post hemodialysis

Genital Herpes, Suppression Therapy, 9 or fewer episodes per year

≥30: 500mg daily
<30: 500mg every other day
HD: 500mg 3x/week post hemodialysis

Genital Herpes, Suppression Therapy, 10 or more episodes per year

≥30: 1g daily (500mg BID for HIV-infected with $CD_4 \geq 100$ cells/mm^3)
<30: 500mg daily
HD: 500mg daily post hemodialysis

Valganciclovir (Valcyte®) (PO)

CrCl	Induction	Maintenance	Prophylaxis
≥60	900 mg BID	900 mg daily	BMT: not indicated SOT: Refer to page 66-67 for specific recommendations
40-59	450 mg BID	450 mg daily	
25-39	450 mg daily	450 mg q48hrs	
10-24	450 mg q48hrs	450 mg BIW	
<10/HD	200 mg TIW after HD	100 mg TIW after HD	

HIV and HCV antiviral dosing and information beginning on page 83-87

Pharmacokinetic Dosing Guidelines

Vancomycin Dosing Guide

ED & Inpatient Vancomycin Loading Dose Guidelines

- Loading Dose = 25mg/kg IV x 1 (rounded to nearest 250mg increment, max dose = 2.5g)
- Loading Doses should be administered in the following patients:
  - Meningitis
  - Endocarditis
  - HAP/VAP
  - Critically-ill / Severe Sepsis / Septic Shock
  - Obese
  - Other clinical situations in which rapid achievement of therapeutic levels desired
- Doses are infused at a rate of ≤ 1g/h

Vancomycin Inpatient Dosing Nomogram

	Actual bodyweight (kg)			
CrCl (mL/min)	< 60	60-80	81-100	> 100
> 90	750 mg q8	1,000 mg q8	1,250 mg q8	1,500 mg q8
50-90	750 mg q12	1,000 mg q12	1,250 mg q12	1,500 mg q12
15-49	750 mg q24	1,000 mg q24	1,250 mg q24	1,500 mg q24
< 15, CRRT, HD	750 mg	1,000 mg	1,250 mg	1,500 mg
	See below for dosing frequency			

PK Documentation Requirements for Vancomycin and Aminoglycosides

- Notes should be written for new consults, any time dose adjusted, in response to a level, every 3 days, and at end of consult.
- Levels may not be necessary if planned duration of therapy expected to be < 2-3 days
- In most cases levels are ordered to assess new dosing, significant renal function changes, worsening clinical status, and every 5-7 days once dosing is therapeutic and renal function stable. This is a general advisement and does not replace clinical judgement.

Patients with CrCl < 15, CRRT, or unstable renal function (e.g. acute renal failure)

1. Give one dose at 20-25 mg/kg actual bodyweight (round to nearest 250mg increment, max dose = 2.5g).
2. Check a random vancomycin level 12-24 hours after the dose.
3. If random level is < 20 mcg/mL, repeat dose. If level is > 20 mcg/mL, do not redose, repeat random level in 12-24 hours.

Patients on intermittent hemodialysis

1. Give one dose at 20-25 mg/kg actual bodyweight (round to nearest 250mg increment, max dose = 2.5g).
2. Check a random vancomycin level 2 hours after hemodialysis.
3. If random level is < 20 mcg/mL, repeat dose. If level is > 20 mcg/mL, do not redose, repeat level after next dialysis.

Patients on peritoneal dialysis

1. Give a one-time dose of 20-25mg/kg actual body weight (max 2g) IV **Or** intra-peritoneal (for PD catheter associated peritonitis) – do not administer both IV and IP at same time, IP administration will rapidly achieve therapeutic concentrations in blood (> 15mg/L)
2. Check random vancomycin level from blood in 3 days, clearance is minimal from peritoneal dialysis mostly dependent on residual urine function.
3. Redose 15mg/kg for random level < 15-20 mg/L (average re-dosing frequency is 5 days, sooner if significant residual urine output)

Therapeutic drug monitoring

- For patients dosed every 8-12 hours, check trough 30 minutes prior to 4th dose.
- For patients dosed every 24 hours, check trough 30 minutes prior to 3rd dose.
- For patients dosed every 48 hours, check trough 30 minutes prior to 2nd dose.

Dose adjustment

- Goal trough is 10-20 mcg/mL in general. Troughs should be ≥ 10 mcg/mL at all times to avoid promoting resistance.
- 15-20 mcg/mL preferred if unknown source or suspect/confirmed bone, cardiac, pulmonary, or CSF infection, but if concomitant bacteremia from SSTI or UTI source 10-15 mcg/mL is likely adequate.
- Vancomycin exhibits linear kinetics, thus expected changes are generally proportional

Continuous Infusion Vancomycin Dosing Recommendations

CrCl (mL/min)	Dose – Actual Body Weight
≥ 90	40mg/kg/day
50-90	30 mg/kg/day
20-50	15mg/kg/day
<20, HD, PD, CRRT	Avoid use of continuous infusion

Steps in Determining Continuous Infusion Dosing:

1. Loading dose should be given (25mg/kg x 1 max: 2.5 g/dose)
    a. Patients that are therapeutic on intermittent dosing **do not** require a loading dose.
    b. A smaller loading dose may be necessary if trough is subtherapeutic and has not received next vancomycin dose. Consider equation, Dose = (25-trough value) x (0.7 x TBW)
2. Establish continuous infusion dose based on above table
    a. Initial dosing should not exceed 5,000mg per day
    b. Helpful equation: Ko (mg/hour) = Css desired (mg/L) X Cl-vanc (L/hr)
        i. Cl-vanc (L/hr) = (CrCl (mL/min) x 0.7) x 0.06
        ii. Ko (infusion rate, mg/hour) = total daily dose (mg) / 24 hours
            1. Multiply Ko by 24 hours to get total daily dose (mg)
    c. Levels will increase when converting from intermittent to continuous vancomycin infusions. For patients who are therapeutic on intermittent dosing, the same total daily dose (TDD) should generally not be given as a continuous infusion (reduce TDD by 10-25%).
3. Draw a random level at ~24 hours and adjust dosing to targeted Css 20-30mg/L
    a. For patients with altered vancomycin clearance, steady state may be reached faster or slower than 24 hours (steady state is ~3.3 half-lives)
        i. i.e. CrCl < 50mL/min, steady state usually not achieved until ~36-48 hours after initiation
    b. Ensure level not drawn from line infusing vancomycin and that infusion was not paused for significant time period
    c. Goal random (Css) = 20-30 mg/L
        i. Adjusting doses:
            1. Consider above equation (re-arranged to solve for Cl-vanc)
                a. Use patient specific Cl-vanc and Css-desired to find new Ko (infusion rate, mg/hr)
            2. Proportion (cross-multiply and divide)
                a. i.e. (dose/current level) = (Xdose/goal level), solve for Xdose

Aminoglycoside Dosing

Extended Interval

Background:

- Extended interval Aminoglycosides administration result in similar efficacy and decreased risk of toxicity
- Aminoglycosides are concentration dependent bactericidal agents with prolonged post-antibiotic effects (continued bacterial killing after concentrations fall to undetectable levels). The rate of bacterial killing increases as the concentration increases. When a peak aminoglycoside concentration: MIC ratio of 8-10:1 is achieved, bacterial efficacy is maximized
- The combination of a high peak and longer drug free interval help to reduce the selection and emergence of resistant organisms and minimize nephrotoxicity
- PLEASE NOTE: Extended-interval dosing should be considered in all patients for which an aminoglycoside is ordered for suspected or documented Gram-negative infection, except those meeting exclusion criteria.

Exclusion criteria:

- Myasthenia gravis, dialysis and presence of severe renal impairment (CrCl < 20 mL/min), gram-positive synergy for endocarditis caused by *S. aureus* (discouraged in most cases due to lack of benefit and increased nephrotoxicity, prosthetic valve endocarditis is exception) and *Enterococcus spp*. unless extended-interval dosing requested by provider for these indications.

Tobramycin and Gentamicin			
Dose (Frequency determined by renal function unless noted)	**Indication**	**Monitoring Peak and Trough Goals**	**Monitoring if using nomogram**
3 mg/kg	Synergy with amp, pen, or vanc for strep endocarditis. Limited evidence for use in staph and enterococcal endocarditis, but may consider this method based on European Guidelines (ask ID preference)	10-12 mg/L < 1 mg/L	*Do not use nomogram. *Obtain 2 levels and calculate patient specific kinetics (peak/trough)
5 mg/kg	Open fracture prophylaxis, UTI	12 – 16 mg/L < 0.5 mg/L	*6-12 hr random level (Graph 1)
7-10 mg/kg	Suspected Pseudomonal infections, pneumonia, or severe sepsis/shock Cystic fibrosis (Tobra 10 mg/kg/day):[10] - **Use IBW or Actual if < IBW** - Order levels with 1st or 2nd dose	16 – 40 mg/L < 0.5 mg/L	*6-12 hr random level (Graph 2) *Do not use nomogram for critically ill, CF, and others with altered Vd – 2 levels
Amikacin			
15-25 mg/kg	Resistant gram-negative infections, including *Pseudomonas*	40-80 mg/L < 5 mg/L	*May consider if using 15 mg/kg dosing (Graph 3) *Higher doses may be necessary to achieve desired PK:PD targets
30-35 mg/kg	Cystic fibrosis[10] • **Use IBW or Actual if < IBW**	80 – 120 mg/L < 1 mg/L	*Do not use *Order levels with 1st or 2nd dose
15 mg/kg qd (M-F)[12] 20-25 mg/kg TIW	Mycobacterial Infections	Pk 35-45 mg/L Pk 65-80 mg/L Tr < 5 mg/L	*Do not use

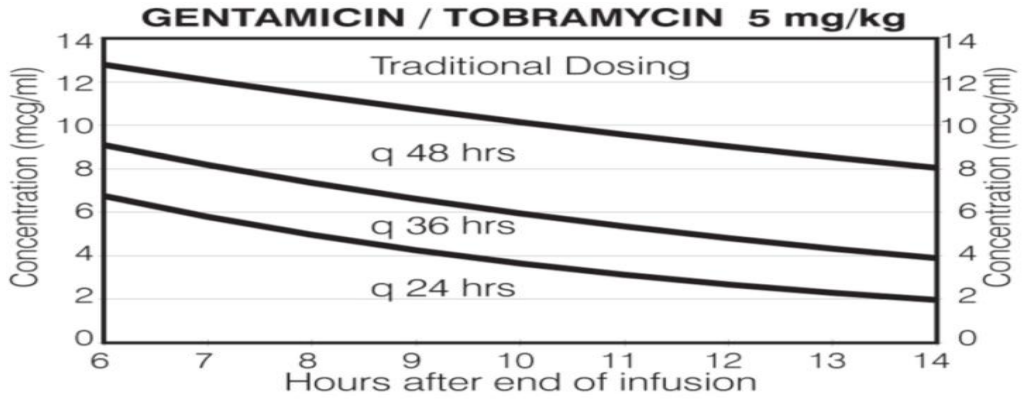
Step 1: Dosing – For Obstetric patients refer to Appendix E

- Use Actual body weight (ABW)
- If patient is obese (>20% over Ideal Body Weight IBW), use dosing weight (DBW)
  - DBW=IBW + [0.4 x (ABW- IBW)]
  - In cystic fibrosis (CF) patients use IBW or ABW if < IBW
- Patients with CrCl < 60 ml/min. Initial interval determined by CrCl.
  - CrCl > 60 ml/min (q24h); 40-59 ml/min (q36h); 20-39 ml/min (q48h); CrCl < 20 ml/min (use caution and consider redose when concentration < 1 mg/L, or convert to traditional dosing once trough < 1 mcg/mL)

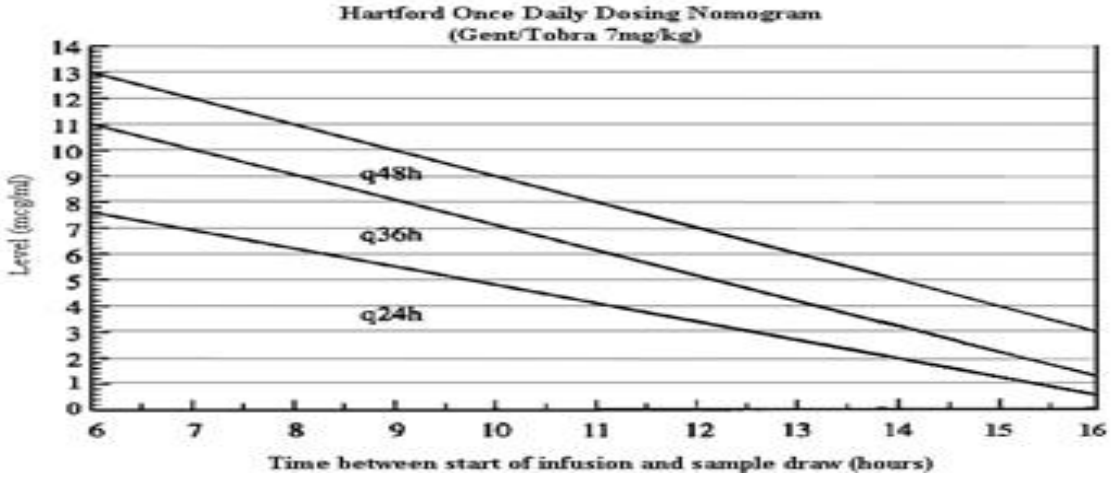
Step: 2 Therapeutic drug monitoring

- Levels may not be necessary if planned duration < 48-72 hours
- 2-point kinetics (peak and 6-12 hour random level) preferred monitoring strategy for those with altered pharmacokinetic values (i.e. critically-ill, burn patients, those with cirrhosis/ascites, pregnancy/less than 7 days post-partum, cystic fibrosis).
    - Draw peak and random with the 1st dose if possible.
        - Step 1: Draw peak 60-120 minutes after end of 1st dose.
            - Peaks are used to verify dose adequacy (i.e. efficacy)
            - Repeat peaks generally not necessary once a therapeutic peak has been achieved.
        - Step 2: Draw the 2nd level (random) 6-12 hours after dose completion.
            - 2nd level used in conjunction with first level to determine clearance and half-life in order to assign an appropriate frequency (i.e. repeat dosing interval).
            - Ideally 2 half-lives should pass between the 1st and 2nd level. Consider obtaining the 2nd level further out in renal impairment (i.e. 10-14 hours).
            - Optimal aminoglycoside free-interval is not known. A free-interval of at least 4 hours was included in published literature.[2]
        - Step 3: Draw trough level 30 min prior to 3rd or 4th dose to confirm appropriate frequency and that no accumulation with repeat dosing has occurred.
            - Repeat troughs every 5-7 days for safety monitoring to avoid accumulation that contributes to nephro/ototoxicity. May also be drawn to confirm lack of accumulation or in patients who are unable to obtain a mid-dose random level (e.g. Outpatient Parenteral Antibiotic Therapy [OPAT]).
            - Troughs may be drawn earlier if acute changes in serum creatinine and/or urine output.
        - Calculations
            - $K_e = [\ln (C_1/C_2)] / \Delta t$
            - $T_{1/2} = 0.693 / K_e$
            - $C_2 = C_1 * e^{-ke * t}$ (This equation helpful to extrapolate to true peak and/or trough)
- Nomogram dosing is an effective strategy for non-critically ill patients and those not belonging to an above group with a high-degree of PK variability not assessed in the initial nomogram studies.
    - Obtain random serum drug level 8-12 (per nomogram) hours after the end of the first dose
    - Compare the level to the appropriate nomogram.
        - Multiple nomograms, use applicable graph based on dose administered
        - If the concentration is in the area designated q 24 hr, q 36 hr or q 48 hr, continue interval.
        - If the point falls on a line, choose the longer interval. If the point is in a different interval, choose that interval
    - If the random level falls above the nomogram, the scheduled therapy should be held. Draw another concentration at 24-36 hr after the start of infusion. If the second level remains elevated, use the 2 levels for patients specific kinetics or convert to transitional dosing

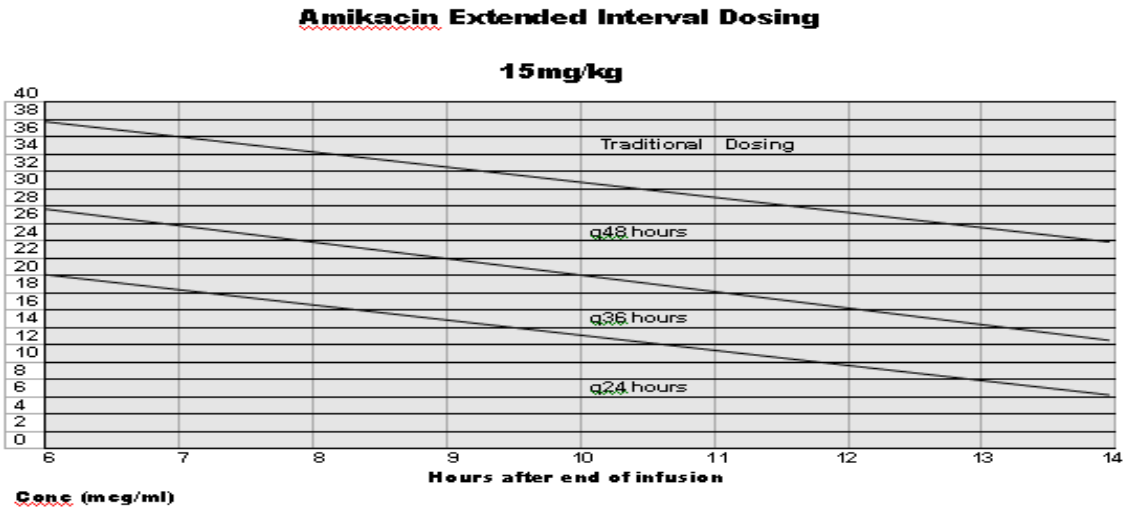
Graph 1 (Gent/Tobra-5 mg/kg)



Graph 2 (Gent/Tobra-7 mg/kg)



Graph 3 (Amikacin 15 mg/kg)



<u>Traditional Dosing</u>:

<u>Empiric dosing – no levels</u>

- Loading dose of 2 mg/kg x 1 (Gent/Tobra) recommended for patients with severe infections
- Use when once daily dosing is contraindicated
- Use the Quick Dosing guide or calculate from population kinetics (see below)

- Use IBW if ABW>IBW, but not obese
- Use DBW if obese (120% IBW)
- DBW=IBW + [0.4 x (ABW- IBW)]
- Use ABW if <IBW

Traditional Dosing Quick Guide			
CrCl	**Gentamicin or tobramycin (gram negative infections)**	**Amikacin**	**Gram positive synergy or Cystitis**
> 60 ml/min	1.5-1.7 mg/kg IV q8h	7.5 mg/kg IV q8h	1 mg/kg q8h
40-60 ml/min	1.5 mg/kg/dose IV q12h	7.5 mg/kg IV q12h	1 mg/kg q12h
20-39 ml/min	1.2 - 1.5 mg/kg/dose IV q12-24h	7.5 mg/kg IV q24h	1 mg/kg q24h
< 20 ml/min	2 mg/kg IV x 1, then redose 1.5 mg/kg/dose based on levels	7.5 mg/kg IV x 1, then redose 5 mg/kg/dose IV based on levels	1 mg/kg q48h

- Use population parameters on www.globalrph.com; the formulas are listed below for your reference
  1. Calculate creatinine clearance (CrCl) = $\frac{(140\text{-age}) \times IBW}{72 \times Scr}$ (x0.85 if female) = _____ mL/min
  2. Calculate Loading Dose (use in life-threatening infections and dialysis patients):
     a. Gentamicin/tobramycin = 2 mg/kg
     b. Amikacin = 7.5 mg/kg
  3. Estimate Vd based on hydration status:
     a. BUN/Scr < 10 – use 0.2 – 0.25 L/kg
     b. BUN/Scr 10-20 – use 0.25 – 0.3 L/kg
     c. BUN/Scr >20 – use 0.3 – 0.35 L/kg
  4. Calculate maintenance dose use population kinetics equations below or on www.globalrph.com
     a. Ke = [0.00293 hr^{-1} (CrCl)] + 0.014 = _____hr^{-1}
     b. Vd = 0.2 – 0.35 L/kg (hydration status) x IBW (use DBW if obese) = _____L
     c. $\tau = \frac{\ln (Cp\ desired/Ct\ desired)}{Ke} + t$ = _____hr
     d. t1/2 = 0.693/Ke = _____ hr
     e. $MD = \frac{t \times Cp\ desired \times Vd \times Ke \times (1-e^{-Ker})}{(1-e^{-Ket})}$ = _____ mg

Definitions
IBW = Ideal body weight
ABW = Actual body weight
DBW = Dosing body weight
MD = maintenance dose
Ke = elimination rate constant
Vd = volume of distribution
τ = dosing interval
t = time of infusion
t1/2 = half-life
Cp = peak serum level
Ct = trough serum level
Scr = serum creatinine
t' = time between levels

Peak and Trough Goals

Drug	Indication	Peaks	Troughs
Gent/Tobra	Cystitis, pyelonephritis	4-10	< 1
	Soft tissue or intra-abdominal infections	6-10	
	Febrile neutropenia, pneumonia, sepsis	8-10	
	Gram positive synergy	3-5	
Amikacin	UTI, pyelonephritis	10-30	5-10
	Soft tissue or intra-abdominal infections	18-30	
	Febrile neutropenia, pneumonia, sepsis	24-30	

[1] Consider targeting lower end of peak range for less severe infections and easy to treat sources (UTI) to minimize ADR risks with exposure to higher than necessary peaks. Targeted peaks may need to be optimized to maximize peak dependent killing (8-10x MIC).

Individualized Dosing – levels obtained

- Use when peak and trough levels have been obtained and they are not within goal
- This can be calculated on www.globalrph.com but the formulas are listed below for ref.

Calculate patient's ke and Vd

1. $Ke = \frac{\ln (Cp/Ct)}{t'}$ = _____hr^{-1}
2. t1/2 = 0.693/Ke = _____hr
3. $Vd = \frac{Dose/t\ (1-e^{-Ket})}{Cp\ (Ke)\ (1-e^{-Ker})}$ = _____L

Calculate patient's new interval, dose, and estimated levels

4. $\tau = \frac{\ln (Cp\ desired/\ Ct\ desired)}{Ke\ (use\ pt\ specific\ from\ \#1)} + t$ = _____ hr (round to nearest 8 or 12)
5. New dose = $\frac{Cp \times Vd \times Ke \times t\ (1-e^{-Ker})}{(1-e^{-Ket})}$ = _____ mg
   * use patient specific Vd from #3 and τ from # 4
6. Estimated Cpss = $\frac{New\ dose}{Ke \times Vd \times t} \times \frac{1-e^{-nKet}}{1-e^{-Ker}}$ = _____= mg/L

Therapeutic drug monitoring:

- Obtain levels if therapy is to continue > 3 days or as clinically appropriate
- Check peak/trough with 3rd or 4th dose, after dose changes, or if renal function changes
- Trough should be drawn 30 minutes before the dose is due
- Peak should be drawn 30 minutes after the end of the infusion

Gram Positive Synergy

Background:

- The addition of gentamicin to a cell wall active agent (ampicillin, penicillin, or vancomycin) enhances bactericidal efficacy against gram positive organisms (enterococcus, streptococcus, and staphylococcus), and is indicated in certain infections (namely infective endocarditis).
- Extended interval dosing is the preferred dosing strategy for indicated streptococcal infections based on AHA/IDSA guidelines
- Divided dosing is preferred per the AHA/IDSA guidelines for staphylococcal and enterococcal endocarditis. This strategy should be utilized initially, unless instructed by ID to dose by extended interval.
    - Due to evidence documenting no mortality benefit and increased nephrotoxic risk, the addition of gentamicin for staphylococcal endocarditis is not indicated except for prosthetic valve involvement.
    - Evidence to date is limited or unavailable to support routine extended interval dosing for enterococcal or staphylococcal infections; however, European endocarditis guidelines list this as a viable dosing option. Extended interval dosing is preferred for home therapy in these situations.
- Very low doses are needed to achieve synergy
    - Goal peak for gentamicin using traditional dosing = 3-4 mg/L
        - Goal peak for extended-interval dosing = 10-12 mg/L
    - Trough goal using traditional/extended-interval dosing is < 1 mg/L
    - Levels may not be necessary in all patients requiring short-courses of synergy
        - Patient's likely needing levels include: elderly, extremes of weight, baseline renal insufficiency, acute changes in urine output/serum creatinine, concern for toxicity, longer duration of therapy (> 2 weeks).
        - Use clinical judgment when determining need for level monitoring

- Use IBW if ABW > IBW, but not obese
- Use DBW if obese (120% IBW)
    - DBW=IBW + [0.4 x (ABW- IBW)]
- Use ABW if < IBW

Dosing:

Dose Strategy	Normal Renal Function (CrCl > 60 mL/min)	Renal Adjustments by CrCl	Targeted Levels
Traditional Dosing	1 mg/kg q8h	- 40-60 mL/min = 1 mg/kg q12h - 30-39 mL/min = 1 mg/kg q24h - < 20 mL/min = 1 mg/kg q48h - < 10 mL/min or HD = 1 mg/kg load, repeat dosing per levels - CRRT = 1 mg/kg Q24h, adjust per levels	Peak 3-4 mg/L Trough < 1 mg/L
Extended Interval Dosing	3 mg/kg q24h	- 40-60 mL/min = 3 mg/kg q36h - 20-39 mL/min = 3 mg/kg q48h - < 20 mL/min = 3 mg/kg x 1, then redose when level < 1 mcg/mL or convert to traditional dosing	Peak 10-12 mg/L Trough < 1 mg/L

Aminoglycoside Dosing in Dialysis

Dosing/ Monitoring:

- Use pulse dosing initially
- Schedule dose
  - If pre-/post-HD level is at goal for 2 consecutive sessions
  - Monitor pre- or post-HD levels weekly if patient is to be on long term aminoglycosides
  - Also, ensure adequate repeat assessments for hearing impairment
- Preferably, doses are given prior to dialysis starting on day of dialysis (troughs drawn 2 hours after session)
  - Remember: aminoglycosides are concentration dependent not time dependent. The appropriate peak is necessary for efficacy. Dialysis will then remove the aminoglycosides to prevent toxicity.[11]

Traditional Dosing Quick Guide			
Dialysis Type	**Gentamicin or Tobramycin (gram negative infections)**	**Amikacin**	**Gram positive synergy or Cystitis**
HD	2-3 mg/kg load, then 1.5-2 mg/kg q48-72h (redose for pre-HD level < 3-5 mg/L or post-HD level < 1-2 mg/L)	7.5 mg/kg IV q48-72h (redose for pre-HD level < 10 mg/L or post-HD level < 6-8 mg/L)	2 mg/kg load, then 1 mg/kg q48-72h (redose for pre-or post-HD level < 1 mg/L)
CRRT	2-3 mg/kg load, then 1.5-2.5 mg/kg q24-48h (redose < 1-3 mg/L)	10 mg/kg load, then 7.5 mg/kg q24- 48h (redose < 10 mg/L)	2mg/kg load, then 1 mg/kg q24-36h (redose < 1mg/L)
PD	0.6 mg/kg intraperitoneal (IP) once daily for intermittent (dose in long-dwell), or 8 mg/L load then 4 mg/L daily in dialysate for continuous dosing. For systemic administration, dose for CrCl < 20.	2 mg/kg (IP) once daily for intermittent (dose in long-dwell), or 25 mg/L load then 12 mg/L daily in dialysate for continuous dosing. For systemic administration, dose for CrCl < 20.	Dose IV for CrCl < 20. Continuous exchange use 3-4 mg/L daily in dialysate solution.

Dosing Prior to Dialysis Therapeutic Monitoring Specifics:

- **Pre-HD** levels are similar to peak concentrations (HD removes ~50% aminoglycoside concentrations)
  - Goals by aminoglycoside:

Gentamicin/Tobramycin	**Amikacin**
Synergy/Mild UTI ≤ 1 mg/L Moderate to severe UTI ≤ 3 mg/L Severe GNR infection ≤ 5 mg/L	≤ 10 mg/L

- **Post-HD** levels are similar to troughs (draw levels at least 2 hours after HD completion)
  - Goal by aminoglycoside:

Gentamicin/Tobramycin	**Amikacin**
Synergy/Mild UTI ≤ 1 mg/L Moderate to severe UTI ≤ 2 mg/L	≤ 8 mg/L

Dosing Post-dialysis Therapeutic Monitoring Specifics:

- Draw peak level. Timing depends on when dose was given with respect to dialysis
  - For doses given in dialysis, draw random level 2 hours after intermittent dialysis session. Immediate post-HD levels are not reliable due to redistribution
  - Goals by aminoglycoside (similar to goals for traditional dosing):

Gentamicin/Tobramycin	**Amikacin**
• Synergy 3-4 mg/L • UTI 4-10 mg/L • Less severe GNR, soft tissue or intra-abdominal 6-10 mg/L • Severe GNR, febrile neutropenia, pneumonia, sepsis 8-10 mg/L	• UTI 10 – 30 mg/L • Less severe GNR, soft tissue or intra-abdominal 18-30 mg/L • Severe GNR, febrile neutropenia, pneumonia, sepsis 24-30 mg/L

- Draw random level with am labs (similar to trough)
  - If < 2 mg/L, but detectable, administer post-dialysis dose
  - If > 2 mg/L, hold post-dialysis dose, redraw random level following am and redose when < 2 mg/L
  - If level undetectable, increase maintenance dose by 25-100%

Inclusion Criteria (patient to meet *all* relevant inclusion criteria)

- Patient is able to tolerate other oral medications or medications via an enteral or, nasogastric tube (NGT);
- Patient is able to eat (or tolerate enteral nutrition with minimal residuals) or has the ability to swallow tablets or other dosage forms (i.e., liquid or solid crushed in applesauce);
- Patient is not experiencing any nausea or vomiting currently, nor in past 24 hours;
- For antibiotics, patient is clinically improving and has the following criteria:
  - Afebrile (temperature < 100.4°F) for at least 24 hours
  - Improved signs and symptoms as documented in prescriber's progress notes
  - Infection is at a site where an oral agent will achieve adequate concentrations

Exclusion Criteria (patients having *one or more* criteria are ineligible for conversion)

- Pancreatitis or active gastrointestinal bleeding;
- Patient is strict NPO or swallow evaluation documents large risk for aspiration;
- Patient experiencing nausea, vomiting or moderate-severe diarrhea;
- Grade III or IV mucositis;
- Gastrointestinal obstruction, ileus, short bowel syndrome, active IBD or other documented malabsorptive syndrome (i.e. high residuals);
- For antibiotics, indication requires extended course of parenteral antibiotics (i.e., bacteremia, endocarditis, cystic fibrosis, meningitis, etc.) or the patient has an ID Consult;
- The patient is hemodynamically unstable, as defined as *two or more* of the below (SIRS criteria):
  - Temperature > 100.4°F or < 96.8°F
  - HR > 90 bpm
  - WBC > 12,000/mm^3 or < 4,000/mm^3 or > 10% bands
  - RR > 20 breaths/min

Guidelines and Documentation

- When converting an IV medication to an ***orally-swallowed dosage form***, the healthcare provider does not need to be contacted. However, when converting an IV medication to a dosage from intended for ***enteral or NGT administration***, the pharmacist will contact the healthcare provider.
- The pharmacist will discontinue the IV medication and reorder and verify the equivalent oral dosage form using ***"Cosign Med"*** order mode. The pharmacist will document the IV to PO conversion by noting the therapeutic interchange in the administration instructions of the electronic MAR.
- The pharmacist will document the conversion using the ***"IV to PO" i-Vent***. In the "response" field, the pharmacist should document ***"accepted"*** once the intervention is completed. The i-Vent can be "closed" as long as there is no need for further follow up regarding the conversion.
- Dosage form changes (e.g., capsule to tablet, tablet to liquid) are not considered therapeutic interchanges. It is within the pharmacist's scope of practice to substitute dosage forms containing the same chemical entities in the same quantities at the same frequency and which will provide the similar pharmacokinetic and bioavailability profiles.

Table 1. Approved Medications for Pharmacist IV to PO Conversion

Medication	IV	PO/NG
H2-Receptor Antagonists		
Famotidine[1]	20mg q6h	*Ranitidine* 300mg q12h
	20mg q8h	*Ranitidine* 150mg q12h
	20mg q12h	*Ranitidine* 150mg q12h
	20mg q24h	*Ranitidine* 150mg q24h
Ranitidine	50mg q6h	150mg q12h
	50mg q8h	150mg q12h
	50mg q12h	150mg q12h
	50mg q24h	150mg q24h
Proton-Pump Inhibitors		
Pantoprazole	1 :1	1 :1
Miscellaneous		
Folic acid	1 :1	1 :1
Thiamine	1 :1	1 :1
Metoclopramide	1 :1	1 :1
Anti-Infectives[2]		
Azithromycin	1 :1	1 :1
Ciprofloxacin	200mg q12h	250mg q12h
	400mg q12h	500mg q12h
	400mg q8h	750mg q12h
Clindamycin	300mg q8h	150mg q8h
	600mg q8h	300mg q8h
	900mg q8h	450mg q8h
Doxycycline	1 :1	1 :1
Fluconazole[3]	1 :1	1 :1
Levofloxacin	1 :1	1 :1
Linezolid	1 :1	1 :1
Metronidazole[4]	1 :1	1 :1
Moxifloxacin	1 :1	1 :1
Rifampin	1 :1	1 :1

[1]Ranitidine is the hospital's preferred oral H2-Receptor Antagonist. Famotidine is on formulary for IV administration, and IV ranitidine may be used due to IV famotidine shortages.

[2]First assess to determine whether or not continued use of the agent is indicated or a narrower spectrum agent can be utilized. If a change in therapy is warranted, a query and recommendation to the patient's provider is to be offered by the pharmacist.

[3]Doses > 400 mg IV daily may be split to orally twice daily – call MD for approval.

[4]Doses > 500mg q6-8h – call MD regarding GI tolerance.

Antimicrobial UCH Cost Information

Antimicrobial	Typical Adult Dose	UCH Daily Cost/ $
Aminoglycosides[1,2]		
Amikacin (IV)	See dosing guidelines; 15mg/kg/d x 70kg	9.1[a]
Gentamicin (IV)	See dosing guidelines; 7mg/kg/d x 70kg	10.41[a]
Tobramycin (IV/INH)	See dosing guidelines; 7mg/kg/d x 70kg	5.67[a]
	300mg q12h via *nebulizer* (TOBI)	64.41
Plazomicin	15mg/kg q24h x 70kg (Non formulary, ID only)	
Cephalosporins[2]		
First Generation		
Cefazolin (IV)	2g q8h	27.60
Cephalexin (PO)	250 – 500mg q6h	1.20 – 2.40
Second Generation		
Cefoxitin[3] (IV)	1-2g q6h	10.68 – 21.28
Cefuroxime (PO)	250-500mg BID	24.24 – 48.48
Third Generation		
Ceftriaxone[4] (IV)	1-2g q24h	1.80 – 2.25
Cefpodoxime (PO)	200-400mg q12h	10 – 20
Ceftazidime (IV)[9]	2g q8hrs	16.50
Ceftazidime-avibactam (IV)[9]	2.5g q8hrs	909.63
Ceftolozane-tazobactam (IV)[9]	1.5-3g q8h	316.32 – 632.64
Fourth Generation		
Cefepime[5,7] (IV)	1g q8h 2g q8h	6.84 12.84
Fifth Generation		
Ceftaroline (IV)	600mg q12h /q8h	313.5 / 470.25
Carbapenems[2,6,7]		
Ertapenem (IV)	1g q24h	82.86
Meropenem (IV)	1g q8h 2g q8h (meningitis dose)	18 36
Meropenem/Vaborbactam (IV)	2/2g q8h (non-formulary, ID approval only)	870.71
Monobactams[8,9]		
Aztreonam (IV)	1-2g q8h	75 – 150
Penicillins[2]		
General		
Penicillin G – K (IV)[10]	18-24 MU/day	29.25[a] / 39[a]
Penicillin VK (PO)[10]	250 – 500mg po q6h	0.28 / 0.40
Ampicillin (IV)	1-2g q 4h	8.46 – 14.34
Amoxicillin (PO)	500mg po q8h	0.18
Penicillinase-resistant		
Nafcillin (IV)	2g q4h	44.70
Dicloxacillin (PO)	500mg po q6h	3.44
Enhanced-spectrum		
Ampicillin-sulbactam (IV)	3g q6h	8.96
Amoxicillin/clavulanate (PO)	875mg q12h	0.98
Piperacillin/tazobactam (IV)[11]	3.375g q8h / 4.5g q8h EI	9.48 / 12.69
Quinolones[2,7,12]		
Ciprofloxacin (IV)	400mg q12h	4.30
Ciprofloxacin (PO)	250 / 500 / 750mg q12h	0.38 / 0.76 / 1.14
Levofloxacin (IV)[13,]	250 / 500 / 750mg qday	2.31 / 3.24 / 3.7
Levofloxacin (PO)[13]	250 / 500 / 750mg qday	0.17 / 0.34 / 0.31
Moxifloxacin (IV)[13, 14]	400mg daily	40.79
Moxifloxacin (PO)[13, 14]	400mg daily	2.12
Macrolides[12]		
Azithromycin IV / PO [12,15]	500mg daily	2.47 / 1.20
Clarithromycin[2] (PO)	500mg BID	1.20
Anti-anaerobe		
Clindamycin (IV)[12]	900 q8h	18.45
Clindamycin (PO)	300mg q6h	2.24
Metronidazole IV[12] / PO	500mg q8h	3.00 / 1.35
Vancomycin (PO-caps)[16]	125mg q6h	12.80
Vancomycin (PO-oral soln)[16]	125mg q6h	2.25[a]

Resistant Gram-positives		
Vancomycin (IV)[2,17]	20mg/kg - 40mg/kg/daily (70kg patient)	4.90 – 9.80[a]
Daptomycin (IV)[2,18]	500mg daily	143.50[a]
Linezolid (IV)[12, 19]	600mg q12h	43.76
Linezolid (PO)	600mg q12h	3.12
Tigecycline (IV)	50mg q12h	156.50
Others		
Bactrim/Septra (IV)[2,12]	10-20mg/kg/daily (TMP) ÷ q6-8h	31.68 – 63.35
Bactrim/Septra DS (PO)[2]	800mg SMX/160mg TMP q12h	0.12
Doxycycline IV / PO[12]	100mg q12h	34.34 / 3.58
Fosfomycin (PO)	3g sachet x1	73.50
Nitrofurantoin (PO)[20]	100mg BID (Macrobid)	3.82
Rifampin IV[12] / PO	600mg/day	68[b] / 2.72
Eravacycline IV	1mg/kg q12h (Non-formulary, ID only)	131.00
Antifungals		
Ambisome (IV)	3mg/kg/daily (200mg daily)	306.00[b]
Fluconazole IV[2,12] / PO	400mg daily	6.00 / 3.16
Isavuconazonium (IV)[12]	372mg q8h x 6 doses, then 372mg daily	661.11 / 220.37
Isavuconazonium (PO)	372mg q8h x 6 doses, then 372mg daily	388.02 / 129.34
Voriconazole (IV)[12,22]	6mg/kg q12h X 2 doses; then 4mg/kg q12h	133.20 – 66.60[b]
Voriconazole (PO-tab / susp)	200mg q12h	25.38 / 125.60
Posaconazole (IV)[12]	300mg q12h on day 1, then 300mg daily	638 / 319[a]
Posaconazole DR Tab (PO)	300mg BID on day 1, then 300mg daily	308 / 154
Posaconazole Suspension (PO)	200mg q6h	205.55
Anidulafungin (IV)[24]	200mg once, then 100mg daily	83 / 41.66
Antivirals[2]		
Acyclovir (IV)	5-10mg/kg q8h	6.30 – 12.60[a]
Acyclovir (PO)	400mg TID – 800mg 5x/day	1.44 – 2.4
Valacyclovir (PO)	1-2 grams BID	5.50 – 11.00
Ganciclovir (IV)	5mg/kg q12-24h	34.37 – 68.75[b]
Valganciclovir (PO)	900mg daily – BID	78.68 – 157.36
Foscarnet (IV)	60mg/kg q8h	822.00
Cidofovir (IV)	5mg/kg qweekly	915.36 /dose
Oseltamivir (PO)	75mg daily – BID	5.22 – 10.44
Peramivir (IV)	600mg once (Non-Formulary, ID only)	879.51
Baloxavir (PO)	20 or 40mg once (Non-Formulary, ID only)	138.87
Ribavirin (INH)	6 grams daily	7,904
Ribavirin (PO)	1,000 – 1,200mg/day (divided doses BID)	2.67 – 3.22
a. MDV (cost calculated per mg); b. SDV (cost calculated up to nearest whole vial size)		

Clinical Pearls

1. All AGs (except inhaled) require monitoring of serum levels & renal fxn with multiple doses. Dept. of Pharmacy will dose and monitor with pharmacy consult. Please state indication/diagnosis when writing order.

2. Represent typical doses. Dose adjustments may be needed for patients with renal dysfunction.

3. Broader gram (-) activity + modest anaerobic activity compared with 1st generation. General use for prophylaxis & therapy of surgical site infections and other infections below diaphragm.

4. Broader than 1st & 2nd generation agents with more gram negative coverage. Part preferred regimen for Community-Acquired Pneumonia (CAP), see footnote 15. Meningitis and enterococcal endocarditis synergy with ampicillin dosing for adults = 2g q12h.

5. Broadest activity of all cephalosporins including anti-pseudomonal activity. Reserve for suspected/documented resistant organisms including *P. aeruginosa*. Change to narrower agent as demonstrated by microbiologic sensitivities.

6. Broadest antibacterial available including anaerobic and anti-pseudomonal activity. Presently, best used for directed therapy toward known ESBL-producing gram-negative pathogens, rather than empiric therapy. Change to narrower agent as demonstrated by microbiologic sensitivities. Ertapenem (Invanz) **does not** cover enterococci, *P. aeruginosa*, *Acinetobacter spp.*, but has activity against other gram-negatives, gram-positives & anaerobes.

7. Use with caution in patients w/ seizures or on concomitant medications that lower seizure threshold. Note severe interaction between all carbapenems and valproic acid (lowers valproate level); recommend pre-emptively increasing valproic acid level and monitoring levels while on carbapenem, or use alternative agent for antibiotic or seizure disorder if possible.

8. May be an acceptable alternative for PCN-allergic patients in whom cephalosporins are contraindicated (Type I/immediate reactions).

9. Possesses only gram(-) activity including anti-pseudomonal activity, Ceftazidime contains marginal gram-positive activity (mostly beta-hemolytic streptococci, not for MSSA or *S. pneumoniae*)

10. Remains drug-of-choice for PCN-susceptible streptococcal infections.

11. Broadest activity of all penicillins including anaerobe activity & anti-pseudomonal activity. Reserve for suspected/documented resistant organisms including *P. aeruginosa*. Change to narrower agent as demonstrated by microbiologic sensitivities.

12. Possess *excellent* bioavailability. Switch from IV to PO dosage form as soon as feasible. For posaconazole IV, suspension is **not** bioequivalent and has erratic absorption – utilize DR tabs whenever possible due to superior bioavailability.

13. Possess activity against *S. pneumoniae* & atypical respiratory organisms, change to narrower agent as demonstrated by microbiologic sensitivities.

14. An alternative to UCH-preferred CAP regimen for penicillin allergic patients used as monotherapy

15. Part of UCH-preferred regimen for Community-Acquired Pneumonia (CAP): Ceftriaxone 1-2g q daily + azithromycin 500mg po q24h if taking any po meds. If NPO, use Azithromycin 500mg IV q daily.

16. Preferred for most cases of C. difficile infection (see C difficile management pathway). Not for systemic infection of any gram(+) organism.

17. Dept. of Pharmacy will dose and monitor with pharmacy consult. Please state indication/diagnosis when writing order.

18. ID approval by phone or formal consult required. For cSSTI & resistant gram-positive bacteremias. Never for pneumonia. Baseline & weekly CPK required monitoring. Higher doses of 8-12mg/kg/dose may be necessary for non-urinary VRE infections and severe, refractory *S. aureus* bacteremia/endocarditis. In certain situations combination therapy may be required.

19. Restricted agent. Should be accompanied by weekly CBC. Observe platelet count closely. Not ideal agent for concurrent bacteremia with VRE or *S. aureus*. Has great activity for MRSA pneumonia compared to vancomycin.

20. Not for systemic infection, relegated only to infections of the bladder (*not* for pyelonephritis or perinephric abscess). Note: To be prescribed to patients with a CrCl $\geq$ 40mL/min; effectiveness is diminished in patients with CrCl < 40mL/min and in those with CrCl < 30mL/min all efficacy is lost and the frequency of ADRs increased.

21. In patients with good-to-modest renal function & cardiac status that can tolerate NaCl, amphotericin B can be successfully dosed without interruption using sodium loading. Patients should receive adequate hydration prior to each amphotericin dose with aggressive monitoring/replacement of electrolytes (especially potassium and magnesium)

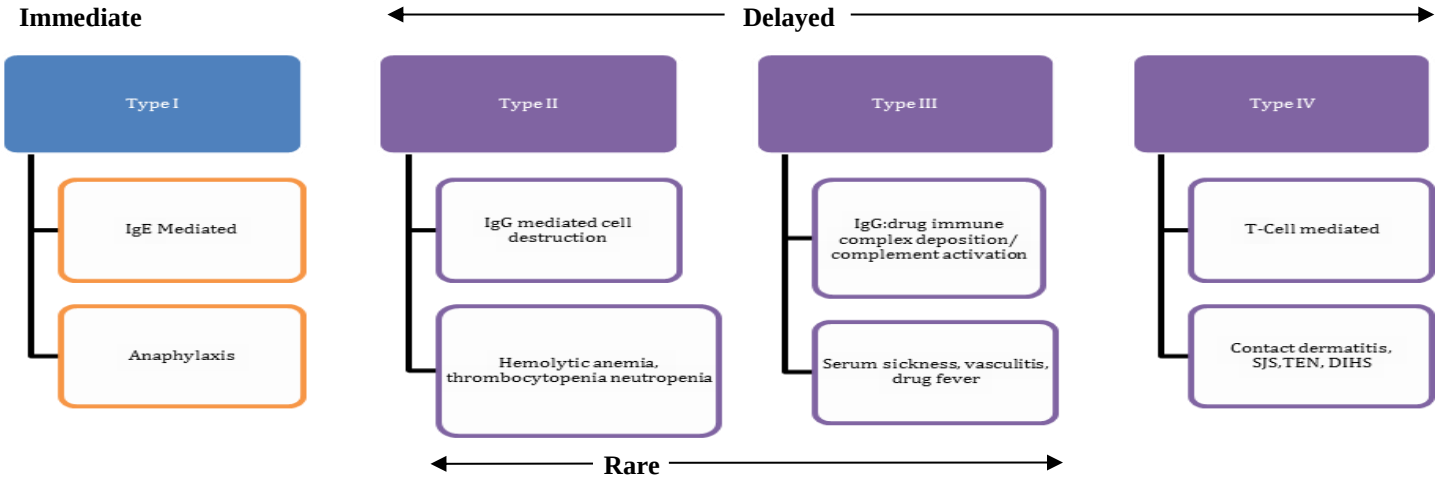
22. Loading dose very important – with loading dose steady state achieved w/in 24 hours. Without loading dose it takes 5 days to achieve serum steady-state concentrations. Pharmacy will dose if requested. For *Aspergillus* species or oral step down for suspected/documented *Candida krusei*

23. Restricted to BMT, lung transplant, CF, and ICUs. For *Aspergillus* species or suspected/documented non-*albicans Candida* species showing resistance to either amphotericin B or azole antifungals. Should be immediately switched to azoles as identification and/or sensitivities dictate. Does not undergo hepatic metabolism and no significant drug interactions.

** Help prevent bacterial resistance and superinfection - change to narrower-spectrum antimicrobial agents as demonstrated by microbiologic sensitivities.

*** Help prevent bacteremias & contamination due to coag neg staph – switch IV therapy as soon as possible to acceptable oral agents with high bioavailability: azithromycin; fluconazole; levofloxacin; linezolid; metronidazole; rifampin; sulfamethoxazole/trimethoprim.

Beta-Lactam Allergies Tip Sheet



- Penicillin anaphylaxis (Type-1 Hypersensitivity) incidence is very low, 0.01-0.04%
- Penicillin allergies frequently reported, up to 5-10% of general population
  - Up to 80-90% of patients who report a penicillin allergy are not truly allergic
- Accurate allergy history is important, patients reporting unknown, mild, and/or delayed reactions likely do not have true allergy and will tolerate a beta-lactam antibiotic

Correlation between reported allergy history and actual reaction

	Immediate reaction (<2 hours)	Delayed reaction (>24 hours)	Any reaction (ST and PO)
History of immediate reaction, n=36	**8 (22%)**	**1 (3%)**	**9/36 (25%)**
History of delayed reaction, n=235	**7 (3%)**	**9 (4%)**	**16/235 (7%)**
Unknown history, n=71	**0**	**1 (1%)**	**1/71 (1%)**

Cross-reactive beta-lactams	Penicillin	Amoxicillin	Ampicillin	Cephalexin	Cefazolin	Cefuroxime	Cefoxitin	Ceftriaxone	Cefotaxime	Cefepime	Ceftazidime
Penicillin		X	X	X			X				
Amoxicillin	X		X	X							
Ampicillin	X	X		X							
Cephalexin	X	X	X								
Cefazolin											
Cefuroxime							X	X	X		
Cefoxitin	X					X					
Ceftriaxone						X			X	X	X
Cefotaxime						X		X			X
Cefepime								X			
Ceftazidime								X	X		

Cross-reactivity between penicillins and cephalosporins or carbapenems is not a class effect but an allergic reaction to antibiotics with similar side chains. (see following page for detailed explanation)

Cross-reactivity with similar side chains:
* PCN-CEPH ≈ 20%
* CEPH-CEPH ≈ 40%

Do's and Don'ts

- **DON'T** accept "penicillin" as an allergy; get specific medication names
- **DO** update allergy label with specific medications, reactions, and tolerances (i.e. "tolerates ceftriaxone")
- **DO** use cephalosporins (excluding cephalexin) in setting of penicillin, amoxicillin, or ampicillin allergy

Cross-reactivity amongst beta-lactams

The over-generalization of cross-reactivity has resulted in the avoidance of beta-lactams in patients labeled as penicillin allergic. Beta-lactam avoidance has resulted in an increase in the use of secondary antibiotics, namely vancomycin and fluoroquinolones, thus an increase in resistant infections, treatment failures, and cost.[1-3]

Penicillins and Cephalosporins

More recent studies challenge the idea of broad cross-reactivity between penicillin and cephalosporins. Side chains, rather than the beta-lactam ring, may better account for cross-reactivity.

- 128 patients with history of immediate hypersensitivity to a penicillin derivative underwent cephalosporin skin testing with cephalothin, cefamandole, cefuroxime, ceftriaxone, cefotaxime, and ceftazidime. Of these, cephalothin is the only cephalosporin with a similar side chain to penicillin, and was the most common cephalosporin to cause a reaction (9/128, 7%). 5 other patients reacted to a different cephalosporin; however, the authors did not include details of which cephalosporin caused the reaction as well as what penicillin derivative was the parent reaction. [4]
- 214 patients with history of delayed hypersensitivity to penicillin underwent skin testing with six beta-lactams, three with similar side chains to penicillins, and three with dissimilar side chains. Cross-reactivity was found in 40 (19%) of patients; all reactions were from the three cephalosporins with side chains similar to penicillin derivatives. Cefaclor and cephalexin have similar side chains to ampicillin and resulted in positive skin tests in 39 and 31 patients respectively. Cefadroxil has a similar side chain to amoxicillin and resulted in positive skin tests in 17 patients.[5]
- See table on the previous page for penicillins and cephalosporins with similar side chains. An X in a square indicates the two beta-lactams share a similar side chain structure. The exact risk of cross-reactivity between each pair is largely unknown and likely varies amongst pairs. Until more data is available avoiding beta-lactams with similar side chains is an appropriately cautious approach (e.g, for a patient with amoxicillin allergy, avoid cephalexin, but ok to use cefazolin).
- Note that a patient could have an allergic reaction to a dissimilar beta-lactam, however this likely represents a second allergic reaction, not cross-reactivity of the parent allergen.

Penicillins and Carbapenems

- Two well-done studies have evaluated the risk of cross-reactivity for penicillin allergic patients with a history of immediate reactions [6] and delayed reactions [7]. Over 400 patients were skin tested and received IV challenges against imipenem, meropenem, and ertapenem. No patients reacted to either the skin test or IV challenge. These data support the safe use of carbapenems in patients with a known penicillin allergy.

Medical Liability Concerns

There is legal precedence regarding the use of cephalosporins and carbapenems in patients with a known penicillin allergy. In 2005 both the hospital and physicians were found not liable for the death of a child with a known penicillin allergy who died of an allergic reaction to ceftriaxone (Boone v. William Backus Hospital, 272 Conn. 551, 864. A.2d. 1). The same outcomes was found when ertapenem was the beta-lactam in question (Soares v. Greenblatt, No. 06-15565, 2013 N.Y. Misc. LEXIS 5841, 2013 NY Slip Op 33130(U)).

References:
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3. Li M, Krishna MT, Razaq S, Pillay D. A real-time prospective evaluation of clinical pharmaco-economic impact of diagnostic label of 'penicillin allergy' in a UK teaching hospital. J Clin Pathol **2014**; 67(12): 1088-92.
4. Romano A, Gueant-Rodriguez RM, Viola M, Pettinato R, Gueant JL. Cross-reactivity and tolerability of cephalosporins in patients with immediate hypersensitivity to penicillins. Ann Intern Med 2004; 141(1): 16-22.
5. Romano A, Gaeta F, Valluzzi RL, Maggioletti M, Caruso C, Quaratino D. Cross-reactivity and tolerability of aztreonam and cephalosporins in subjects with a T cell-mediated hypersensitivity to penicillins. J Allergy Clin Immunol 2016; 138(1): 179-86.
6. Gaeta F, Valluzzi RL, Alonzi C, et al. Tolerability of aztreonam and carbapenems in patients with IgE-mediated hypersensitivity to penicillins. J Allergy Clin Immunol. 2015;135(4):972-6.
7. Romano A, Gaeta F, Valluzzi RL, et al. Absence of cross-reactivity to carbapenems in patients with delayed hypersensitivity to penicillins. Allergy. 2013;68(12):1618-21.

Penicillin Skin Testing at UCH

- **Outpatients with mild/moderate/unknown PCN allergies can be referred to Allergy Clinic for skin testing.**
- **Inpatients with mild/moderate/unknown PCN allergies and who need PCN/beta-lactam therapy can be evaluated for inpatient skin testing. Call the Antibiotic Approval Pager to request evaluation for a penicillin skin test.**

Antimicrobials in Pregnancy

Antimicrobial	Category	Lactation
Amoxicillin	B	Enters milk-caution
Liposomal Amphotericin B	B	Unknown
Ampicillin/sulbactam	B	Enters milk-caution
Anidulafungin	B	Enters milk-caution
Azithromycin	B	Enters milk-caution
Aztreonam	B	Not recommended
Cefditoren	B	Unknown
Cefazolin	B	Enters milk-caution
Cefoxitin	B	Enters milk-caution
Ceftazidime +/- avibactam	B	Enters milk-caution
Ceftriaxone	B	Enters milk-caution
Cefepime	B	Enters milk-caution
Ceftaroline/ceftolozane-taz	B	Enters milk-caution
Ciprofloxacin	C	Not recommended
Clindamycin	B	Not recommended
Daptomycin	B	Enters milk-caution
Doxycycline/Minocycline	D	Not recommended
Ertapenem	B	Enters milk-caution
Fluconazole	C/D^	Enters milk-caution
Fosfomycin	B	Enters milk-caution
Gentamicin	C	Enters milk-caution
Isavuconazole	C	Not recommended
Ketoconazole/posaconazole	C	Not recommended
Levofloxacin	C	Not recommended
Linezolid	C	Enters milk-caution
Meropenem	B	Enters milk-caution
Metronidazole	B*	Not recommended
Moxifloxacin	C	Not recommended
Nafcillin	B	Enters milk-caution
Nitrofurantoin	B	Not recommended
Penicillin	B	Enters milk-caution
TMP/sulfa	C	Enters milk-caution
Vancomycin IV	C	Not recommended
Vancomycin Oral	B	Preferred CDI treat
Voriconazole	D	Not recommended

^Category C for vulvovaginal candidiasis 150mg x1; Category D for all other indications/doses

Pregnancy Category
A – Controlled studies show no risk
B – No evidence of risk in humans
C – Risk cannot be ruled out
D – Positive evidence of risk
X – Contraindicated in pregnancy

Sodium Content for Select Intravenous Antimicrobials

Drug	Sodium / 1g of Drug	Sodium / Typical Daily Dose
Penicillin (~40mEq K^+/24Mu)	6.8mg/Million units	163mg/24Munits
Nafcillin	66.2mg	794mg/12g
Ampicillin/sulbactam	115mg	920mg/12g
Ampicillin	66mg	528mg/8g
Piperacillin / tazobactam	64mg	1024mg/18g
Aztreonam	None	N/A
Cefazolin	48mg	288mg/6g
Cefotaxime	50.5mg	404mg/8g
Cefoxitin	53.8mg	430mg/8g
Ceftriaxone	83mg	83-332mg/1-4g
Ceftazidime	54mg	324mg/6g
Ceftazidime-Avibactam	58.4 mg	438mg/7.5g
Cefepime	None	N/A
Ceftaroline	None	N/A
Ceftolozane-Tazobactam	325mg	1461mg/4.5g
Ertapenem	137mg	137mg/1g
Meropenem	90.2mg[a]	271mg/3g
Imipenem/Cilastatin	75mg	300mg/4g
Colistimethate Sodium	99mg	30mg/300mg
Azithromycin	None	N/A
Ciprofloxacin	None	N/A
Moxifloxacin	None	N/A
Levofloxacin	None	N/A
Vancomycin	None	N/A
Tigecycline	None	N/A
TMP/Sulfa	None	N/A
Linezolid	190mg	228mg/1200mg
Daptomycin	None	N/A
Clindamycin	None	N/A
Metronidazole	1580mg	2370mg/1500mg
Gentamicin	None	N/A
Tobramycin	None	N/A
Amikacin	None	N/A
Ambisome	None	N/A
Fluconazole-NaCl diluents	4500mg	1800mg/400mg
Isavuconazonium sulfate	None	N/A
Posaconazole	None	N/A
Voriconazole	None	N/A
Anidulafungin	None	N/A
Acyclovir	98mg	Varies
Ganciclovir	92mg	Varies
Cidofovir	None	N/A
Foscarnet	Not Listed	N/A

References

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CNS, Bone, and Urinary Penetration for Select Antimicrobial Agents

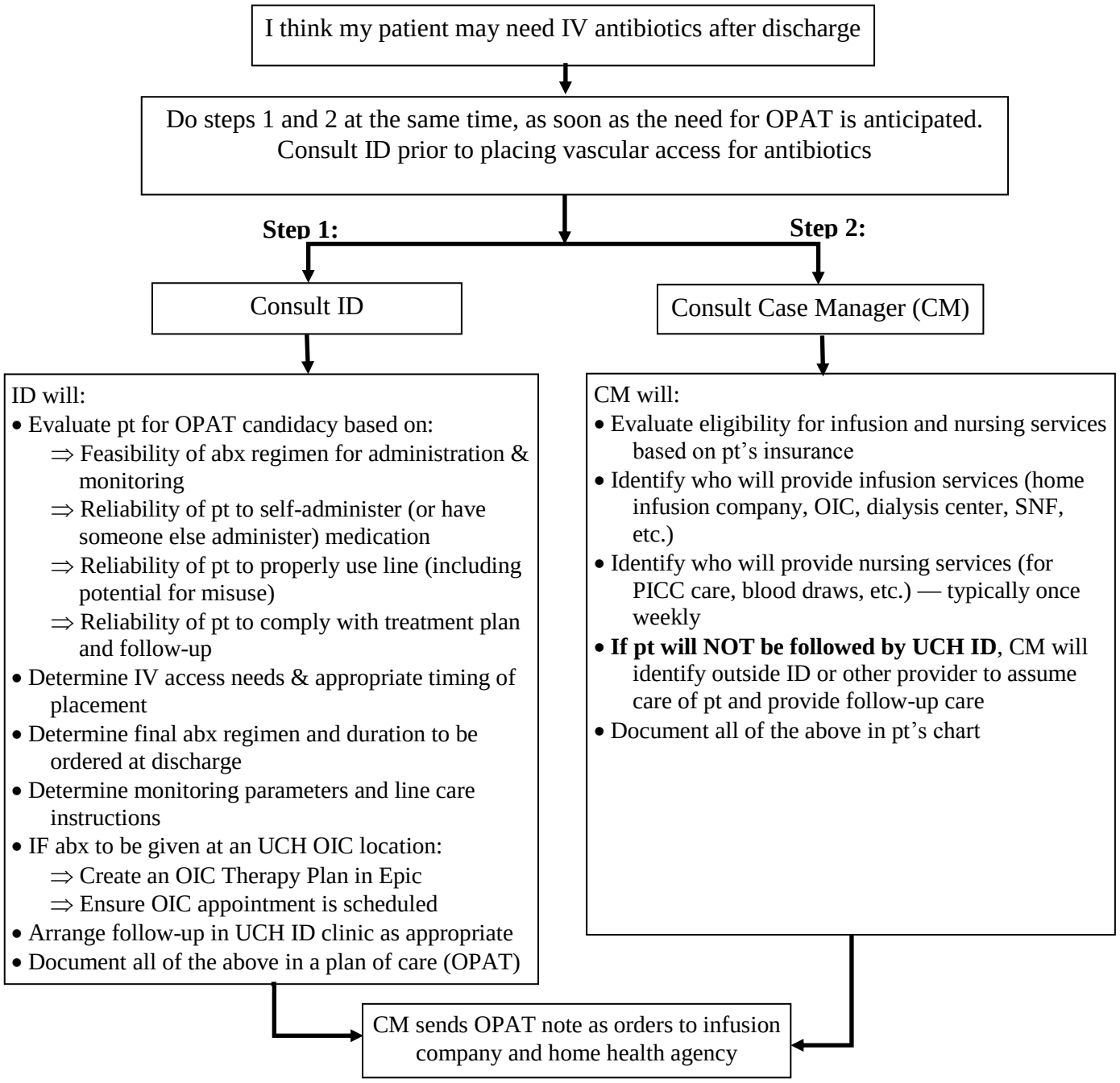
Drug	CNS Uninflamed (%)	CNS Inflamed (%)	Bone	Urine
Beta-Lactams - Penicillins				
Penicillin G/V	Low	Moderate (30)	N/A	Excellent
Nafcillin	Low (1-2)	Moderate (20-30)	Moderate	Good
Ampicillin	Low (1.6)	Moderate (39)	Mod-Good	Good
Sulbactam	Low (7)	Low (10)	Mod-Good	Good
Amoxicillin	Low	Low (5.8)	Moderate	Excellent
Clavulanic Acid	Low (3.7)	Low (8.4)	Moderate	Excellent
Piperacillin / tazobactam[2]	Low (3.7/10.6)	Moderate (32)	Moderate	Good
β-Lactams- Monobactam				
Aztreonam	Moderate	Moderate (13-18)	Moderate	Good
β-Lactams – Cephalosporins				
Cefazolin[2]	Low	Low (9-10)	Moderate	Excellent
Cefotaxime	Low (9)	Moderate (17)	Moderate	Good
Cefoxitin[2]	Low (0-9)	Good (41-50)	Moderate	Good
Ceftriaxone	Low (0.7-2)	Moderate (20-35)	Moderate	Good
Ceftazidime	Low (2-8)	Moderate (36-40)	Mod-Good	Excellent
Ceftazidime-Avibactam[2]	N/A	N/A	N/A	Excellent
Cefepime	Low (8-10)	Moderate (20-34)	Good	Good
Ceftolozane-Tazobactam[2]	N/A	N/A	N/A	Excellent
Ceftaroline[2]	Low (3)	Moderate (15)	N/A	Good
β-Lactams – Carbapenems				
Ertapenem[2]	?	Low-Moderate	Moderate	Good
Meropenem	Moderate (5-25)	Good (39-75)	Moderate	Good
Imipenem/Cilastatin	Low	Moderate (14)	Low	Good
Fluoroquinolones				
Ciprofloxacin[2]	Good (24-43)	Excellent (92)	Excellent	Excellent
Moxifloxacin[2,3]	Good (46)	Excellent (71-94)	Excellent	Low
Levofloxacin[2]	Good (71)	Excellent (>90)	Excellent	Excellent
Aminoglycosides				
Gentamicin[2]	Low	Low	Moderate	Excellent
Tobramycin[2]	Low	Low	Moderate	Excellent
Amikacin[2]	Low	Low	Moderate	Excellent
Macrolides				
Clarithromycin[1,3]	Low	Moderate (18)	Low	Moderate
Azithromycin[1,3]	Low	Low	Low	Low
Tetracyclines/Glycylcyline				
Doxycycline[2]	Moderate (20)	Moderate (26)	Excellent	Good
Tigecycline[2,3]	Low (5-10)	Good (52-86)	Excellent	Good
Miscellaneous Antibiotics				
Vancomycin	Moderate (14-18)	Moderate (30-48)	Moderate	Excellent
Linezolid	Excellent (80-100)	Excellent	Good	Good
Daptomycin (10mg/kg)[2]	Low	Low (0.1-1.7)	Moderate	Excellent
Colistin[2,3]	Low	Low (5)	N/A	Low
TMP/Sulfa	Moderate (12-18)	Good (24-51)	Good	Good
Metronidazole	N/A	Good (87)	Good	Moderate
Clindamycin[1,3]	Low (2)	N/A	Good	Low
Antifungals				
Ambisome[3]	Low (< 5)	N/A	Low	
Fluconazole	Good (80)	Moderate	Excellent	
Isavuconazonium[2,3]	N/A	N/A	Low	
Posaconazole[2,3]	Moderate (30)	N/A	Low	
Voriconazole[3]	Good (60)	N/A	Low	
Anidulafungin[2,3]	Low (< 5)	N/A	Low	
Flucytosine	Excellent (60-100)	N/A	Excellent	
Antivirals				
Acyclovir/valacyclovir	Good (30-50)	N/A	Excellent	
Ganciclovir/valganciclovir	Good (24-70)	N/A	Excellent	
Cidofovir[2]	Low	N/A	Excellent	
Foscarnet	Good (23-69)	N/A	Excellent	

****CNS Penetration does not always correlate to clinical efficacy or place in therapy****

Low, ≤ 10%; Moderate, 11-40%; Good, 41-89%; Excellent, ≥ 90%; N/A, Not Available

1. Low CSF concentrations, but high concentrations in brain tissues (a. Azithromycin and Clindamycin used to treat brain infections,)
2. Agents not generally recommended to treat meningitis or other CNS infections, especially without ID consultation
3. Agents not generally recommended to treat urinary tract infections

How to Set Up OPAT (Outpatient Parenteral Antibiotic Therapy)



Primary team to-dos:
- Add antibiotics (both IV and PO) to discharge med rec
- **IF** abx to be given in a UCH OIC,
  - ⇒ Create an OIC Therapy Plan in Epic
  - ⇒ Ensure OIC appointment is scheduled
- Ensure appropriate follow-up is arranged. **If pt will NOT be followed by UCH ID**,
  - ⇒ Doc-doc communication should be performed with the accepting provider for verbal transfer of care
  - ⇒ Fax OPAT note, discharge summary if available, and other pertinent records needed for follow-up care

Patient may be eligible for discharge after all of the above completed.
Communicate with ID and/or CM about any questions regarding dispo plan.

Prepared July 2018 by the UCH Antimicrobial Stewardship Team

Outpatient Parenteral Antimicrobial Therapy (OPAT) Dosing and Monitoring

Class	Antibiotic	Room Temp	Standard Dose	Dose Adjustments	Adverse Reactions	Monitoring-ADR
β-Lactam -Penicillins	Penicillin G-IV	24 hours	18-24 million units/day CI	Renal, CrCl 10-50ml/min: 13.5-18 MU/day	Rash, diarrhea, **↑LFTs, ↑SCr ↓platelets, ↓WBC**	CBC, BMP, LFTs
	Ampicillin-IV	8-12 hours	8-12 g/day CI	Renal, CrCl 10-50ml/min: 4-8g/day CI (2g q6-12h)	Rash, diarrhea, ↑LFTs, ↑SCr **↓platelets**, ↓WBC	CBC, BMP, LFTs
	Ampicillin/sulbactam-IV	8-12 hours	6-12 g/day CI	Renal, CrCl 15-30ml/min: 3-6g/day CI	Rash, diarrhea, ↑LFTs, ↑SCr **↓platelets**, ↓WBC	CBC, BMP, LFTs
	Piperacillin/tazo-IV	24 hours	13.5g CI–mild/mod infx; 18g CI-severe/pseudo	Renal, CrCl 20-40ml/min: 9-13.5g/day CI, CrCl < 20ml/min: 6.75-9g/day CI	Rash, diarrhea, ↑LFTs, **↑SCr ↓platelets**, ↓WBC	CBC, BMP, LFTs
	Nafcillin/Oxacillin-IV	24 hours	12g/day CI	None	Rash, diarrhea, **↑LFTs, ↑SCr ↓platelets**, ↓WBC	CBC, BMP, LFTs
β-Lactam -Monobactam	Aztreonam-IV	24 hours	2 g q6-8 hours OR 6-8 g/day CI	Renal, CrCl 10-30ml/min: 1g q6-8h OR 3-4g/day CI	Rash, diarrhea, nausea, ↑LFTs	CBC, BMP, LFTs
β-Lactam -Cephalosporins	Cefazolin-IV	24 hours	2g q6-8 hours or 6-8g/day CI	Renal, CrCl 10-50ml/min: 2g q12h or 4g CI CrCl < 10ml/min: 2g qday	Rash, diarrhea, ↑LFTs, ↑SCr, ↓platelets, ↓WBC	CBC, BMP, LFTs
	Ceftriaxone-IV	24 hours	1-2g once daily	None	Rash, diarrhea, **↑LFTs-bili**, ↑SCr, ↓platelets, ↓WBC	CBC, BMP, LFTs
	Ceftazidime-IV	24 hours	2g q8 hours or 6g/day CI	Renal, CrCl 30-50ml/min:2g q12h (4g/day CI); CrCl 10-30ml/min: 2g qday	Rash, diarrhea, **↑LFTs,** ↑SCr **↓platelets,** ↓WBC	CBC, BMP, LFTs
	Cefepime-IV	24 hours	2g q8 hours or 6g/day CI	Renal, CrCl 30-60ml/min: 2g q12h (4g/day CI); CrCl 10-30mL/min: 2g qday	Rash, diarrhea, **↑LFTs,** ↑SCr ↓platelets, ↓WBC, Anemia, **seizures-possible**	CBC, BMP, LFTs
β-Lactam -Carbapenems	Ertapenem-IV	4 hours	1g daily	Renal, CrCl < 30ml/min: 500mg qday	Rash, **nausea/diarrhea, ↑LFTs,** ↑SCr ↓platelets, ↓WBC, seizures-0.5%	CBC, BMP, LFTs
	Meropenem-IV	4 hours	1g q8 hours	Renal, CrCl 26-50ml/min: 1g q12 hours, CrCl 10-25ml/min: 500mg q12 hours	Rash, **diarrhea**, **↑LFTs**, ↑SCr ↓platelets**,** ↓WBC, **seizures-0.7%**	CBC, BMP, LFTs
	Imipenem/cilastatin-IV	4 hours	500mg q6-8 hours Up to 1g q6-8h (severe)	Renal, – look up dosing, too much to list and depends on severity of infection	Rash, diarrhea, **↑LFTs,** ↑SCr **↓platelets,** ↓WBC, **seizures-1.8%**	CBC, BMP, LFTs
Aminoglycosides	Tobramycin-IV	24 hours	*Adjust by levels*	Renal, follow levels	**↑SCr, ototoxicity (tinnitus, vertigo, hearing loss)**	BMP, drug levels
	Amikacin-IV	24 hours	*Adjust by levels*	Renal, follow levels	**↑SCr, ototoxicity (tinnitus, vertigo, hearing loss)**	BMP, drug levels
Glycopeptide	Vancomycin-IV *PO for C. diff only*	> 24 hours	*Adjust by levels*	Renal, follow levels	**↑SCr,** ototoxicity-rare, rash, ↓platelets, ↓WBC	CBC, BMP, drug levels
Lipopeptide	Daptomycin-IV	12 hours	4-12 mg/kg once daily	Renal, CrCl< 30ml/min: 4-10mg/kg q48 hours	**Muscle aches/pain-myopathy**, ↑LFTs, nausea/diarrhea	CPK, LFTs
Oxazolidinone	Linezolid-IV/PO	N/A	600 mg BID	None	**↓platelets, ↓WBC, ↑LFTs**, **anemia**, ↓ANC, SS	CBC, LFTs
Fluoroquinolones	Ciprofloxacin-PO Levofloxacin-PO Moxifloxacin-PO	N/A	500-750 mg BID 500-750 mg once daily 400 mg once daily	CrCl < 30ml/min: 250-500mg qd CrCl 20-50ml/min: 750mg q48h CrCl < 20ml/min: 500mg q48h None for moxifloxacin	**↑LFTs**, **↑QTc, nausea**, rash, **diarrhea**, tendon rupture, neuropathy, photosensitivity	CBC, BMP, LFTs, EKG
Antifungal -Azoles	Fluconazole-PO	N/A	400-800mg qday	Renal, CrCl < 50ml/min: 200-400mg/day	**↑LFTs, nausea/diarrhea, QTc**	LFTs, EKG
	Voriconazole-PO *Round dose*	N/A	Loading: 6mg/kg x 2 doses Maintenance: 4mg/kg BID,	No Renal, except with IV form Child Pugh A-B, decrease 50%; class C, avoid	**↑LFTs, nausea/diarrhea, hallucinations, visual disturbances,** ↑QTc	LFTs, EKG
	Posaconazole DR tabs	N/A	300mg BID x 2 doses, then 300mg once daily	No renal or hepatic adjustment	**↑LFTs, nausea/diarrhea,** ↑QTc	LFTs, EKG
-Polyene	Ambisome-LAmB-IV	Start infusion w/in 6h	3-5mg/kg once daily	None – may reduce interval frequency to q48h in patients that develop AKI 2/2 to Ambisome	**↑SCr, ↓electrolytes (K/Mg/Ca), infusion reactions**, ↑LFTs, metallic taste, nausea	BMP, Mg^{++}, Ca^{++}, LFTs
-Echinocandin	Anidulafungin-IV	24 hours	200mg x1, then 100mg qday	None	**Infusion reaction-rash**, ↑LFTs **diarrhea**	LFT

- Agents dosed once-twice daily are preferred for outpatient management. Some agents needing multiple doses administered daily may be given continuously, and thus changed out once daily.
- Abbreviations: IV, intravenous; PO, by mouth; CI, continuous infusion; RT, room temperature; g, grams; mg, milligrams; kg, kilograms; q, every; SCr, serum creatinine; LFT, liver function tests; WBC, white blood cell count; CPK, creatinine phosphokinase; ANC, absolute neutrophil count; QTc, corrected QT interval; EKG, electrocardiogram; BMP, basic metabolic panel; CBC, complete blood count; K, potassium; Mg, magnesium; Ca, calcium; SS, serotonin syndrome
- Serotonin Syndrome: palpitations, tremor, hyperthermia, anxiety, agitated delirium, myoclonus, rigidity, hyperreflexia, tachycardia, hypertension

Transplant Prophylaxis

Solid Organ Transplant Antimicrobial Prophylaxis Quick Reference Table

Organ	Risk Group	Medication	Timing/Duration	Comments
Liver	CMV D+/R- CMV D+/R+ or D-/R+ and received antibody-depleted induction or treatment for steroid-resistant rejection	Ganciclovir 5 mg/kg IV q24h *OR* Valganciclovir 900 mg PO q24h	Day 0 to +1 → Day +90	-Renally adjusted
	HSV1 or HSV2 negative AND CMV prophylaxis not indicated (i.e. not on valganciclovir or ganciclovir)	Acyclovir 800 mg PO BID *OR* Acyclovir 5 mg/kg IV q12h	Day 0 to +1 → Day +30	-Renally adjusted
	Everyone	TMP/SMX 400/80 mg (SS) PO daily	Day +7 → D +90	-Consider pentamidine 300 mg Inh qMonth if TMP/SMX contraindicated
Heart	CMV R-	Ganciclovir 2.5 mg/kg IV q12h	Day 0 → Day +365	-Renally adjusted -Can switch to valganciclovir 900 mg PO q24h when taking PO
		CMVIg 150 mg/kg IV @ +72 hours 100 mg/kg IV @ weeks +2, 4, 6, & 8 50 mg/kg IV @ weeks +12, 16	Only if stable renal fxn	
	CMV R+	Ganciclovir 2.5 mg/kg IV q12h	Day 0 → prednisone ≤ 10 mg daily (or ≤ 5 mg daily if diabetic)	-Renally adjusted -Switch to Valcyte when taking PO
	Everyone	Nystatin 500,000u, swish/swallow 4x/d	Day 0 → prednisone ≤ 10 mg daily (or ≤ 5 mg daily if diabetic); when taking PO Day 0 → prednisone ≤ 10 mg daily (or ≤ 5 mg daily if diabetic); in place of nystatin if poor swallow fxn or not taking PO	
		TMP/SMX 800/160 mg PO MWF	Day 0 → prednisone ≤ 10 mg daily (or ≤ 5 mg daily if diabetic); when renal fxn is stable and taking PO	
Renal	CMV D+/R-	Valganciclovir 450 mg PO q24h *OR* Ganciclovir 2.5 mg/kg IV q24h	Day 0 to +1 → Day +180	-Renally adjusted
	CMV D+/R+ or D-/R+ with lympholytic therapy		Day 0 to +1 → Day +90	
	Everyone	TMP/SMX 400/80 mg PO q24h	Day +7→ Day +180* When renal fxn stable, start later if DGF	-Consider dapsone** 100 mg PO q24h or Inh pentamidine 300 mg qMonth if TMP/SMX contraindicated
		Cephalexin 250 mg PO q24h	Day +1 → Day +30 or ureteral stent removal (whichever is longer)	-If PCN allergic consider FQ
	Anti-Thymocyte Globulin (ATG) for ACR	Restart Bactrim and Valganciclovir (except CMV D-/R-) prophylaxis	Continue ≥ 6 weeks from last ATG dose	- Renally adjusted

Solid Organ Transplant Antimicrobial Prophylaxis Quick Reference Table, Continued

Organ	Risk Group	Medication	Timing/Duration	Comments
Lung	CMV D+/R-	Ganciclovir 5 mg/kg IV q12h	Day 0 → Day +14	-Renally adjusted
		CMVIg: 150 mg/kg IV @ Day +1 100 mg/kg IV @ weeks +2, 4, 6, & 8 50 mg/kg IV @ weeks +12 & 16	Day +1 Weeks +2, 4, 6, 8, 12, & 16	
		Valganciclovir 450 mg PO BID	Day +15 → Day +365	-Renally adjusted
		Acyclovir 200mg PO BID	Day +365 → Lifelong	-Renally adjusted
	CMV D+/R+, D-/R+, or D-/R-	CMVIg: 150 mg/kg IV @ Day +1 100 mg/kg IV @ Day +15 & +30	Day +1, +15, & +30	
		Valganciclovir 450 mg PO BID *OR* Ganciclovir 2.5 mg/kg IV q12h	Day +1 → Day +180	-Renally adjusted
		Acyclovir 200 mg PO BID	Day +181 → Lifelong	-Renally adjusted
	Fungal prophylaxis (Based on respiratory cultures)	-Anidulafungin 200mg IV once, then 100mg daily (starts day 0) -Itraconazole 100 mg PO BID (start once taking PO)	Anidulafungin continues through removal of chest tubes. Overlap with Itraconazole to allow adjustment of immunosuppression due to interaction.	-Itraconazole trough levels are encouraged. Trough should be ordered one week after Itraconazole initiation. Target trough for prophylaxis is 0.5-2 mcg/mL
	Everyone (May differ based on pre-transplant history/cultures)	Cefepime 2 g IV q8-12h	Day 0 → variable based on OR cx	-Renally adjusted
		Vancomycin (targeting trough 15-20)	Day 0 → Until all chest tubes removed	-Renally adjusted, refer to Blue Book for nomograms
		TMP/SMX 800/160 mg PO MWF	Day 0 → Lifelong, when able to take PO	-Consider INH pentamidine 300 mg qMonth if TMP/SMX contraindicated
		Nystatin 500,000u swish/swallow QID	Day 0 → Lifelong, when able to take PO	

Bone-Marrow Transplant (BMT) / Hematologic Oncology (HemeOnc) Antimicrobial Prophylaxis Quick Reference Table

Type	Risk Group	Medication	Timing/Duration	Comments
Autologous	Everyone	Levofloxacin 750 mg PO/IV q24h	Day +1 → ANC > 1000 cells/mL	-Renally adjusted
		Acyclovir 400mg PO BID (myeloma) Acyclovir 800mg PO BID *OR* Acyclovir 5 mg/kg IV q12h	Day +1 → Day +365 (lymphoma) Day +1 → Day +180 (myeloma)	
		Fluconazole 400 mg PO/IV q24h	Day +1 → ANC > 1000 cells/mL	
		TMP/SMX 800/160 mg PO BID MoTh	Day +21 if ANC > 2500 cells/mL → Day +180 (lymphoma, no ppx for myeloma)	-Discuss with provider if renal fxn is an issue
Allogeneic	Everyone	Levofloxacin 750 mg PO/IV q24h	Day +1 → ANC > 1000 cells/mL	-Renally adjusted
		Acyclovir 800mg PO BID *OR* Acyclovir 5 mg/kg IV q12h	Day +1 → Day +365	
		Fluconazole 400 mg PO/IV q24h	Day +1 → Day +75	
		TMP/SMX 800/160 mg PO BID MoTh	Day +21 if ANC > 2500 cells/mL → Day +180	-Discuss with provider if renal fxn is an issue
CMV+ Cord	Everyone	Levofloxacin 750 mg PO/IV q24h	Day +1 → ANC > 1000 cells/mL	-Renally adjusted
		Letermovir 240mg IV/PO q24h And Acyclovir 800mg PO BID, Or 500mg/m^2 IV q12h	Day 0 → Day +100	-Letermovir not renally adjusted. Use 480mg daily dosing if NOT receiving concomitant CSA for GVHD ppx. - Watch for drug interactions, moderate 3A4 inhibitor and 2C9/19 inducer (drops voriconazole exposure 50%) - Late CMV monitoring qweek D+100 - +180
		Acyclovir 800 mg PO BID	Day +101 → Off immunosuppression	-Renally adjusted
		Fluconazole 400 mg PO/IV q24h	Day +1 → Day +75	
		TMP/SMX 800/160 mg PO BID MoTh	Day +21 if ANC > 2500 cells/mL → Day +180	-Discuss with provider if renal fxn is an issue
AML Inductions	Everyone	Levofloxacin 500 mg PO q24h	Completion of Chemotherapy → ANC > 500 cells/mL	-Renally adjusted
		Acyclovir 400 mg PO BID		
		Fluconazole 200 mg PO q24h		
Others (HemeOnc)	Protocol specific, please refer to individual protocols			

CMV = cytomegalovirus; HSV = herpes simplex virus; D = donor; R = recipient; CMVIg = Cytomegalovirus Immune Globulin aka Cytogam®; fxn = function; cx = culture; tx = treatment; MWF = Monday, Wednesday, and Friday; TMP/SMX = Trimethoprim/Sulfamethoxazole, FQ = fluoroquinolone

* = May continue or reinitiate prophylaxis for the following: >20 mg daily prednisone equivalents, prolonged neutropenia, flares of autoimmune diseases, recurrent or chronic active CMV infection, rejection requiring lympholytic therapy (Thymoglobulin®), GVHD (BMT patients), increased immunosuppressant doses over baseline (as might be needed for prolonged or severe rejection)

** = Do not use if glucose-6 –phosphate dehydrogenase (G6PD) deficient, unacceptable risk of hemolytic anemia

Renal Dose Adjustments for Prophylactic Regimens

Ganciclovir IV		Valganciclovir	
BMT & Liver & Renal	per AMSGB for CMV prophy w/o loading doses	**Liver**	per AMSGB for CMV prophylaxis after solid organ transplant
Lung	per AMSGB for CMV induction w/o loading doses	**Heart & Renal**	per AMSGB starting at 450 mg for CMV prophylaxis after solid organ transplant
Heart	per AMSGB at 50% dose for CMV induction w/o loading doses and dose max of 2.5 mg q12h	**Lung**	per AMSGB for CMV prophylaxis after solid organ transplant except 900 mg q24h given as 450 mg q12h
Fluconazole IV/PO		**Acyclovir PO**	
BMT	per AMSGB w/o loading doses	**BMT & Liver & Renal**	per AMSGB for post BMT prophylaxis with higher dose range for CRRT
HemeOnc	per AMSGB at ½ the usual dose and w/o loading doses	**Lung**	per AMSGB at 50% dose for prophylaxis for pre-BMT pts
		HemeOnc	per AMSGB for prophylaxis for pre-BMT pts
Levofloxacin IV/PO		**Acyclovir IV**	
BMT	per AMSGB for severe infections	**BMT**	CrCl 25-50 mL/min = 500 mg/m^2 q12h; CrCl 10-24 mL/min = 500 mg/m^2 q24h; CrCl <10 mL/min = 250 mg/m^2 q24h
HemeOnc	per AMSGB for mild-moderate infections	**BMT**	CrCl 25-50 mL/min = 500 mg/m^2 q12h; CrCl 10-24 mL/min = 500 mg/m^2 q24h; CrCl <10 mL/min = 250 mg/m^2 q24h
Cefepime		**Valacyclovir**	
Lung	per AMSGB at higher dose range for mild-moderate infections	**BMT**	2 g TID dosing: CrCl 25-50 mL/min = 2 g BID; CrCl 10-24 mL/min = 2 g q24h; CrCl <10 mL/min = 1 g q24h

CrCl = creatinine clearance (via Cockcroft Gault); BMT = Bone Marrow Transplant; HemeOnc = hematologic oncology; AMSGB = Antimicrobial Stewardship Guidebook

Immunosuppressant/Azole Antifungal Drug Interactions

Azole Added	Cyclosporine (CSA)	Tacrolimus (TAC)	Everolimus/Sirolimus (EVO/SRO)
Fluconazole*	↓ CSA by 20-66%	↓ TAC by 40-50%	Do not coadminister / ↓SRO by 50-70%
Itraconazole	↓ CSA by 33-80%	↓ TAC by 50-66%	Do not coadminister either
Voriconazole	↓ CSA by 50-70%	↓ TAC by 50-70%	Do not coadminister / ↓SRO by 75-90%
Posaconazole	↓ CSA by 25-50%	↓ TAC by 50-80%	Do not coadminister / ↓SRO by 70%
Isavuconazole (single substrate dose)	300 mg CSA AUC ↑'d ~1.5x	5 mg TAC AUC ↑'d ~2-2.5x	2 mg SRO AUC ↑'d ~1.5-2x

*A single dose of 150 mg does not require dose adjustment

- Dose adjustments expressed as ranges from clinical specialists and Dodds-Ashley *Pharmacotherapy* 2010; 30(8):842-54.
- Consider current level of immunosuppression, goal immunosuppressant level, and transplant service when deciding on dose adjustments.
- Additional interactions can influence overall immunosuppressant levels.

List is not comprehensive refer to tertiary drug interaction reference for additional interactions

BMT / HemeOnc *Clostridium difficile* Infection Pathway

Diagnosis:

- Diarrhea (≥ 3 liquid/unformed stool – NOT just Soft) and positive *C. difficile*
  - ***C. difficile* Toxin PCR Test (Preferred)**
  - GI PCR may be ordered for any outpatient and inpatients admitted < 72 hours
- Colonization without infection is not an indication for treatment.
- The microbiology lab will not process orders if repeated within 7 days
  - For initially negative test results. Please assess patient for other causes of diarrhea (both infectious and non-infectious)
  - DO NOT send repeat stool for test of cure, remains positive for up to 6-8 weeks
  - DO NOT send stool for testing in patients on therapy

Treatment:

- Treatment: Duration is 14 days unless otherwise specified. See prevention below for duration and dosing of therapy for patients remaining on broad spectrum antibiotics after 14 days of *C. difficile* treatment.
  - For patients with failure to respond on preferred therapy, multiple recurrences, and/or presence of severe and complicated disease, consider early ID +/- Surgery Consultation.
  - Metronidazole is no longer recommended for treatment

Table 1. Treatment of *C. difficile* Infection

Severity	1st Occurrence	2nd Occurrence	3rd Occurrence
Non severe	Vancomycin 125mg PO QID	Fidaxomicin 200mg PO BID OR Vancomycin Pulse/Taper[1] (if fidaxomicin unavailable) *Consider bezlotoxumab (see prevention below)	Vancomycin Pulse/Taper[1] OR Fidaxomicin Taper (200mg PO BID x 5 days, then 200mg every other day for 10 doses) *GI consult for Fecal Microbiota Transplantation (FMT)[2] or consider bezlotoxumab if not tried previously
Severe	Vancomycin 125mg PO QID ± Metronidazole 500mg IV q8h (consider bezlotoxumab – see prevention section)		
Complicated	Vancomycin 500mg PO QID + Metronidazole 500mg IV q8h (Add Vancomycin 500mg Q6h Enema if Ileus) – d/c IV and enema once clinical improvement (consider bezlotoxumab – see prevention section)		

[1] Pulse and Taper Dose: Vancomycin 125mg PO Q6h x 14 days, then 125mg PO BID x 7 days, then 125 mg PO once daily x 7 days, then 125 mg PO every other day x 7 doses, then 125mg PO every 3rd day x 10 doses
[2] FMT after 2 or more adequately treated recurrences. Pre-treat with vancomycin x4-5 days

Table 2. Prevention of *C. difficile* Infection Recurrence

Persistent Diarrhea	For persistence at end of 14 day duration, work up other causes. Consider change to fidaxomicin, vancomycin taper[1], or consult GI for FMT[2]. Increasing PO vancomycin doses and/or adding metronidazole has not shown to improve response and may result in severe microbiota disruption.
Prevention	- Bezlotoxumab 10mg/kg IV once over 60 minutes should be considered for patients with severe first episode infection, any recurrence, or presence of GVHD • Administer before active *C. difficile* treatment has completed • Bezlotoxumab is for outpatient use only. A referral order should be placed to outpatient infusion to obtain insurance approval. In extenuating circumstances in which inpatient administration is desired, talk to pharmacy for review. - Patients remaining on broad-spectrum antibiotics[3] at the end of *C. difficile* treatment, change to prophylactic vancomycin 125mg PO BID • Continue prophylactic vancomycin for 7 days after broad-spectrum antibiotic is discontinued • Do not use prophylaxis if bezlotoxumab is given

[1] Pulse and Taper Dose: Vancomycin 125mg PO Q6h x 14 days, then 125mg PO BID x 7 days, then 125 mg PO once daily x 7 days, then 125 mg PO every other day x 7 doses, then 125mg PO every 3rd day x 10 doses
[2] FMT after 2 or more adequately treated recurrences . Pre-treat with vancomycin x4-5 days
[3] Broad spectrum antibiotics = fluoroquinolones, 3rd/4th generation cephalosporins, piperacillin-tazobactam, amoxicillin-clavulanate, ampicillin-sulbactam, carbapenems, clindamycin, aztreonam

BMT / HemeOnc Neutropenic Fever Pathway, Cont.

Table 1. Vascular Device Management

	Work-up	Management	Duration
Vascular Device	1. Swab entry site drainage if present for culture 2. Blood cultures x 2 sets, 1 set peripheral and 1 set from line a. Send quantitative (pour plate) cultures = add green top tubes for each culture	**Treatment Guided by Culture Findings and Susceptibilities**. Catheter removal is strongly encouraged with positive blood culture results for the following pathogens: *Candida spp.*, *Staphylococcus aureus*, *Pseudomonas spp.*, *Corynebacterium jekeium*, *Acinetobacter spp.*, *Bacillus spp.*, Atypical mycobacteria, molds, yeasts, *Enterococcus spp.* (esp. VRE), and *Stenotrophomonas*. Line removal also encouraged for septic phlebitis, tunnel infection, or port pocket infection.	Variable depends on organism and infection source. **See table 2 below**

Table 2. Blood Stream Infection Management

Pathogen	Line removal	Primary Treatment[1]	Alternative Treatment[1]	Duration/Comments[2]
S. aureus and *S. lugdenensis*	Yes	- MRSA: Vancomycin - MSSA: Cefazolin 2g q8h	- MRSA: Daptomycin 6-8mg/kg q24h **OR** Ceftaroline 600mg IV q8h - MSSA: Nafcillin 12g/d	-≥ 4 weeks, ID consult recommended due to propensity for metastatic infections. - Vancomycin is inferior if MSSA - Daptomycin is inactivated by lung surfactant - Resume neutropenic prophylaxis if ANC < 1000
Coagulase-negative *Staphylococci*	Not Generally	- Vancomycin	- Oxacillin-resistant (see above for choice) - Oxacillin-sensitive: cefazolin 2g q8h	- 7-14 days, 7 days sufficient if line removed and rapid response. 14 days if retained line
Enterobacteriacae (i.e. *E coli*, *Klebsiella.*, etc)	Varies	- Cefepime 2g q8h (empiric)→Adjust based on Cx/Sensitivities	- Pip-taz 4.5g q8h EI or Meropenem 1g q8h (empiric) →Adjust based on Cx/Sensitivities	- 14 days. Persistent bacteremia and/or hemodynamic instability = remove line
Pseudomonas spp., *Acinetobacter spp.*, *Stenotrophomonas*	Yes	- Pseud: Cefepime 2g q8h ± Tobra - Acineto: Meropenem 1g q8h ± Tobra - Steno: TMP-SMZ 5mg/kg TMP q8h	- Pseud: Base on sensitivities - Acineto: Base on sensitivities - Steno: Ceftazidime ± minocycline IV/PO	- 14 days. Consider ID Consult - Consider up-front aminoglycoside combo for critically ill/non-response while awaiting sensitivities - Do not use aminoglycoside or polymyxin monotherapy
Candida spp.	Yes	- Anidulafungin 200mg x 1, then 100mg q24h	- Fluconazole/Voriconazole if sensitive - Liposomal amphotericin-b 3mg/kg q24h	-≥ 14 days, ID consult recommended - Echo to r/o endocarditis / Ophthalmology for eye exam to r/o endophthalmitis
Enterococcus spp.	Varies	- Vancomycin	- Daptomycin 10-12mg/kg q24h (VRE) - Ampicillin 2g q4h or Pip-taz 4.5g q8h (amp-sensitive)	- 7-14 days, 7 days sufficient if line removed and rapid response. 14 days if retained line - Remove line if possible, esp. VRE o May retain line if impending neutrophil recovery anticipated in ≤ 7 days.
Bacillus spp.	Yes	- Vancomycin	- Variable activity , Consult ID for Recommendations	- 7-14 days

[1] All dosing recommendations are based on assumption of normal renal function

[2] Duration of therapy is general for most uncomplicated cases of bacteremia, and should not replace clinical judgement and is not intended to apply to patients with complex/metastatic infections.

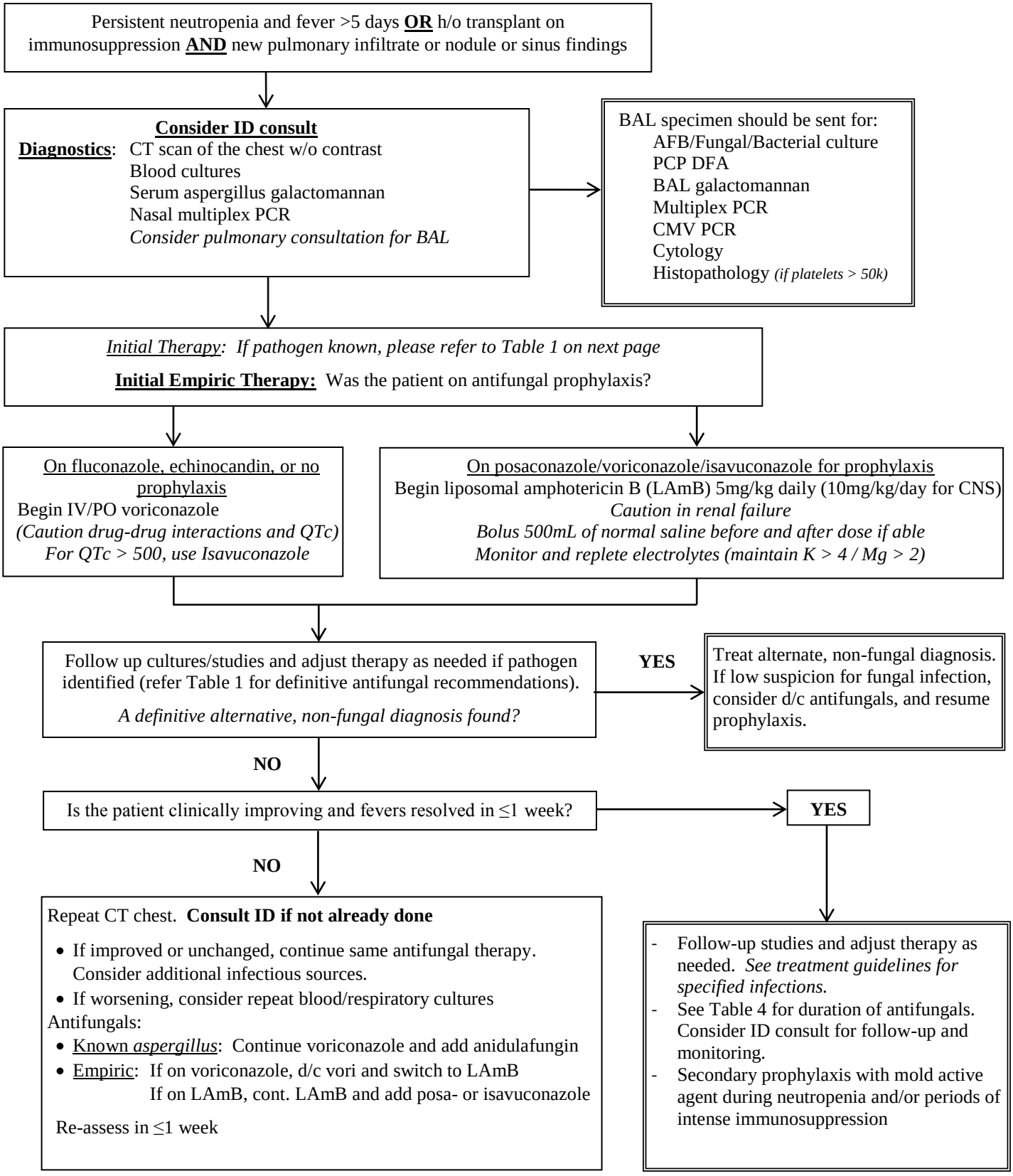
Line removal may not always be necessary in every case, but for those without initial removal the line should be removed if bacteremia persists > 48-72 hours, patient has persistent signs of sepsis, thrombophlebitis, tunneled line infection, and/or port pocket infection. In cases of persistent bacteremia, consider echocardiography to rule out endocarditis. Candidemia should always receive ophthalmology consult for eye exam.

BMT / HemeOnc RSV Pathway

- Patients to be treated:
  - Hematologic malignancy receiving chemotherapy
  - Allogeneic HSCT patients
  - Autologous HSCT < 6 months post-transplant

	Dosing by Creatinine Clearance		
	CrCl > 50 mL/min	CrCl 30 -50 mL/min	CrCl < 30 mL/min including HD
Oral Ribavirin	**Loading dose**: RBV 10mg/kg PO (max 2 g) x 1 **Maintenance**: 40-60kg = 400mg PO TID 61-90kg = 600mg PO TID 91-120kg = 800mg PO TID >120kg = 1000mg PO TID	**Loading dose**: RBV 10mg/kg PO (max 2 g) x 1; **Maintenance**: 200mg PO q8h	**Loading dose**: RBV 10mg/kg PO (max 2 g) x 1; **Maintenance**: Limited data, may consider 200mg PO 24h
	Comments: Formulation available as 200mg capsules/tablets, **round dosing to closest 200mg**; oral suspension available for inpatient use in patients with enteral access and unable to swallow **Duration**: 5 days		
Inhaled Ribavirin Severe mucositis/gut-GVHD (grade ≥ 3), Mechanical Ventilation without reliable enteral access	Inhaled ribavirin 2g nebulized over 3 hours every 8 hours - Inhaled ribavirin must be administered in a negative pressure room - May cause bronchoconstriction, cough, wheezing - Transition to PO with improvement after 2-3 days (use above dosing, omit loading dose)		

BMT / HemeOnc Fungal Pathway



- Routine ordering of beta-D-glucan as initial workup is not routinely recommended.
- Serum galactomannan most effective when used for serial monitoring for response to therapy.

Table 1: Treatment Recommendations for Specified Fungi/Infections

Fungi/Condition	Antifungal	Comments
Aspergillus (invasive, pulmonary, CNS, endocarditis, osteoarticular)	Voriconazole IV/PO[1]: Load 6 mg/kg IV q12h x 2 doses then maintenance 4 mg/kg IV q12h. *Monitor voriconazole levels (see below)*	Consult ID for management. Minimum 6–12 weeks of therapy.
	2nd Line: Isavuconazole[2] IV/PO Load 372mg q8h x 6 doses, then 372mg daily or posaconazole 300mg PO q12h x 2 doses then 300mg qday	*Salvage: addition of anidulafungin to azole.* monitor posa levels
Mucormycoses/ Zygomyces	Liposomal amphotericin B (LAmB) 5mg/kg IV daily (CNS infections up to 10mg/kg IV daily).	Consult ID. Consult surgery for resection of infected tissue.
	2nd Line: Posaconazole 300mg PO q12h x 2 doses then 300mg daily or Isavuconazole[2] IV/PO Load 372mg q8h x 6 doses, then 372mg daily	Overlapping posa and LAmB when transitioning; monitor posa levels.
Scedosporium/ Pseudallescheria	Voriconazole IV/PO[1] 6 mg/kg IV q 12h x 2 doses, then 4 mg/kg IV q12h *Monitor voriconazole levels (see below)*	Consult ID. Consult surgery for resection of infected tissue.
Fusarium	Voriconazole IV/PO[1] 6 mg/kg IV q12h x 2 doses then 4 mg/kg IV q12h *Monitor voriconazole levels (see below)*	Consult ID. Consult surgery for resection of infected tissue.
Candidemia, hepatosplenic candidiasis	Anidulafungin 200mg x1 then 100mg IV daily	Adjust antifungals based on sensitivities. Consult ophthalmology, consider central line removal, and TTE for fungemia.

[1] Use Total Body Weight for Voriconazole dosing, except in obese patients (>120% IBW) utilize Adjusted Body Weight for dosing.
[2]Isavuconazole may be preferred in patients with QTc prolongation (> 500msec) or creatinine clearance < 50 mL/min and need for IV therapy due to NPO status. Isavuconazole shortens QTc and does not contain cyclodextrin in IV formulation.

Drug	Trough Targets
Voriconazole	Day 3-5: 2 – 4 mcg/dL (Treatment); >0.5-1 (Prophylaxis)*
Posaconazole	Day 5-7: > 1 mcg/dL; > 0.7 (Prophylaxis)*
Isavuconazole	No recommendations

- Always check Voriconazole and Posaconazole levels when used for treatment.
- Do not repeat levels once therapeutic, unless presence of new toxicity, worsening clinical picture, new drug-drug interactions.

*Levels not routinely needed for prophylaxis though may consider in patient for new toxicity, possible failure, and/or significant drug-drug interaction.

Table 2: Azole Therapeutic Drug Monitoring

Table 3: Antifungal Prophylaxis

Diagnosis/Transplant	Agent[3]	Timing/Duration	Alternative	Comments
AML / MDS / ALL [1,2]	Fluconazole 200mg daily	Start 24h after last chemo dose; Stop once ANC > 500	Anidulafungin 100mg IV daily if azole intolerant	**Fluconazole** Dose Adjust in Renal Impairment - CrCl < 50: 200mg qday - CrCl < 10: 100mg qday Drug Interactions - CYP 3A4 Inhibitor, monitor immunosuppression closely
Allo-HSCT [1,2]	Fluconazole 400mg daily	D+1 → D+80		
Auto-HSCT [1,2]	Fluconazole 400mg daily	D+1 → ANC > 2500		
Others – multiple myeloma, lymphoma[2]	Consider fluconazole	Anticipated neutropenia lasting > 7-10 days, continue until count ANC > 500		
Acute/Chronic GVHD	Voriconazole 200mg PO BID	*Restart/continue for Intensive immunosuppression; Stop with GVHD resolution and decreased immunosuppressive doses	Posa 300mg PO q12h x 2 doses, then 300mg qday or Isavuconazole 372mg PO q8h x 6 doses, then 372mg qday or Anidulafungin 100mg IV qday	Vori, Posa, and Isavu have strong interactions with immuno-suppressants (esp. CNIs), dose reduction necessary.

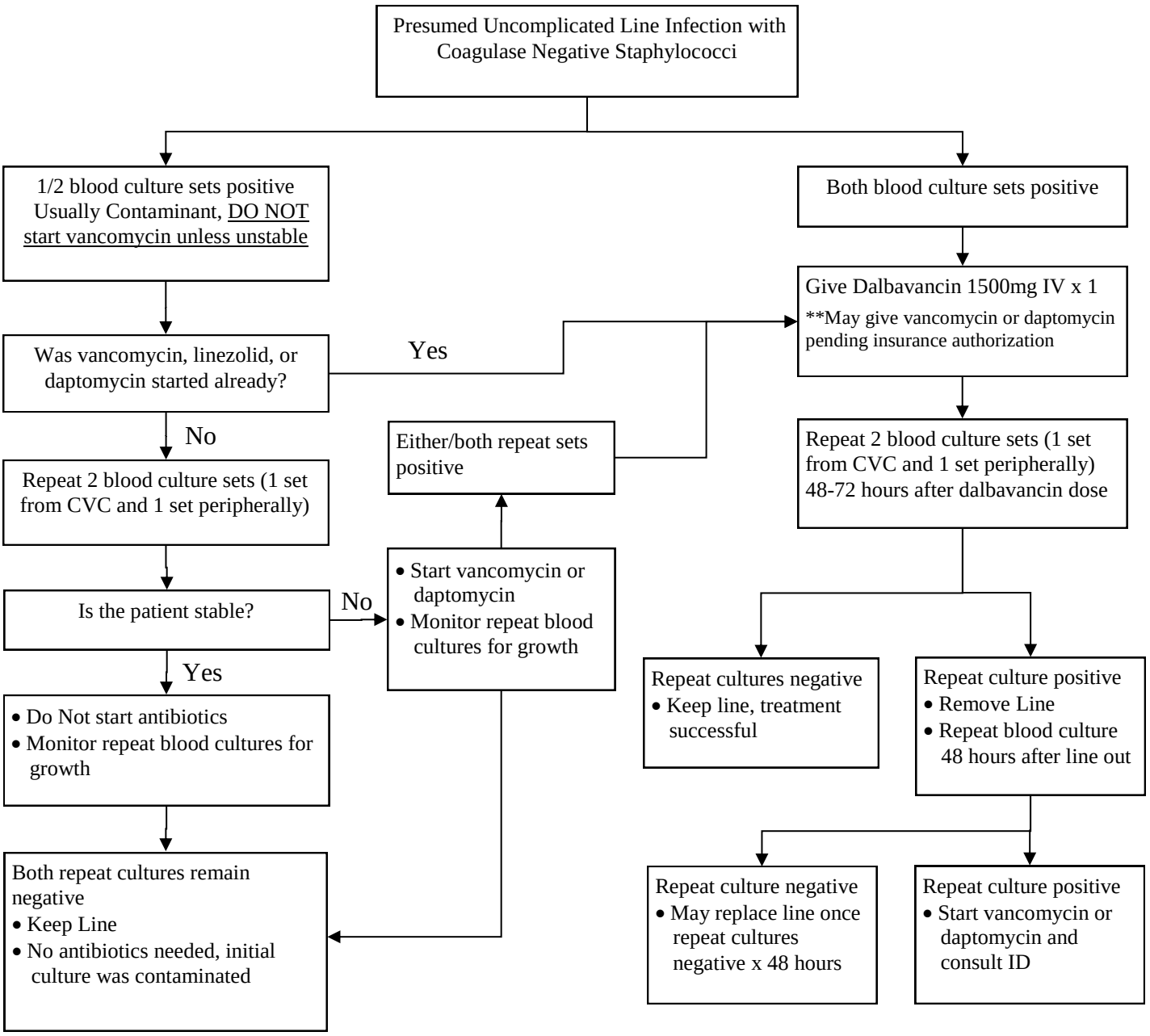
*Intensive immunosuppression: prednisone ≥ 0.5 mg/kg/day or equivalent planned duration > 2 weeks or steroid refractory disease with treatment including antithymocyte globulin, alemtuzumab, etanercept, and MMF. Consult Attending in setting of secondary agent use.
[1]Patients with relapsed/refractory disease and profound and prolonged neutropenia consider primary mold prophylaxis with vori or posa
[2]Patients with prior history of mold infection, use vori or posa for secondary prophylaxis during neutropenic periods lasting > 7 days, allogeneic transplant through Day +80, autologous transplant until ANC > 2500, and/or during intensive immunosuppression for GVHD.
[3]Anidulfungin may be used as prophylaxis for *Candida spp.* and/or *Aspergillus spp.* during periods of actual/expected liver impairment.

Table 4: Duration of Empiric Antifungal Therapy

- Continue antifungals until neutrophil recovery (ANC >500)
- There are no published national guidelines on the empiric treatment of pulmonary nodules, and the following is not to be used as definitive standards of practice. Always adjust treatment duration based on clinical presentation.
- Consider ID consult and/or follow-up to determine duration of antifungal therapy

Follow-up CT in 2-4 weeks	Initial Antifungal Duration	Step-down and Prophylaxis
Pulmonary nodule resolved	Continue antifungals for at least 6 weeks. If clinically improved, no concern for recurrent infection, and no neutropenia → consider d/c antifungals	Consider anti-mold prophylaxis during periods of neutropenia or intensive immunosuppression (See Table 3 for Indications/Definitions)
Pulmonary nodule slightly improved	Continue antifungals for 4 more weeks and repeat CT. - If resolved, no concern for recurrent infection, and no neutropenia → consider d/c antifungals as indicated - If improving, continue antifungals for 4 more weeks and repeat CT chest - Unchanged or worse: consider alternative diagnoses +/- biopsy and ID consultation	
Pulmonary nodule unchanged	Continue antifungals for 4 more weeks and repeat CT - If resolved, no concern for recurrent infection, and no neutropenia → consider d/c antifungals as indicated - If improving, continue antifungals for 4 more weeks and repeat CT chest - Unchanged or worse: consider alternative diagnoses +/- biopsy and ID consultation	
Pulmonary nodule worse	Consider alternative diagnoses. Consider biopsy and ID consultation.	

BMT / HemeOnc Uncomplicated Coagulase Negative Staphylococci Line Infection – Dalbavancin Pathway



- Uncomplicated Coagulase Negative Staphylococcus Bacteremia:
  - Patient DOES NOT have any implanted devices/prosthetics (e.g. artificial joint, pacemaker, prosthetic heart valve, vascular grafts, etc.)
  - No suspicion for or evidence of metastatic/uncontrolled infection (e.g. septic emboli, undrained abscess, etc.)
- *Staphylococcus lugdenensis* should not follow this protocol and is treated similarly to *Staphylococcus aureus* bacteremia
- Dalbavancin is a long-acting gram-positive antibiotic (similar to vancomycin). The half-life is ~10-14 days. Spectrum of activity is vancomycin susceptible strains of *Staphylococcus spp.*, *Streptococcus spp.*, *Enterococcus faecalis*.
- Dalbavancin should not be routinely used as inpatient. If an inpatient is a candidate for dalbavancin, please submit outpatient infusion referral order to start authorization process. If authorized, dalbavancin dose may be scheduled to be given at least 24 hours after discharge from inpatient unit.
- Do not administer dalbavancin if < 72 hours of planned antibiotic duration left to complete

BMT / HemeOnc CNS Infection Suspected after HSCT

Suspect CNS Infection after HSCT

- Consult Infectious Diseases
- MRI brain with and without contrast
- Lumbar puncture - large volume, send for standard testing:
  - CSF Fluid analysis (cell count, glucose, protein)
  - Cultures - aerobic, anaerobic, and AFB
    - Add MTB PCR (Xpert) if high risk for TB (incarceration, travel/residence in endemic area, known/possible exposure, history of prior TB, imagine appearance)
  - HSV 1/2 PCR
  - VZV PCR
  - CMV PCR
  - EBV PCR
  - HHV-6 PCR
  - Cryptococcal antigen (add-on fungal culture if antigen positive)
  - +/- JC virus PCR (imaging appearance of PML)

≤ 100 days post-HSCT

- Not on Azole prophylaxis (consider)
  - +/- Coccidioides antibody panel
  - +/- Histoplasma urine antigen
- +/- Toxoplasma PCR (imaging w/ ring– enhancing lesions, +IgG pre-transplant)
- +/- WNV serum IgG/IgM (not inpatient and seasonality)

> 100 days post-HSCT

- Serum HIV antibody/antigen and viral load
- Treponema antibody with reflex to RPR
- +/- Coccidioides antibody panel
- +/- Histoplasma urine antigen
- +/- Toxoplasma PCR (not taking Bactrim, imaging w/ ring– enhancing lesions, +IgG)
- +/- WNV serum IgG and IgM (seasonality)

Empiric Treatment Considerations:

- Anti-bacterials:
  - Vancomycin IV with pharmacy to dose consult + Cefepime 2g IV q8h + Ampicillin 2g IV q4h
    - For severe penicillin/ampicillin allergy, substitute cefepime and ampicillin for meropenem 2g IV q8h
  - Add Metronidazole 500mg IV/PO q8h if MRI brain results concerning for abscess (Don't add this if meropenem used)
- Add acyclovir 10-15mg/kg q8h if encephalitis to cover HSV/VZV (ganciclovir and foscarnet covers HSV/VZV, CMV, and HHV-6)
- Add Liposomal Amphotericin-B (AmBisome) 7-10mg/kg IV q24h if concurrent sinusitis and concern for mucormycosis

Diagnosis	Primary Treatment	Alternative Treatment	Duration
Bacterial	Tailor to organism susceptibilities, duration depends on organism		
Cryptococcus neoformans	Induction (2-4 weeks): LAmB 3mg/kg q24h plus Flucytosine 25mg/kg q6h	Consolidation (8 weeks): Fluconazole 800mg PO qday Maintenance (6-12 months): Fluconazole 200-400mg PO qday	Total duration 6-12 months
Candida	LAmB 5mg/kg q24h plus Flucytosine 25mg/kg q6h	May step down to fluconazole or Voriconazole based on sensitivities after several weeks of improvement	Prolonged, resolution of all clinical, CSF, and radiographic abnormalities
Aspergillus	Voriconazole 6mg/kg IV q12h x 2 doses (load), then 4mg/kg IV q12h (maintenance)	LAmB 5mg/kg q24h	Minimum 12 months
Mucormycosis	LAmB 7-10mg/kg q24h +/- Posaconazole or Isavuconazole	Posaconazole or Isavuconazole	Minimum 12 months
HSV	Acyclovir 10mg/kg IV q8h	Ganciclovir 5mg/kg 12h Foscarnet 90mg/kg q12h	
VZV	Acyclovir 15mg/kg IV q8h	Ganciclovir 5mg/kg 12h Foscarnet 90mg/kg q12h	
CMV	Ganciclovir 5mg/kg q12h	Foscarnet 90mg/kg q12h	
HHV-6	Foscarnet 90mg/kg q12h	Ganciclovir 5mg/kg q12h	
EBV	Reduced immunosuppression	+/- Acyclovir or ganciclovir	
WNV	Reduced immunosuppression	+/- IVIG	

Management of Infectious Diarrhea (non-*C. difficile*) among HSCT Recipients and those with Hematologic Malignancies

- **Management:**
  - Infections may arise from nosocomial spread, please refer to the Infection Prevention Guidelines regarding Contact Precautions (available at: https://thesource.uchealth.org/PaS/Services/infection/uch/Pages/Contact-Precautions.aspx)
  - Standard approaches to management:
    - Fluid hydration and electrolyte replacement
    - Reduction in immunosuppression
    - May consider anti-motility agents in patients WITHOUT Shiga-toxin *E. coli* (STEC/EHEC) and/or *C. difficile*
    - Supportive care – dietary considerations (avoid milk and other dairy products, caffeine, fried/fatty/spicy foods)
  - Pathogen Specific Therapy Recommendations

Pathogen/Result	Microbiology	Treatment for Gastrointestinal Disease
Campylobacter	Major cause of dysenteric diarrhea worldwide, derived from consuming undercooked meat, contaminated water	Azithromycin 500mg PO QD x 7d (preferred) – High rates of FQ resistance Consider ID consult for alternative treatment recommendations in GI disease and for severe infections (including those with bacteremia)
C difficile toxin AB	Antibiotic associated; healthcare outbreaks	See separate management pathway
Salmonella	Typhoid most common in travelers. Non-typhoid common in US. May cause extra-intestinal disease (e.g. endovascular) and chronic disease/carriage.	1. Azithromycin 500mg PO QD x 14d (preferred) 2. Bactrim DS 1 tab PO BID x 14d 3. Ciprofloxacin 500mg PO BID x 14d Consider ID consultation for extra-intestinal/invasive infections Bacteremia/extra-intestinal disease, prefer Ceftriaxone 1g q24h initially
Y enterocolitica	Associated w/cecitis/terminal ileitis, pseudo-appendicitis and post-transfusion sepsis	1. Bactrim DS 1 tab PO BID x 7 days 2. Doxycycline 100mg PO BID x 7 days 3. Ciprofloxacin 500mg PO BID x 7 days Consider ID consultation for severe infection / septicemia, combination of doxycycline and gentamicin has been utilized in such cases.
Enteroaggregative E coli (EAEC)	Associated w/ chronic diarrhea in immunocompromised patients.	Significance of EAEC and EPEC are unclear in immunocompromised hosts. These organisms may be found colonizing patients without symptoms. If no other causes (infectious or non-infectious) identified and symptoms persist > 7 days or is severe consider treatment, for ETEC consider treatment with: 1. Azithromycin 500mg PO QD x 7 days 2. Rifaximin 200mg PO TID x 7 days 3. Ciprofloxacin 500mg PO BID x 7 days
Enteropathogenic E coli (EPEC)	Gastroenteritis, most often in kids.	
Enterotoxigenic E coli (ETEC)	Common cause for traveler's diarrhea	
Shiga toxin producing E coli (STEC/EHEC)	Non- O157:H7 E coli that may cause enterohemorrhagic E coli.	Supportive care. Antibiotics may increase risk for Hemolytic Uremic Syndrome.
E coli 0157	Common cause for enterohemorrhagic E coli.	
Shigella / Enteroinvasive E coli	Common cause of diarrhea.	1. Ciprofloxacin 500mg PO BID x 7 days 2. Azithromycin 500mg PO QD x 7 days 3. Bactrim DS 1 tab PO BID x 7 days
Cryptosporidium	Diarrhea in AIDS and immunocompromised patients. Associated w/ food/water-borne outbreaks	Consult ID. Reduction in immunosuppression is key to clearance. Prolonged courses of nitazoxanide, paromomycin, and azithromycin may be effective in treating disease, along with anti-motility agents and fluid/electrolyte replacement.
Giardia lamblia	Associated w/ contaminated water supply	Metronidazole 500mg BID x 7 days
Cyclospora/ Cystoisospora	Ingestion of contaminated food/water	Bactrim DS 1 PO BID x 10 days, then 1DS PO thrice weekly for relapse prevention
Adenovirus F 40 41	Gasteroenteritis in children and immunocompromised patients.	Refer to Adenovirus Management Pathway.
Astrovirus/Sapovirus	Gasteroenteritis in children and immunocompromised patients.	Supportive care only.
Norovirus GI GII	Most common cause of acute gastroenteritis in the US	Supportive care for almost all cases. Patients with severe presentation, recurrent infection, and/or refractory disease = Consult ID +Norovirus and symptoms lasting > 7 days = Nitazoxanide 500mg PO BID x 7 days
Rotavirus A	Common cause for gastroenteritis in children	Supportive care only.

Allogeneic HSCT Adenovirus Management Pathway

Background:

Adenovirus is a DNA virus with significant pathologic potential in immunocompromised patients. Though more common in pediatric patients, it may infect adult stem cell transplant patients. It may infect multiple organ systems, and disseminated disease is associated with high mortality. Risk higher in more immunosuppressed situations.

Evaluation:

Systemic infection/viremia: Positive PCR, virus isolation, or antigen detection in peripheral blood.

Local infection: Positive PCR, virus isolation, or antigen detection in biopsy material or in body fluids other than peripheral blood.

Probable disease: Infection plus corresponding symptoms and signs without histological confirmation.

Proven disease: Infection plus corresponding symptoms related to the infection and histological confirmation in the appropriate location.

Potential organs involved and samples to test: Lungs (biopsy/BAL), bladder (biopsy/urine), intestine (biopsy/stool), liver (biopsy), kidney (biopsy/urine), CNS (CSF)

Management:

When to treat:

Any single quantitative PCR value >5000 in the setting of symptoms or any positive PCR or histological confirmation of disease in more than 1 tissue site in any allo patient <6 months post-transplant or any allo patient with active steroid refractory GVHD or on > 0.5 mg/kg prednisone

For positive PCR levels <5000 or single organ positive PCRs, patients may be observed closely with serial testing q 3 days to weekly to trend quantitative PCR or confirm organ involvement. Decisions to treat will be at the discretion of the attending physician.

Other patients may be monitored and decision to treat at attending discretion.

Treatment:

Cidofovir 5 mg/kg/week for 2 weeks, and 5 mg/kg every 2 weeks thereafter (use orderset). Discontinue when viral load negative.

- Adjunctive medication:
    - Probenecid 2,000mg PO once 3 hours before Cidofovir, then 1,000mg PO x 2 doses at 2h and 8h after Cidofovir infusion complete.
    - Hydration – 1,000mL NS over 2 hours before and after Cidofovir infusion

Adeno specific T cells

BMT / HemeOnc Influenza Management

- Treatment of suspected/confirmed influenza infection should be commenced as soon as possible (ideally within the first 48 hours of symptoms); however, administration should not be withheld if presenting after 48 hours of symptoms given prolonged viral shedding and symptomology.
- For local patients with adequate resources to obtain drug promptly and for whom PCR results are expected with 24 hours, PCR results may be obtained before deciding to initiate therapy to confirm influenza diagnosis. If there is any possibility in delay of PCR results or patients with difficult access to fill oseltamivir, treatment should be initiated ASAP in suspected cases prior to results of definitive testing.
- Recommendations for treatment are outlined below. Peramivir is a newly approved IV neuraminidase inhibitor. It has shown equivalency to oseltamivir, and is thus only necessary in situations of decreased GI.
- The dosing of oseltamivir is controversial for immunocompromised hosts. Studies in immunocompetent patients with severe influenza infection requiring ICU admission and mechanical ventilation have failed to identify benefits of 150mg BID vs. 75mg BID. Despite this some experts recommend high dose for immunocompromised patients.
- Duration of therapy for immunocompromised patients should be extended to 10 days, and continued longer if patient remains symptomatic due to longer viral shedding in this patient population.
- IVIG use is not routinely recommended. Combination therapy has been used in the setting of neuraminidase resistant virus (2008-2009). Provided lack of definitive evidence showing benefit, it is not routinely recommend.

Table 1. Treatment of Influenza

	1st Line Treatment	**Alternate**	**Comments**
• Allogenic HSCT > day +80 • Upper RTI and o Autologous HSCT o Non-transplant on active therapy	Oseltamivir 75mg PO BID x 10 days	Peramivir 600mg IV once daily x 5-10 days **Only if unable to take PO because of severe gut GVHD**	- Renal adjustment needed for both agents - If still symptomatic after 10 days, may extend course for another 10 days
• Allogenic HSCT ≤ day +80 • Lower RTI and o Autologous HSCT o Non-transplant on active therapy o Severe GVHD	Oseltamivir 150mg PO BID x 10 days	Peramivir 600mg IV once daily x 5-10 days **Only if unable to take PO because of severe gut GVHD**	- Renal adjustment needed for both agents - If still symptomatic after 10 days, may extend course for another 10 days
Non transplant patients not receiving active therapy	Oseltamivir 75mg PO BID x 5 days	Peramivir 600mg IV once **Only if unable to take PO because of severe gut GVHD**	- Renal adjustment needed for both agents

Prevention:

- Vaccination; Inactivated quadrivalent influenza vaccine
  - Influenza vaccination should be given during influenza season for transplant patients after day +90.
  - For non-transplant patients, vaccine should be given at least 2 weeks after last chemotherapy dose.
- Post exposure prophylaxis**
  - Oseltamivir 75 mg PO daily x 10 days

** Exposure defined as documented influenza infection in person with whom patient has had close contact within the last week.

BMT / HemeOnc IVIG Use Pathway

Prophylaxis:

- Several meta analyses and a randomized trial have demonstrated no benefit to empiric repletion of IVIG following allogeneic stem cell transplantation.[1-3] As such, empiric IVIG repletion will not be administered following allogeneic transplantation.
- However, expert opinion does suggest that patients with hypogammaglobulinemia <400 mg/dL and recurrent sino-pulmonary or viral infections may benefit from empiric IVIG repletion.
    - Patients with two or more sino-pulmonary or viral infections (excluding CMV reactivation), empiric IVIG may be administered.
        - Dosing: 0.5 grams/kg rounded to the nearest 10 grams.*
        - Frequency: Check IgG levels monthly. Replete for IgG <400.
        - Duration: After six month trial, consider stopping infusions on case by case basis. Strong consideration should be given to stopping IVIG if no infections during this period.

Acute Infections:

- There is limited evidence available to support routine use of IVIG in the treatment of acute infections.

Administration of IVIG in the management of acute infections may be considered on a case-by-case basis.

Allogeneic HSCT BK Virus Management

Background:

BK virus is ubiquitous. In the post stem cell transplant population it is a frequent source of cystitis. Symptoms of urinary frequency and pain are common and are generally self-limited. In some cases hematuria may be present, and hemorrhagic cystitis leading to renal obstruction is a potential serious complication.[1-3]

Evaluation:

- Diagnosis may be made clinically, and includes clinical symptoms of cystitis (dysuria, urgency, frequency, etc.), hematuria, and presence of BK viral replication.
- BK viruria is common if tested for prospectively following transplantation and does not correlate well with symptomatic disease. BK PCR testing of the urine, therefore, is of limited value in confirming symptomatic BK virus, but can effectively rule out BK related disease.
- BK viremia may correlate more closely with symptomatic disease, but plasma PCR is not generally needed. (For isolated urinary symptoms, concurrent adenovirus PCR testing may be considered but is generally of low yield if there are no additional systemic symptoms.)

Management:

- Mild disease: urinary frequency, pain, and/or hematuria without clots
    - Supportive care only, includes Ditropan, pyridium, and systemic pain medicines
- Moderate to severe: hematuria with clots
    - Admit for continuous bladder irrigation and consider antiviral treatment (Table 1.)

Table 1. Treatment Options for BK Hemorrhagic Cystitis

	Drug/Dose	Duration	Comments
Preferred if normal renal function	Cidofovir 1mg/kg IV Qweek **without** probenecid; Fluid hydration 500mL/hr x 2 hours before & after dose	4 weeks average, up to 10 weeks may be required Treat until symptomatic improvement	-Monitor SCr, urine protein, and CBC. -May dose twice weekly if not improving
Patients with renal dysfunction*	Intravesicular Cidofovir 5 mg/kg in 60mL NS instilled over 15 minutes and clamped for 1 hour 1-2x per week		Tolerability may be problematic
Inability to tolerate or failure of above	Leflunomide 100mg daily x 5 days, then 20mg daily. (Levels may be monitored, if so check day 6 trough, goal 50-100)	Until symptom improvement	-Monitor CBC, LFTs, rash, blood pressure, cough/dyspnea.
* Renal dysfunction = SCr > 1.5 mg/dL, CrCl ≤ 55 mL/min, and/or urine protein ≥ 100 mg/dL			

HIV and HCV Antiretroviral Dosing Recommendations

Current Treatment Guidelines:

- DHHS HIV Treatment Guidelines: http://www.aidsinfo.nih.gov/guidelines
- AASLD HCV Treatment Guidelines: http://hcvguidelines.org/

Medication Interactions:

- Each individual agent has a different drug interaction profile. Particularly complex interactions come from the CYP3A4 interactions of HIV and HCV Protease Inhibitors. Drug classes to closely monitor include but are not limited to: anticoagulants/antiplatelets, anticonvulsants, antifungals, anti-mycobacterials, benzodiazepines, cardiac medications, corticosteroids, herbal products, hormonal contraceptives, HMG-Co A Reductase Inhibitors, Methadone, and PDE5- Inhibitors
- Check each medication profile closely for medication interactions
- Many resources available, including Micromedex®, Lexi-Comp® (UpToDate®), DHHS Guidelines, University of Liverpool Interaction Checker (HIV and HCV)

Nucleo(t)side Reverse Transcriptase Inhibitors (NRTIs):

- Can be taken without regards to food (exception: didanosine EC)
- Common class side effect of lactic acidosis and hepatic steatosis (black box warning)

Medication	Recommended Dosing	Dose Adjustment	Common Adverse Effects/Comments
Abacavir (ABC) *Ziagen* ®	300mg PO BID or 600mg PO daily	Hepatic	Hypersensitivity reaction in patients with HLA-B*5701 – must test before treatment Combination with nevirapine increases hypersensitivity reaction risk Increase in cardiovascular risk Contraindicated in severe hepatic impairment.
Didanosine EC (ddI) *Videx EC* ®	400mg PO daily on empty stomach (<60kg: 250mg PO daily)	Renal	Pancreatitis, peripheral neuropathy, Contraindicated with allopurinol and ribavirin Decrease dose to 250mg PO daily when given with tenofovir. Do not crush, solution available
Emtricitabine (FTC) *Emtriva* ®	Capsule: 200mg PO daily Solution: 240 mg (24 ml) PO daily	Renal	Headache, diarrhea, hyperpigmentation of skin, severe acute exacerbation of hepatitis may occur in HBV-coinfected patients who discontinue FTC.
Lamivudine (3TC) *Epivir* ®	150mg PO BID or 300mg PO daily	Renal	Headache, nausea, vomiting, pancreatitis, severe acute exacerbation of hepatitis may occur in HBV-coinfected patients who discontinue 3TC. Used in HBV/HIV co-infected patients. Consult hepatology.
Stavudine (d4T) *Zerit* ®	40mg PO BID (<60kg: 30mg PO BID)	Renal	Peripheral neuropathy, lipoatrophy, neuromuscular weakness, pancreatitis Combination of stavudine + didanosine not recommended (toxicity) Antagonistic relationship with zidovudine
Tenofovir DF (TDF) *Viread* ® Tenofovir alafenamide (TAF) *Vimlidy*®	300mg PO daily 25mg PO daily	Renal	Diarrhea, nausea, vomiting, rash, potential for renal impairment, osteopenia, severe acute exacerbation of hepatitis may occur in HBV-coinfected patients who discontinue TDF. Do not crush and no solution available HBV: 300 mg daily; used in HBV/HIV co-infected patients. Consult hepatology.
Zidovudine (AZT) *Retrovir* ®	300mg PO BID or 200 mg TID	Renal	Bone marrow suppression (anemia/neutropenia), lipoatrophy, myopathy and myositis with prolonged exposure, lactic acidosis with hepatic steatosis
Zidovudine/ Lamivudine *Combivir* ®	1 capsule PO BID	Renal	Bone marrow suppression, peripheral neuropathy, pancreatitis, lactic acidosis. See individual agents
Zidovudine/Lamivudine/ Abacavir - *Trizivir* ®	1 capsule PO BID	Renal	Bone marrow suppression, peripheral neuropathy, hypersensitivity reaction, rash, lactic acidosis. HLA-B*5701 Testing. See individual agents
FTC/TDF *Truvada ® and Cimduo* **FTC/Tenofovir alafenamide (TAF) - *Descovy*®**	1 tablet PO daily	Renal	Diarrhea, nausea, vomiting, severe acute exacerbation of hepatitis may occur in HBV-coinfected patients who discontinue Truvada. See individual agents. Descovy (FTC/TAF) is a new combination product with a different tenofovir salt, benefit is in long-term safety profile (reduced bone-mineral-metabolism and nephrotoxic events compared to old TDF formulations. CrCl cutoff for TAF use is 30 mL/min (not studied for < 30 mL/min, no dose adjustment for ≥ 30 mL/min).
Lamivudine/Abacavir *Epzicom* ®	1 tablet PO daily	Renal	Nausea, vomiting, hypersensitivity reaction, rash. HLA-B*5701 Testing. See individual agents. Avoid initiation in combination with EFV or ATV when pre-ART viral load ≥ 100,000 copies/mL

Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs):

- Drug interactions due to metabolism via CYP3A4 and others (including but not limited to: anticoagulants/antiplatelets, anticonvulsants, antifungals, anti-mycobacterials, benzodiazepines, cardiac medications, corticosteroids, herbal products, hormonal contraceptives, HMG-Co A Reductase Inhibitors, Methadone, and PDE5- Inhibitors)
- Rash

Medication	Recommended Dosing	Dose Adjustment	Common Adverse Effects/Comments
Efavirenz (EFV) *Sustiva* ®	600mg PO QHS on empty stomach, Usually dosed at night	Use w/ caution in hepatic impairment	Rash, neuropsychiatric side effects. May cause false positive THC test. CYP3A4 inducer Not to be used during first trimester of pregnancy or in women trying to conceive. Women who are of child-bearing age should be on 2 forms of birth control
Etravirine (ETR) *Intelence* ®	200mg PO BID, following a meal	None	Rash, including serious rashes that require discontinuation. CYP3A4 inducer, 2C9 and 2C19 inhibitor. Should be swallowed whole, may be dispersed in water
Nevirapine (NVP) *Viramune* ®, *Viramune XR* ®	200mg PO daily x2 weeks then BID, with or without food XR: 400 mg PO daily	Hepatic	Rash, including serious rashes that require discontinuation, diarrhea, hepatotoxicity. Contraindicated in moderate/severe hepatic failure. CYP3A4 and 2B6 inducer. Use with caution in combination with abacavir due to increased risk of hypersensitivity reaction Do not crush XR formulation, solution is available, IR may be crushed
Rilpivirine (RPV) *Edurant* ®	25 mg PO daily. Take with a moderate to high calorie meal.	None	Contraindicated with PPIs, Separate doses from H2-blockers or anti-acids by 4 hours before or 12 hours after Rilpivirine administration. CYP3A4 substrate. Fewer rash, depression, headache and CNS effects compared to efavirenz. Caution with drugs that cause QTc prolongation. Do not crush and no solution available

Receptor Antagonist Inhibitors (Entry Inhibitors):

- Increased risk of bacterial pneumonia; hypersensitivity reactions are common
- May be taken without regards to meals

Medication	Recommended Dosing	Dose Adjustment	Common Adverse Effects/Comments
Enfuvirtide (T20) *Fuzeon* ®	90mg (1ml) subcut BID	None	Injection site reactions in up to 100% of patients Hypersensitivity reaction
Maraviroc (MVC) *Selzentry* ®	300mg PO BID 150mg PO BID + CYP3A **inhibitors** 600mg PO BID + CYP3A **inducers** All with or without food	Renal - Caution in patients with severe renal insufficiency	Rash, abdominal pain, musculoskeletal symptoms, hepatotoxicity, orthostatic hypotension. CYP3A4 substrate Perform tropism testing before initiating, patients must have CCR5-tropic virus

Integrase Inhibitors (INSTIs)

Medication	Recommended Dosing	Dose Adjustment	Common Adverse Effects/Comments
Raltegravir (RAL) *Isentress* ® / HD	400mg PO BID (1200mg PO qday – HD form) with or without food If with Rifampin: 800mg PO BID (non HD form)	None	Rash, including serious rashes that require discontinuation, myopathy and rhabdomyolysis (monitor CPK), diarrhea, nausea, vomiting. Increase dose to 800mg PO BID with concomitant rifampin therapy
Dolutegravir (DTG) *Tivicay*®	Treatment naïve or experienced w/o an INSTI mutation: 50mg PO daily Treatment experienced (with an INSTI mutation) or co-administration with a UGT or 3A4 inducer: 50mg PO BID May give doses with or without food	None Severe renal fxn may lower concentrations – use caution	Nausea, diarrhea, headache, dizziness, insomnia, rash, and increased serum creatinine from baseline (~0.1 mg/dL)-result of inhibiting tubular secretion of SCr, no kidney toxicity has been seen with DTG. Separate 2 hours before or 6 hours after use of poly-valent cations (i.e. Al, Mg, Ca, Fe). Co-administration with efavirenz, fosamprenavir/ritonavir, tipranavir/ritonavir, rifampin may lower DTG concentrations, use twice daily dosing if these agents are used together
Elvitegravir (EVG) *Vitekta*®	If with ATV/r or LPV/r: 85mg PO daily If with DRV/r, FPV/r, or TPV/r: 150mg PO daily Administer with food	None (Not studied in severe hepatic impairment)	Headache, diarrhea, nausea. CYP 3A4 substrate (Major) and moderate/weak inducer CYP 2C9 Do not coadminister with strong CYP 3A4 Inducers Coadministration with antacids decrease elvitegravir concentrations, doses should be separated by at least 2 hours to minimize risk of interaction.

Protease Inhibitors (PIs):

- Many drug interactions due to inhibition of CYP3A4 (including but not limited to: anticoagulants, anticonvulsants, antifungals, anti-mycobacterials, benzodiazepines, cardiac medications, corticosteroids, herbal products, hormonal contraceptives, HMG-Co A Reductase Inhibitors, Methadone, PDE5- Inhibitors)

Medication	Recommended Dosing	Dose Adjustment	Common Adverse Effects/Comments
Atazanavir (ATV) *Reyataz* ® Atazanavir/Cobicistat 300/150mg-*Evotaz*®	300mg PO daily with RTV 100mg daily (w/ food) or 400mg daily (unboosted) If w/ EFV: 400 mg w/ RTV 100 mg PO daily	Hepatic, Renal	Increased bilirubin, cardiac conduction abnormalities, rash, decreased lipids, nephrolithiasis, increased transaminases, increase serum creatinine (with cobicistat) Treatment experienced patients and those on TDF require ritonavir boosting Separate PPIs and H2 blockers (See Lexi-comp for specific information) Do not coadminister ritonavir with Evotaz (atazanavir/cobicistat)
Darunavir (DRV) *Prezista* ® Darunavir/Cobicistat 800/150mg *Prezcobix*®	Treatment naïve or experienced without a DRV mutation: 800 mg PO daily with RTV 100mg or cobi 150mg PO daily Treatment experienced (with a DRV mutation): 600mg PO BID with RTV 100mg PO BID	Hepatic	GI upset, hepatotoxicity, rash, increased transaminases, hyperlipidemia, hyperglycemia, possible increased bleeding episodes in patients with hemophilia Increase serum creatinine (with cobicistat) Contains sulfonamide – caution in patients with sulfonamide allergy Concomitant use with saquinavir or lopinavir/ritonavir not recommended Must be given w/ food to achieve adequate concentrations. Do not crush DRV/Cobi Do not coadminister ritonavir with Prezcobix (darunavir/cobicistat)
Fosamprenavir (FPV) *Lexiva* ®	PI experienced: 700mg PO BID with RTV 100mg PO BID PI naïve: 1400mg PO BID unboosted OR 1400mg PO daily w/ RTV 100-200mg daily OR 700mg PO BID w/ RTV 100mg PO BID	Hepatic	Nausea, vomiting, diarrhea, rash, increased transaminase levels Treatment naïve patients also taking efavirenz require ritonavir boosting dose of 300mg PO daily; ritonavir dose increase not necessary when dosed BID Caution in patients with sulfonamide allergy (contains sulfonamide moiety) Give at least 2 hours before H2 receptor antagonist if concomitant use necessary
Indinavir (IDV) *Crixivan* ®	800mg PO Q8H on empty stomach (unboosted) 800mg PO BID boosted w/ RTV 100-200mg PO BID w/ or without food	Hepatic	Nephrolithiasis, increased bilirubin, metallic taste, GI upset, hemolytic anemia, leukocyturia Dose adjustment required when used with certain drugs
Lopinavir/Ritonavir (LPV/r) *Kaletra* ®	Treatment experienced and naïve: 400/100mg PO BID or 800/200 mg daily W/ EFV or NVP: 500/125mg PO BID	Hepatic, Renal	Cardiac conduction abnormalities (QTc prolongation), GI intolerance increased transaminase levels With or without food (take solution w/ food) Do not crush, liquid formulation is available
Nelfinavir (NFV) *Viracept* ®	1250mg PO BID or 750mg PO TID w/ food	Hepatic	Diarrhea, nausea, increased transaminases, QTc prolongation, Torsades de pointes Can dissolve with a small amount of water – consume immediately
Ritonavir (RTV or r) *Norvir* ®	Only for dosing as a PK booster for other PIs. 100-400mg in 1-2 divided doses, depending on other PI. Take w/ food.	Hepatic	GI upset, nausea, diarrhea, perioral tingling, hepatitis, taste disturbances Many drug interactions due to CYP450 Capsules should be refrigerated (can last for 30 days outside of fridge). Tablets can be stored at room temperature. Do not crush, solution is available
Saquinavir (SQV) *Invirase* ®	1000mg PO BID (boosted w/ RTV 100mg PO BID) w/ food	Hepatic	Nausea, vomiting, diarrhea, increased transaminase levels. QTc prolongation (not recommended to initiate in patients with a QTc of >450 msec)
Tipranavir (TPV) *Aptivus* ®	500mg PO BID boosted w/ RTV 200mg PO BID; give w/ food (Must boost to achieve antiviral effect)	Hepatic	GI upset, hepatotoxicity, rash, bleeding, rare intracranial hemorrhage. Contains sulfonamide – caution in patients with sulfonamide allergy Give 2 hours before or 1 hour after antacids;

Multi-Class Combinations:

Medication	Recommended Dosing	Dose Adjustment	Common Adverse Effects/Comments
FTC/TDF/EFV *Atripla* ® and Symfi and Symfi LO	1 tablet PO daily on an empty stomach, usually given at night	Not recommended in moderate/severe renal impairment (CrCl < 50)	Diarrhea, nausea, vomiting, neuropsychiatric side effects. See individual agents Do not crush, no solution available
FTC/TDF/RPV *Complera* ® FTC/Tenofovir alafenamide/RPV *Odefsey*®	1 tablet PO daily with a meal	Not recommended in moderate/severe renal impairment (CrCl < 50) *Odefsey CrCl cutoff for use is < 30mL/min*	Contraindicated with PPIs, Separate doses from H2-blockers or anti-acids by 4 hours before or 12 hours after rilpivirine administration. CYP3A4 substrate. Caution with drugs that cause QTc prolongation. Fewer rash, depression, headache and CNS effects compared to efavirenz. Avoid initiation when pre-ART HIV Viral Load ≥ 100,000 copies/mL and/or CD_4 < 200 cells/mm^3 See individual agents. Odefsey is a new combination product with a different tenofovir salt (TAF vs. TDF), benefit is in long-term safety profile (reduced bone-mineral-metabolism and nephrotoxic events compared to old TDF formulations.
FTC/TDF/EVG/Cobi *Stribild* ® FTC/Tenofovir alafenamide/EVG/Cobi *Genvoya*®	1 tablet PO daily with food	Initiation not recommended in CrCl<70, continuation not recommended if CrCl < 50 *Genvoya CrCl cutoff for use is < 30mL/min*	Decreases creatinine excretion in renal tubules, can increase SCr during initiation Nausea, diarrhea, abnormal dreams, fatigue, headache, dizziness, increased cholesterol, abnormal dreams, and rash. CYP3A4 substrate and inhibitor. See individual agents *Genvoya* is a new combination product with a different tenofovir salt (TAF vs. TDF), benefit is in long-term safety profile (reduced bone-mineral-metabolism and nephrotoxic events compared to old TDF formulations.
ABC/3TC/DTG *Triumeq*®	1 tablet PO daily with or without food	Not recommended in moderate/severe renal impairment (CrCl < 50) Contraindicated in moderate/severe hepatic impairment	HLA-B*5701 testing required with ABC use. Increased ALT/AST. See individual agents
DRV/cobi/FTC/TAF *Symtuza*®	1 tab PO daily with food	Not recommended with CrCl < 30 mL/min or severe hepatic impairment (C-P C)	Tablet is large and may be split into 2 pieces with a tablet cutter in patients unable to swallow the tablet whole; administer entire dose immediately after splitting. Assess for drug interactions See individual components for more information
Bictegravir/TAF/FTC *Biktarvy*®	1 tab PO daily with or without food	Not recommended with CrCl < 30 mL/min or severe hepatic impairment (C-P C)	Bictegravir is an integrase inhibitor. It is a substrate of CYP 3A4 and UGT 1A1, assess for significant interactions. It inhibits OCT2 and MATE1. Dofetilide and metformin concentrations are increased by Biktarvy.
Doravirine/3TC/TDF *Delstrigo*®	1 tab PO daily w/ or w/o food	Not recommended w/ CrCl < 50 ml/min, no adjustment for mild-mod liver dysfx	Doravirine is available as individual agent and belongs to the non-nucleoside reverse transcriptase inhibitor class of ARTs. Use is contraindicated with strong 3A4 inducers (if concurrent administration with rifabutin, take 1 tab Delstrigo daily followed by doravirine 100mg PO qday 12 hours after Deslstrigo dose). Doravirine is associated with fewer neuropsychiatric events vs. efavirenz in phase 3 studies. Active vs. NNRTI resistance mutations K103N and Y181C,

Hepatitis C Virus Direct Acting Antiretrovirals (HCV-DAAs):

- Many drug interactions / Consult Hepatology or Infectious Diseases
- Currently approved only in combination with ribavirin and peg-interferon[1] or ribavirin with or without peg-interferon[2] or sofosbuvir[3]
- Dosing regimen and duration based on patient response[4] or specific HCV genotype and/or clinical scenario[5]

Medication	Recommended Dosing	Dose Adjustment	Common Adverse Effects/Comments
Sofosbuvir[2,5] (Sovaldi®)	400mg PO daily with or without food	Renal: do not use with CrCl ≤ 30mL/min	Dosing schedule based on HCV genotype and clinical status (degree fibrosis/prior trx). Fatigue, headache, insomnia, rash, increased lipase. P-gP substrate: contraindicated with strong P-gP inducers (rifampin, anti-epileptics)
Simeprevir[1,3-5] (Olysio®)	150mg PO daily with food	None: not studied in severe renal or liver disease	Dosing schedule based on patient response. Rash (photosensitivity), nausea, increased bilirubin, myalgias. Substrate of CYP 3A4 and P-gP and inhibits intestinal 3A4 (mild): Contraindicated for use with moderate-strong inhibitors and inducers of CYP 3A4
Ledipasvir and Sofosbuvir[5] (Harvoni®)	90mg/400mg (1 tab) PO daily with or without food	Renal: do not use with CrCl ≤ 30mL/min	Dosing schedule based on HCV genotype and clinical status (degree fibrosis/prior trx). Fatigue, headache, insomnia, nausea/diarrhea, increased lipase Antacids, PPIs, and H2RAs reduce ledipasvir concentrations, avoid concomitant use and/or use lower PPI dose (≤20mg omeprazole equivalent) with adequate spacing (avoid PPI within 2 hours prior to ledipasvir dosing). Ledipasvir increases rosuvastatin (avoid combination) and tenofovir levels
Ombitasvir, Paritaprevir, Ritonavir and Dasabuvir[5] (Viekira Pak®)	Ombita/Paritap/Riton: 2 tab PO QAM Dasabuvir: 250mg PO BID Administer doses with food	Renal: none Hepatic: CI w/ severe disease	Dosing schedule based on HCV genotype and clinical status (degree fibrosis/prior trx) Fatigue, headache, insomnia, nausea, diarrhea, dermatological reactions, increased LFTs Multiple drug interactions including CYP 3A4, 2C8, 2D6 and P-glycoprotein pathways
Ombitasvir, Paritaprevir, Ritonavir[5] (Technivie®)	2 tab PO daily Administer doses with food	Renal: none Hepatic: CI w/ severe disease	Dosing schedule based on HCV genotype and clinical status (degree fibrosis/prior trx). Headache, weakness, fatigue, nausea, insomnia. Multiple drug interactions including CYP 3A4, 2C8, 2D6 and P-glycoprotein pathways
Daclatasvir[3,5] (Daklinza®)	60 mg PO qday with or without food	None	Dosing schedule based on HCV genotype and clinical status (degree fibrosis/prior trx). Headache, fatigue, nausea, diarrhea. CYP 3A4 substrate; avoid/caution with inducers/inhibitors of CYP 3A4
Elbasvir and Grazoprevir (Zepatier®)	50mg/100mg (1 tab) PO once daily Administer with or without food	None (incl. ESRD on HD)	Dosing schedule based on HCV genotype and clinical status. Use is contraindicated with Child-Pugh Class B/C Cirrhosis. Fatigue, headache, insomnia, and nausea. CYP-3A4 substrates: Do not coadminister with strong inhibitors or moderate to strong inducers. Also substrate for OATP 1B1/3.
Sofosbuvir and Velpatasvir (Epclusa®)	400mg/100mg (1 tab) PO once daily Administer with or without food	Renal: do not use with CrCl ≤ 30mL/min	Dosing schedule based on HCV genotype and clinical status (degree fibrosis/prior trx). Fatigue, headache, insomnia, rash, nausea, and diarrhea. P-gP and CYP-2B6, 2C8, and 3A4 substrate: contraindicated with strong inducers. Avoid concurrent antacids, H2RAs, and PPIs, or separate doses.

Alternative Antiretroviral Formulations for Patients Unable to Tolerate Tabs/Caps

Medication	Liquid	Formulation	Alcohol (%)	Extemporaneous Preparation Options
Nucleos(t)ide Reverse Transcriptase Inhibitors				
Abacavir (ABC)	Y	20mg/mL – 240mL	N	No data on crushing, film-coated tablet
Didanosine (ddI)	Y	2g/100mL, 4g/200mL	N	Can crush/dissolve buffered tabs in water, apple juice, or chocolate milk
Emtricitabine (FTC)	Y	10mg/mL – 170mL	N	Can open capsules and mix w/ water
Lamivudine (3TC)	Y	5 and 10mg/mL – 240mL	Y-6%	Can crush tabs
Stavudine (d4T)	Y	1mg/mL – 200mL	N	Can open capsules & mix w/ food or 5-10mL cool tap water
Tenofovir DF (TDF)	Y	Powder 40mg/1g – 60g	N	Mix powder w/ 2-4oz soft food (applesauce, yogurt) not liquid (floats). Crushed tabs in 100mL in water or grape juice
Zidovudine (AZT)	Y	50mg/5mL – 240mL	N	Open capsules & mix w/ small amount of food or 5-10mL cool tap water.
Combivir (AZT/3TC)	N	N/A	N/A	Can crush and admin immediately
Epzicom (ABC/3TC)	Y	See individual components	N/A	Tab is film coated & immediate release, may split/crush and add to food/water
Trizivir (ABC/3TC/AZT)	Y	See individual components	N/A	No info; film coated and immediate release tab
Truvada (TDF/FTC)	N	N/A	N/A	May crush and stir in water, OJ, grapefruit juice and administer immediately
Non-Nucleoside Reverse Transcriptase Inhibitors				
Efavirenz (EFV)	N	N/A	N/A	Open capsules and mix with applesauce, grape jelly, yogurt, or infant formula. Insoluble in H2O and PEG. Admin mix w/in 30min, rinse container containing mixture 3x w/ 50mL water and swallow each rinse. For NG admin, mix w/ 5mL MCT oil or 15mL Ora-sweet, grind powder first to improve dissolution.
Nevirapine (NVP)	Y	50mg/5mL – 240mL	N	Can crush IR forms only
Delavirdine (DLV)	N	N/A	N/A	100mg tabs can be dispersed in 90mL water. Drink immediately, rinse glass/mouth, swallow rinse
Rilpivirine (RPV)	N	N/A	N/A	No data. Rilpivirine insoluble in water.
Etravirine (ETR)	N	N/A	N/A	Disperse tabs in ≥ 1 tsp H2O, stir until milky, add more H2O or milk or OJ and take immediately. Rinse glass 2-3 times and drink contents. Do not give w/ grapefruit, carbonated drinks. Use cooled liquids.
Atripla (EFV/TDF/FTC)	N	N/A	N/A	Crush and dissolve in 5mL H2O, then dilute to 20mL with Ora-Sweet. Administer w/in 24hr of preparation.
Complera and Odefsey (RPV/TDF or TAF/FTC)	N	N/A	N/A	No data. RPV is insoluble in water.
Protease Inhibitors				
Atazanavir (ATV)	N	N/A	N/A	Open capsules and mix contents w/ applesauce for immediate use. No data for ATV/COBI, but given Cobi is water insoluble would not advise crushing.
Darunavir (DRV)	Y	100mg/mL – 200mL	N	No studies to evaluate PK, may crush tab as they are only film coated and not ER and dissolve in H2O per Man. Prezcobix (DRV/COBI) and Symtuza (DRV/Cobi/FTC/TAF) should be swallowed whole without crushing/breaking. In the split group there was an 11% decrease in TAF Cmax only (not clinically relevant). In the crushed group there was a 17% decrease in the emtricitabine Cmax and TAF Cmax and AUC were decreased by 29% and 18%, respectively (clinical relevance not assessed, but impact expected to be minimal based on wide therapeutic window for TAF). (Brown et al. EACS 2017, #PS8/3)
Fosamprenavir (FPV)	Y	50mg/mL – 225mL	N	Take susp on empty stomach. Discard 28d after opening. Refrigerate, do not freeze. No data on crushing or dissolving 700mg tabs.
Indinavir (IDV)	N	N/A	N/A	DO NOT open capsules. Recipe for compound that's stable for 14d refrigerated. *Hugen. AJHP. 2000; 57(14): 1332-39*.
Nelfinavir (NFV)	N	N/A	N/A	Dissolve tabs in water, 250mg per 5mL sterile water (conc. 50mg/mL) Good for 6hr refrigerated. May mix w/ food or drink
Ritonavir (RTV)	Y	80mg/mL – 240mL	Y-43%	Can mix liquid w/ chocolate milk or liquid nutritional supplements (Boost). Do not crush/chew tabs.
Saquinavir (SQV)	N	N/A	N/A	6x200mg Fortavase whole caps mixed in 50mL of whole milk or nutritional supplement dissolved over 5-15min with heat to 40-80C and remained in soln for 1hr at RT, refrigerated soln gelled, but liquefied upon warming to 30C, drug stable for 24hr, per Hoffmann-LaRoche.
Tipranavir (TPV)	Y	100mg/mL – 95mL	N	No data
Kaletra (LPV/RTV)	Y	80mg/20mg/mL – 160mL	Y-42%	DO NOT Crush/chew/break tablets. AUC decreased 45% if tablet crushed.
Integrase Inhibitors and Entry Inhibitor				
Raltegravir (RAL)	N	N/A	N /A	Chewable tab in 100mg and 25mg. May crush tabs and dissolve in 60mL warm water. Drink immediately
Dolutegravir (DTG)	N	N/A	N/A	May crush and add to small amount of semi-solid food or liquid. Consume immediately – ViiV
Bictegravir (BIC) and Biktarvy (BIC/TAF/FTC)	N		N/A	No data, not recommended. BIC is practically insoluble in water. Would consider alternative regimen of Dolutegravir plus TAF/FTC (Descovy) or TDF/FTC (Truvada), all of which may be crushed (no PK evidence for crushing TAF, but is water soluble and well absorbed orally so unlikely to be impacted)
Stribild or Genvoya (EVG/Cobi/FTC/TDF or TAF)	N	N/A	N/A	No data, not recommended. EVG and COBI are insoluble in water. Case report with crushed Stribild in Juice; AJHP. 2014; 71(10): 784-786.
Triumeq (ABC/3TC/DTG)	N	N/A	N/A	No data- film coated, non-scored, and non-SR form. Splitting/crushing tab not expected to affect dissolution/absorption. May crush and add to small amt. food or liquid and consume immediately.
Maraviroc (MVC)	N	N/A	N/A	No data for crush/chew, though not expected to negatively affect bioavailability

Antibiogram and Dosing Guidelines Development Team

Misha Huang, MD, MS
Matthew Miller, PharmD
Gerard Barber, RPh, MPH
Michelle Barron, MD
Josh Bayer, PharmD
Veronica Broslawik, MLS(ASCP), MPH
Monica Calderon, PharmD
Matt Casciano, PharmD
Lisa Ferrigno, MD
Doug Fish, PharmD
Jasjit Gill, PharmD
Amy Go, PharmD
Larry Golightly, PharmD
Meghan Jeffres, PharmD
Jeff Kaiser, PharmD
Ty Kiser, PharmD
Matt Klein, PharmD
Patrick Klem, PharmD
Victor Lewis, PharmD
Katie Levin, PharmD
Nancy Madinger, MD
Bruce McCollister, MD
Pierre Moine, MD
Taylor Morrisette, PharmD
Scott Mueller, PharmD
Nichole Neville, PharmD
Alex Novin, PharmD
Larissa Pisney, MD
Paul Reynolds, PharmD
Carla Saveli, MD
Kelly Schoeppler, PharmD
Courtney Shakowski, PharmD
Deborah Sherman, PharmD
Sarah Totten, Dr.PH, M(ASCP)

Notes