GUIDE TO ANTIMICROBIALS

San Francisco VA Medical Center

2017

Guide to Antimicrobials
2017

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Drug Category may be changed from time to time. Please consult the hospital computer for current classification. **Category I** agents are available without prior approval although some restrictions may apply. **Category II** agents are restricted and require approval prior to use. To obtain approval for a Category II agent, page digital beeper (415) 804-5982 prior to ordering.

Current antimicrobial sensitivity patterns and *UCSF/SFGH/VASF Guidelines for Antimicrobial Use in Adults* are available on the Antibiotic Stewardship Program page on Sharepoint (http://vaww.visn21.portal.va.gov/sanfrancisco/ic/SitePages/AntibioticStewardship.aspx).

Acknowledgments: Thanks to past and current staff of the Pharmacy Service and Infectious Diseases Section for preparing, compiling, and reviewing the materials contained in this pamphlet.

This material has been endorsed by the San Francisco VA Medical Center Infectious Diseases Section, and represents recommended Medical Center policy.

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Sensitivity Patterns of NON-URINE Isolates (First isolate per patient per organism)
San Francisco VA Medical Center **January-December 2016**
Confidential: For official use by San Francisco VA Medical Center Employees and Students only.

		Percent Sensitive							
ORGANISM	**TOTAL #ISO***	**AMP**	**ZOS**	**ERTA**	**CIP**	**T/S**	**CTRI**	**CPIM**	**GEN**
Enterobacter cloacae	23	**NA**	100	100	96	96	**NA**	**NA**	100
Escherichia coli †	61	39	90	100	74	59	87	87	87
Klebsiella pneumoniae †	35	0	94	100	97	86	94	94	94
Proteus mirabilis	19	63	100	100	84	84	68	68	95
Pseudomonas aeruginosa	51	**NA**	82	**NA**	90	**NA**	**NA**	90	90
				VANC	**OXAC**	**T/S**	**ERYT**	**CLIN**	**TCN**
Staphylococcus aureus	305			100	64	92	49	73	92
MRSA	110			100	0	93	**NA**	56	87
MSSA	195			100	100	92	**NA**	83	95
Staphylococcus **coag neg**	223			100	58	71	44	65	86

NA = not available

AMP - ampicillin, ZOS - Zosyn, ERTA - ertapenem, CIP - ciprofloxacin, T/S - trimethoprim/sulfamethoxazole, CZOL - cefazolin, CTRI - ceftriaxone, CPIM - cefepime
ERTA - ertapenem, GEN - gentamicin, TOB - tobramycin, VANC - vancomycin, OXAC - oxacillin, ERYT - erythromycin, CLIN - clindamycin, TCN - tetracycline
*Statistical validity of % susceptible is decreased if fewer than 30 isolates are tested.
7.8% (33/424) of all enterococcal isolates were vancomycin-resistant
†Extended-Spectrum Beta-Lactamase (ESBL) Positive - *E. coli - 13%; K. pneumoniae - 6%*

Sensitivity Patterns of URINE Isolates (First isolate per patient per organism)
San Francisco VA Medical Center **January-December 2016**
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		Percent Sensitive				Percent Sensitive				
ORGANISM	**TOTAL #ISO***	**AMP**	**AUG**	**CEPH**	**CTRI**	**CIP**	**GEN**	**NITR**	**T/S**	**TCN**
Enterobacter cloacae	23	**NA**	**NA**	**NA**	**NA**	100	100	87	91	91
Escherichia coli †	326	52	92	77	91	74	89	99	71	75
Klebsiella oxytoca †	24	0	79	62	96	100	100	100	100	100
Klebsiella pneumoniae †	93	0	99	93	94	96	96	92	90	88
Morganella morganii	21	5	5	0	95	86	86	5	81	0
Proteus mirabilis	86	0	100	76	79	85	95	0	74	0
Pseudomonas aeruginosa	51	**NA**	**NA**	**NA**	**NA**	88	92	**NA**	**NA**	**NA**
						OXAC	**VANC**	**NITR**	**T/S**	**TCN**
Staphylococcus aureus	55					69	100	100	95	91
Staphylococcus **coag neg**	178					57	100	100	71	81

NA = not available

AMP - ampicillin, AUG - amoxicillin/clavulanate, CEPH - cefazolin, CTRI - ceftriaxone, CIP - ciprofloxacin, GEN - gentamicin, NITR - nitrofurantoin, TCN - tetracycline, T/S - trimethoprim/sulfamethoxazole, OXAC - oxacillin, VANC - vancomycin

*Statistical validity of % susceptible is decreased if fewer than 30 isolates are tested.

7.8% (33/424) of all enterococcal isolates were vancomycin-resistant

†Extended-Spectrum Beta-Lactamase (ESBL) Positive - *E. coli - 8%; K. oxytoca - 4%; K. pneumoniae - 6%*

Prepared by D. Maddix, Pharm.D. 1/08/2017

San Francisco VA Medical Center Guidelines for the Use of Antimicrobial Agents in Febrile Neutropenic Cancer Patients

DEFINITIONS

Fever: A single oral temperature > 38.3ºC (101ºF); or > 38.0ºC (100.4ºF) over at least 1 hour
Neutropenia: ANC < 500/mm^3 or predicted decline to < 500/mm^3 during the next 48 hours

INITIAL ANTIMICROBIAL THERAPY

Cefepime 2 gm IV q8h

or

Piperacillin/tazobactam (Zosyn) 4.5gm IV q6h

Note: Infectious Diseases consultation is recommended for patients with severe penicillin allergy (i.e., anaphylactic shock, bronchospasm, or hives)

Consider including **vancomycin** in the initial regimen in patients with:

a) pneumonia documented radiographically
b) serious catheter-related infection
c) hemodynamic instability or other evidence of severe sepsis
d) colonization with MRSA or penicillin-resistant pneumococci
e) a preliminary blood culture with gram-positive bacteria
f) skin or soft-tissue infection

Vancomycin should be discontinued if cultures are negative after 48-72 hours

TREATMENT OF PATIENTS WITH PERSISTENT FEVER DURING THE FIRST 3-5 DAYS OF THERAPY

(Patients should be reassessed on days 4-5)

a) continue the initial antibiotic regimen in otherwise stable patients
b) documented infections should be treated with antibiotics appropriate for the site of infection and susceptibilities of isolated organisms
b) add **vancomycin** in patients with progressive disease if not included in initial regimen
c) add **tobramycin** in patients with progressive disease if not included in initial regimen
d) add **amphotericin B** (0.6- 1 mg/kg IV q24h), **micafungin** (100 mg IV daily), or **voriconazole** (6mg/kg IV q12h x 2 doses, then 4mg/kg IV q12h) if febrile through days 4-7 and neutropenia is expected to persist > 10 days

DURATION OF THERAPY

	ANC ≥ 500/mm^3	ANC < 500/mm^3
Afebrile by days 3-5	Stop 48 hours after afebrile and ANC ≥ 500/mm^3	Low risk (clinically well and no evidence of infection): Stop when afebrile for 5-7 days High risk: (ANC < 100/mm^3, mucositis, unstable vital signs): Continue antibiotics
Persistent fever	Stop 4-5 days after ANC ≥ 500/mm^3 and reassess	Continue antibiotics for at least 7 days or ideally until ANC > 500 or suspected source treated (if patient is high risk). . Consider switch to oral ciprofloxacin + amoxiciliin/clavulanate or can d/c antibiotics if afebrile for > 7 days (if patient low risk).

Adapted from: Freifeld AG, et al. Clinical practice guidelines for the use of antimicrobial agents in neutropenic patients with cancer: 2010 update by the. Infectious Diseases Society of America. Clin Infect Dis 2011;52:e56-e93.

San Francisco VA Medical Center Guidelines for the Use of Antimicrobial Agents in the Prevention of Bacterial Infection in Cirrhotic Patients

I. Prevention of Bacterial Infection in Cirrhotic Patients with Gastrointestinal Bleeding

Rationale: Approximately 50 percent of cirrhotic patients, including patients without ascites, with gastrointestinal bleeding become infected during hospitalization.[1] Bacterial infections including spontaneous bacterial peritonitis (SBP) are a major risk for rebleeding and are associated with failure to control variceal bleeding during the first 5 days of hospitalization.

Efficacy: A meta-analysis of 5 clinical trials demonstrated that antibiotic prophylaxis results in significantly fewer infections and increased survival (see table).[2] One study utilized oral, non-absorbable antibiotics (gentamicin/vancomycin/nystatin or neomycin/colistin/nystatin). The remaining studies involved fluoroquinolones alone or in combination with amoxicillin/clavulanic acid. Two of the studies initiated therapy by the parenteral route followed by oral administration. Another study showed that ceftriaxone 1 gm IV q24h was more effective than oral norfloxacin in patients with two or more of the following: malnutrition, ascites, encephalopathy, or serum bilirubin >3 mg/dl.[3]

	Prophylaxis Group	Control Group
Mean percentage of patients free of infection	86%	55%
Mean percentage of patients free of SBP and/or bacteremia	92%	73%
Mean percentage of patients free of SBP	95%	87%
Survival rate	85%	76%

Recommendation: Ciprofloxacin 500 mg orally twice daily for 3-7 days (Infectious Diseases Section approval required for inpatients). Patients who are unable to take oral medications (bleeding, NG tube, intubated, etc.) should receive intravenous ciprofloxacin 400 mg every 12 hours for the first day or two. Ceftriaxone 1 gm IV q24h should be considered for patients with at least 2 of the following: malnutrition, ascites, encephalopathy, or serum bilirubin >3 mg/dl. The presence of infection should be excluded prior to the initiation of prophylaxis.

II. Prevention of Spontaneous Bacterial Peritonitis in Cirrhotic Patients with Ascites

Rationale: Cirrhotic patients with ascites and total ascitic fluid protein concentration < 1 g/dL are at increased risk of developing SBP. Some studies have indicated that the 1-year probability of developing SBP is as high as 40% in this population, but these studies did not include patients who received short-term prophylaxis following GI bleeding. Utilization of short-term prophylaxis following episodes of GI bleeding reduces the 1-year probability of developing SBP to 20%.[1] Cirrhotic patients with ascites and total ascitic fluid protein concentration > 1 g/dL are at virtually no risk of developing SBP as long as they receive short-term antibiotic prophylaxis following episodes of GI bleeding.

The 1-year probability of developing SBP in cirrhotic patients with previous episodes of SBP is 40-70%.

Efficacy[1]: Norfloxacin 400 mg/day reduced the 1-year probability of developing SBP from 68% to 20% in patients with a history of SBP. In hospitalized patients with low ascitic fluid protein, including some with a previous history of SBP, norfloxacin 400mg/day reduced the development of SBP from 22% to 0% during hospitalization. In a primary prophylaxis study,

norfloxacin 400 mg/day reduced the 6-month probability of developing SBP from 9% to 0%, but the risk of gram-negative bacillary SBP was not significantly reduced. Ciprofloxacin 750 mg once weekly reduced the 6-month probability of developing SBP from 22% to 3.6% in patients with low ascitic fluid protein, but only 2 of 28 patients treated with ciprofloxacin had a previous history of SBP.[4] Patients treated with ciprofloxacin also experienced a significant reduction in duration of hospitalization. Trimethoprim-sulfamethoxazole double-strength tablet administered daily for 5 days each week reduced the rate of SBP from 30% to 3% in patients with cirrhosis and ascites.[5] There was also a trend toward reduced mortality. Eight of 30 patients treated with trimethoprim-sulfamethoxazole had a previous history of SBP. Norfloxacin 400mg/day was evaluated in a placebo-controlled study that included patients with cirrhosis and low (< 1.5 g/L) ascites protein who also had advanced liver failure (Child-Pugh score $\geq$ 9 with serum bilirubin $\geq$ 3 mg/dL) or renal dysfunction (serum creatinine ≥ 1.2 mg/dL, BUN ≥ 25 mg/dL, or serum sodium level ≤ 130 mEq/L). A reduction in the 1-year probability of SBP (7% vs. 61%), hepatorenal syndrome (28% vs. 41%), and 3-month mortality was noted.[6] Fluoroquinolone prophylaxis increases the risk of development of gram-positive SBP and infections with antibiotic resistant gram-negative bacteria.

Recommendation:

Primary Prophylaxis
Preferred regimen: ciprofloxacin 250 mg orally daily in patients with cirrhosis and low ascites protein (< 1.5 g/L) who have either advanced liver failure or renal dysfunction as defined by Fernández et al.[5]

Secondary Prophylaxis
Preferred regimen: ciprofloxacin 250-500 mg orally daily
Alternative: trimethoprim-sulfamethoxazole 1 double-strength tablet daily

References:

1. Rimola A, Garcia-Tsao G, Navasa M, et al. Diagnosis, treatment and prophylaxis of spontaneous bacterial peritonitis: a consensus document. International Ascites Club. J Hepatol 2000;32:142-53.
2. Bernard B, Grange JD, Khac EN, et al. Antibiotic prophylaxis for the prevention of bacterial infections in cirrhotic patients with gastrointestinal bleeding: a meta-analysis. Hepatology 1999;29:1655-61.
3. Fernandez J, Ruiz del Arbol L, Gomez C, et al. Norfloxacin vs ceftriaxone in the prophylaxis of infections in patients with advanced cirrhosis and hemorrhage. Gastroenterology 2006;131:1049-56.
4. Rolachon A, Cordier L, Bacq Y, et al. Ciprofloxacin and long-term prevention of spontaneous bacterial peritonitis: results of a prospective controlled trial. Hepatology 1995;22:1171-4.
5. Singh N, Gayowski T, Yu, VL, Wagener MM. Trimethoprim-sulfamethoxazole for the prevention of spontaneous bacterial peritonitis in cirrhosis: a randomized trial. Ann Intern Med 1995;122:595-8.
6. Fernández J, Navasa M, Planas R, et al. Primary prophylaxis of spontaneous bacterial peritonitis delays hepatorenal syndrome and improves survival in cirrhosis. Gastroenterology 2007;133:818-24.

San Francisco VA Medical Center Guidelines for the Empiric Therapy of Community Acquired Pneumonia and Urinary Tract Infections

I. Community-Acquired Pneumonia (CAP)

Patient Location	Therapy
Outpatients*	Doxycycline 100 mg PO q12h
Medical Ward	Ceftriaxone 1 gm IV q24h & Doxycycline 100 mg PO q12h
Medical Ward, severe penicillin allergy	Levofloxacin 750 mg PO daily
ICU, no *Pseudomonas* risk†	Ceftriaxone 1 gm IV q24h & Azithromycin 500 mg IV/PO q24h
ICU, *Pseudomonas* risk†	Zosyn 4.5 gm IV q6h & Levofloxacin 750 mg IV q24h#
Inpatients with CA MRSA risk‡	Vancomycin 15 mg/kg IV q8h added to appropriate regimen listed above
ICU, severe penicillin allergy	Aztreonam 2 gm IV q8h & Levofloxacin 750 mg IV q24h# ± Vancomycin 15 mg/kg IV q8h
NHCU, mild to moderate	Levofloxacin 750 mg PO daily#
NHCU, hospitalization required	Doxycycline 100 mg PO/IV q12h & Zosyn® 4.5 gm IV q8h

*__Amoxicillin__ 1 gm PO tid may be added in patients at risk for drug-resistant *S. pneumoniae* (e.g., comorbidities, immunosuppression, β-lactam therapy in the past 3 months). **Levofloxacin** 750 mg PO daily may be used in patients failing doxycycline or with a history of allergy to tetracyclines

†Risk factors include advanced HIV, bronchiectasis, and nursing home transfers

‡ Risk factors for community-acquired methicillin-resistant *Staphylococcus aureus* include end-stage renal disease, injection drug abuse, prior influenza, prior respiratory MRSA colonization, and prior antibiotic therapy

#Infectious Diseases Section approval required

Duration of Therapy: Patients with CAP should be treated for a minimum of 5 days, should be afebrile for 48 – 72 hours, and clinically stable prior to discontinuation of antibiotic therapy.

Recommendations for Patients with Suspected Influenza: Obtain nasopharyngeal swabs for influenza antigen testing and respiratory virus DFA; if patients are hospitalized place patient on droplet precautions until tests are negative, and treatment with oseltamivir 75 mg PO bid for 5 days (reduce dose in renal insufficiency). ICU patients, immunocompromised patients, and obese patients may require higher doses and/or prolonged therapy.

II. Urinary Tract Infections

The resistance of urinary isolates of *Escherichia coli* has increased. Over 27% of isolates were resistant to quinolones, cotrimoxazole, and ampicillin. Susceptibility testing should be reviewed for the presence of resistant organisms. Non-urine isolates of *E. coli* remain susceptible to most beta-lactam antibiotics, aminoglycosides, and quinolones. The following table lists recommended empiric therapy for urinary tract infections. **Susceptibility test results should be used to modify therapy.** Patients with recurrent or relapsing UTIs should be referred to Urology for further evaluation.

Urinary Tract Infection	Empiric Therapy
Febrile UTIs requiring hospitalization (e.g., pyelonephritis, acute bacterial prostatitis*)	Ceftriaxone or ertapenem1 gm IV q24h for 14 days If severely ill, recent hospitalization, or nursing home patient: Zosyn 4.5 gm IV q8h
Cystitis in men or catheter associated cystitis (no systemic toxicity)	Nitrofurantoin (Macrobid®) 100 mg PO bid (not if CrCl < 40ml/min) **OR** Augmentin 500 mg PO bid for at least 7 days
Asymptomatic bacteriuria	Treatment and cultures not generally recommended except in renal transplant or pregnant patients
Epididymitis, age > 35	Levofloxacin# 500 mg PO daily for 10 days Consider culture if no response in 3-4 days
Epididymitis age, < 35	Check GC, *Chlamydia* LCR Consider single dose Azithromycin 1 gm PO + Ceftriaxone 250 mg IM Obtain urine culture to rule out other uropathogens
Chronic bacterial prostatitis	Ciprofloxacin 500 mg PO bid for 4 weeks (if possible based upon results of antimicrobial sensitivities)

San Francisco VA Medical Center Guidelines for the Treatment of Diarrhea Associated with *Clostridium difficile* Infection

Diagnosis

- Presence of diarrhea (3+ unformed stools within 24 hours)
- A stool test* for the presence of *C. difficile* toxin, OR the presence of pseudomembranous colitis on colonoscopic or histopathologic exam
    - The stool sample sent to the lab must be diarrheal
    - If the patient has an ileus or clinical suspicion of toxic megacolon and no active diarrhea, a stool swab can be cultured or tested by toxin assay, but the lab must be notified.
    - Each patient is allowed a maximum of 1 toxin assay per week, given the high sensitivity of the test. Testing for cure is NOT recommended.
- Note that the majority of patients presenting with *C. difficile* colitis have a history of antibiotic use within the past 8 weeks, although this is not necessary to make the diagnosis.

*At VA, testing is for C. *difficile* toxin B by PCR

Classifying Severity of Disease

Mild/Moderate	WBC $\leq$ 15,000 **&** SrCr < 1.5x Premorbid level
Severe	WBC > 15,000 **OR** SrCr $\geq$ 1.5x Premorbid level
Severe, Complicated	Presence of hypotension, shock, ileus, or megacolon

Treatment Regimens - as determined by severity of disease

	Inpatient	Outpatient
Mild/Moderate	Vancomycin 125 mg PO q6h x10-14 days	Metronidazole 500mg PO Q8H x10-14 days
Severe	Vancomycin 125mg PO Q6H x10-14 days (needs ID approval for outpatients)	
Severe, Complicated (admit to hospital)	Vancomycin oral solution 500mg PO Q6H **AND** Metronidazole 500mg IV Q8H If ileus is present, consider Vancomycin 500mg in 100ml normal saline given as a retention enema Q6H. Therapy should be followed by a vancomycin taper (see below) ID or GI and surgical consultation should be obtained for severely ill patients.	
Recurrence, Prolonged IV antibiotic course, Hospitalized patients with severe liver disease on lactulose, or Hospitalized patients on chemotherapy	Treat with Vancomycin in a tapered regimen. 125mg PO Q6H x10-14 days, then 125mg PO Q12H x7 days, then 125mg PO daily x7days, then 125mg PO every other day x7 days then 125 mg every 3rd day x14 days Consider matching taper to length of antibiotic course	

Notes:

-Zar et al (CID 2007;45:302-7) showed that for patients with mild/moderate infection, treatment with metronidazole or vancomycin resulted in cure rates of 90% and 98%, respectively (p = 0.36). However, for patients with severe infection, treatment with metronidazole or vancomycin resulted in cure rates of 76% and 97%, respectively (p = 0.02). Of note, rates of clinical symptom recurrence were about 15%, regardless of disease severity or treatment regimen.

-If an inciting antimicrobial is suspected (most commonly clindamycin, aminopenicillins, third-generation cephalosporins, and flouroquinolones), discontinue the agent as soon as possible.

-The use of antiperistaltic agents (loperamide, etc.) should be avoided.

-If severe or complicated disease is suspected, initiate empiric treatment while awaiting assay results. If the assay is negative, use clinical judgment when deciding if therapy should be discontinued.

Fidaxomicin 200 mg PO q12h for 10 days may be considered in the following:1) patients with recurrence following a recent severe, complicated *C. difficile* episode, 2) vancomycin treatment failures[1], 3) patients with history of life-threatening vancomycin allergy. Infectious Diseases Section approval is required.

Points to Consider

-Use caution with high dose oral/rectal vancomycin (500mg Q6H) in patients with renal insufficiency, as significant absorption can occur in the setting of colitis and systemic accumulation could lead to ototoxicity, nephrotoxicity, or other adverse effects.

-Always wash hands with soap and water after examining a patient with suspected/confirmed *C. difficile*, as alcohol based sanitizers do NOT kill spores.

-Patients should remain on contact isolation until no diarrhea for 24 hours.

Adapted from: Cohen SH, et al. Clinical practice guidelines for *Clostridium difficile* Infection in Adults: 2010 update by the Society for Healthcare Epidemiology of America (SHEA) and the Infectious Diseases Society of America (IDSA). Infect Control Hosp Epidiol 2010;31:431-55.

[1] Defined as: persistence of symptoms after successful initial therapy

San Francisco VA Medical Center Guidelines for the Empiric Therapy of Skin and Soft Tissue Infections in Inpatients

Diagnosis	Common Pathogens	Empiric Therapy	Total Duration of Therapy	Possible oral step-down regimens
Abscess	*S. aureus*	Vancomycin 10-15mg/kg IV q12h (target trough of 10-15 mcg/ml)	5-10 days	Doxycycline 100 mg PO q12h or TMP/SMX 1-2 DS tablet PO q12h
Cellulitis	Beta-hemolytic streptococci including Group A streptococci, *S. aureus*	Vancomycin 10-15mg/kg IV q12h (target trough of 10-15 mcg/ml) OR Cefazolin 1 gm IV q8h if patient is stable and there is an absence of purulence	5 days, extend if **no** improvement within 5 days	Cephalexin 500 mg PO QID
Necrotizing fasciitis	Group A streptococci, *S. aureus,* Anaerobes, Enterobacteriaceae	Vancomycin 15-20mg/kg IV q8h-q12h (target trough of 15-20 mcg/ml) PLUS ONE OF Ertapenem 1 gm IV q24h OR Piperacillin/tazobactam 4.5 gm q6-8h ALL WITH Clindamycin 600-900 mg IV q8h	Dependent on source control & clinical improvement; Antibiotics are adjunctive; Consult ID	Not recommended
Diabetic foot infections*	*S. aureus* Enterobacteriaceae Anaerobes	Vancomycin 10-15mg/kg IV q12h (target trough of 10-15 mcg/ml) PLUS Ertapenem 1 gm IV q24h	Discontinue once signs & symptoms resolve, usually 7-14 days	Doxycycline 100 mg PO q12h or TMP/SMX 1-2 DS tablet PO q12h PLUS Levofloxacin 750 mg PO daily

*antipseudomonal therapy should be reserved for patients with risk factors including warm climate, frequent exposure of the foot to water, and prior documented infection due to *Pseudomonas aeruginosa*

DEPARTMENT OF

VETERANS AFFAIRS

Memorandum

Date: March 31, 2017

From: Pharmacy and Therapeutics Committee

Subj: Administration of ß-lactam antibiotics to penicillin-allergic patients

To: Physicians, Dentists, Nurses, and Pharmacists

This memorandum is intended to inform and remind health care providers about the policy for administering ß-lactam antibiotics to penicillin-allergic patients. Several patients with documented histories of serious allergic reactions to penicillin have recently received other penicillins or ß-lactam antibiotics. Such errors have frequently involved piperacillin-tazobactam (Zosyn).

1. Patients with histories of immediate type hypersensitivity reactions (e.g., anaphylaxis, hives) or other serious immune mediated reactions (e.g., Stevens-Johnson syndrome, serum sickness) to penicillin antibiotics shall not receive any other ß-lactam antibiotic with the exception of aztreonam. Penicillins shall not be administered to patients with less serious penicillin allergies (e.g., rash), but cephalosporins may be administered if appropriate.

2. If a physician determines that a patient's history of penicillin allergy is incorrect, the physician should document this fact in a progress note. The physician should also delete the allergy entry from the computerized medical record.

3. If Pharmacy Service receives an order for a ß-lactam antibiotic in a patient with a history of serious penicillin allergy, a pharmacist will contact the prescribing physician and inform him/her that the antibiotic cannot be dispensed. The pharmacist will ask the physician to order an alternative antibiotic. If the prescribing physician believes that there is no alternative antibiotic, then an Infectious Diseases consult is required. If the Infectious Diseases consultant determines that no alternative antibiotic exists (e.g., neurosyphilis), a desensitization protocol may be attempted for a patient with a history of immediate type hypersensitivity (IgE mediated). For a patient with a history of a non-IgE mediated serious penicillin allergy (e.g., Stevens-Johnson syndrome), a ß-lactam antibiotic cannot be safely administered under any circumstances.

4. If the Infectious Diseases consultant determines that a patient should undergo desensitization to penicillin or another ß-lactam, the patient must be admitted to the Intensive Care Unit. The consultant will recommend a specific desensitization protocol based upon the ß-lactam antibiotic that the patient will receive.

5. Piperacillin-tazobactam (Zosyn) will only be ordered by **generic name** to help reinforce that it is a penicillin. A reminder message has also been added to CPRS under the drug name.

Harry Lampiris, MD
Chief, Infectious Disease

David Daikh, MD, PhD
Chair, P&T Committee

Distribution: D

ACYCLOVIR

INDICATIONS

- **Drug of choice for treatment of infections caused by herpes simplex virus**
- **Drug of choice for treatment of infections caused by varicella-zoster virus**

ANTIVIRAL ACTIVITY

Acyclovir (ACV) is an acyclic nucleoside analogue of 2'-deoxyguanosine. Viral thymidine kinase phosphorylates ACV to its monophosphate derivative. ACV monophosphate is further phosphorylated to its active triphosphate form. ACV triphosphate is a competitive inhibitor of viral DNA polymerase. ACV has antiviral activity against herpes simplex virus (HSV) 1 and 2, Epstein-Barr virus, and varicella-zoster virus. The concentration of ACV required to produce 50% inhibition of viral cytopathic effect or plaque formation (ID_{50}) of HSV-2 is 0.027-0.36 µg/ml.

DOSING/PHARMACOKINETICS

INFECTION	DOSAGE REGIMEN	DURATION OF THERAPY
First episode genital herpes	200 mg PO 5 times/day or 400 mg PO tid	7-10 days
Recurrent genital herpes	400 mg PO tid	5 days
Suppressive therapy for recurrent genital herpes	400 mg PO bid	Up to 1 year
Herpes simplex encephalitis	10 mg/kg IV q8h	21days
Mucocutaneous herpes in immunocompromised host	5 mg/kg IV q8h or 400 mg PO 5 times/day	7 days
Herpes zoster in normal host	800 mg PO 5 times/day	7-10 days
Varicella or herpes zoster in immunocompromised host	10 mg/kg IV q8h	7 days

ADJUSTMENT OF ORAL DOSAGE REGIMENS IN PATIENTS WITH RENAL INSUFFICIENCY

USUAL DOSAGE	CREATININE CLEARANCE	ADJUSTED DOSAGE
200 mg PO 5 times/day	0-10 ml/min	200 mg PO q12h
800 mg PO 5 times/day	11-25 ml/min	800 mg PO q8h
800 mg PO 5 times/day	0-10 ml/min	800 mg PO q12h

Adjustment of intravenous dosage regimens in patients with renal insufficiency

CREATININE CLEARANCE	% OF USUAL DOSE	DOSING INTERVAL (HOURS)
> 50 ml/min	100	8
26-50 ml/min	100	12
11-25 ml/min	100	24
≤ 10 ml/min	50	24

The oral bioavailability of ACV is 15 to 30 percent. The elimination half-life of ACV is 2.1 to 3.5 hours in patients with normal renal function. ACV is renally eliminated; therefore dosage adjustment is necessary in patients with renal insufficiency (see above). The drug is removed by hemodialysis, therefore doses should be administered following hemodialysis. Probenecid inhibits the renal tubular secretion of ACV. ACV is well-distributed to most body tissues and fluids. Cerebrospinal fluid levels are about 50 percent of serum levels. Peak serum levels of 0.3 to 1.0 µg/ml are achieved following oral administration of a 200 mg dose of ACV. A 5 mg/kg intravenous dose of ACV results in peak levels of approximately 10 µg/ml. Parenteral ACV should be infused intravenously over one hour.

DRUG	INTERACTION	MECHANISM
Probenecid	↓ acyclovir clearance	Inhibition of renal secretion
Theophylline	↑ theophylline levels	Inhibition of theophylline metabolism

FORMULARY STATUS

Acyclovir is a **CATEGORY I (Formulary)** agent at San Francisco VA Medical Center.

AMIKACIN

INDICATION

•Treatment of **infections caused by amikacin-susceptible aerobic gram-negative bacilli resistant to gentamicin and tobramycin**

SPECTRUM

Amikacin is an aminoglycoside antibiotic with bactericidal activity against most aerobic gram-negative bacilli and gram-positive cocci. Amikacin is active against most gentamicin-resistant and tobramycin-resistant gram-negative rods. Like other aminoglycosides, amikacin lacks anaerobic activity. Organisms with an MIC ≤ 16 µg/ml are considered sensitive, while organisms with an MIC ≥ 64 µg/ml are considered resistant.

DOSING/PHARMACOKINETICS

Traditional dosing

Therapeutic **peak** and **trough** amikacin serum levels are **20 to 30 µg/ml** and **4 to 10 µg/ml**, respectively. In order to obtain the most useful information, serum levels of aminoglycosides should be drawn after the third or fourth dose. Peak serum levels of aminoglycosides should be drawn 30 minutes after the end of infusion, while trough levels should be drawn immediately before the next maintenance dose. The following nomograms may be used to calculate initial loading and maintenance doses for patients receiving amikacin. The nomograms should not be used in hemodialysis patients, obese patients, or patients with significant third-spacing. Serum levels should be used to make further dosage adjustments.

Loading Dose*	Expected Peak Serum Level
7.5 mg/kg	30 µg/ml
7 mg/kg	28 µg/ml
6 mg/kg	24 µg/ml
5 mg/kg	20 µg/ml
4 mg/kg	16 µg/ml

*Select loading dose based on ideal body weight (IBW) to provide desired peak serum level.
(Hull JH, Sarubbi FA. Ann Intern Med 1976;85:183-9.)

Creatinine Clearance (CrCl) (Males) = $\frac{(140\text{-age}) \times \text{IBW}}{72 \times \text{serum creatinine}}$

CrCl (Females) = 0.85 x Male value

Maintenance dose as a percentage of loading dose required for dosage interval selected

CrCl (ml/min)	8 Hours	12 Hours	24 Hours
90	**84%**	-	-
80	**80%**	91%	-
70	**76%**	88%	-
60	**71%**	84%	-
50	**65%**	79%	-
40	57%	**72%**	92%
30	48%	**63%**	86%
25	43%	**57%**	81%
20	37%	**50%**	75%
17	33%	**46%**	70%
15	31%	42%	**67%**
12	27%	37%	**61%**
10	24%	34%	**56%**
7	19%	28%	**47%**
5	16%	23%	**41%**
2	11%	16%	**30%**
0	8%	11%	**21%**

(Bold areas indicate suggested dosage intervals)

The plasma elimination half-life of amikacin is usually 2-3 hours in patients with normal renal function and ranges from 24-60 hours in adults with severe renal impairment. Significant amounts of amikacin are removed during hemodialysis, therefore a supplemental dose is necessary after dialysis.

Once-Daily Dosing

Dose-dependent bacterial killing and a relatively long postantibiotic effect against most gram negative rods make once-daily aminoglycoside dosing a viable alternative to traditional aminoglycoside dosing. Most studies have shown similar efficacy with similar to less nephrotoxicity as compared to traditional aminoglycoside therapy. The recommended once-daily dose is 15 mg/kg based on ideal body weight. Obese patients (≥20% over IBW) should be dosed using obese dosing weight [IBW + 0.4(actual body weight-IBW)]. Once-daily, 15 mg/kg dosing should **not** be used for patients with an estimated creatinine clearance < 60 ml/min, treatment of endocarditis, or synergy against gram positive organisms. A serum trough level should be obtained prior to the second dose and should be undetectable. Peak levels are generally not recommended.

FORMULARY STATUS

Amikacin is a **CATEGORY II (restricted)** agent at San Francisco VA Medical Center. This drug will not be dispensed by pharmacy without prior approval by the Infectious Diseases Section.

AMOXICILLIN/CLAVULANIC ACID (AUGMENTIN®)

INDICATIONS

- Treatment of infections caused by **ß-lactamase producing strains of *Haemophilus influenzae***
- Treatment of **acute bacterial rhinosinusitis**
- Treatment of **cystitis or catheter-associated cystitis** in patients without systemic toxicity
- Treatment of **infected human, cat, or dog bites**

SPECTRUM

Augmentin® is a fixed combination of amoxicillin and the ß-lactamase inhibitor clavulanic acid. In combination with amoxicillin, clavulanate expands the spectrum of activity of the ß-lactam against many strains of ß-lactamase producing bacteria, including *S. aureus, H. influenzae, B. catarrhalis,* and *E. coli.* Augmentin® also has activity against anaerobes including *Clostridium, Peptococcus*, and many strains of *Bacteroides fragilis*. It is not active against *Serratia, E. cloacae, Pseudomonas sp.* or *Providencia.* Gram-negative aerobes with an MIC of amoxicillin/clavulanic acid $\leq$ 8/4 µg/ml are considered sensitive, while organisms with an MIC $\geq$ 32/16 µg/ml are considered resistant.

DOSING/PHARMACOKINETICS

CREATININE CLEARANCE (ML/MIN)	DOSE*	FREQUENCY
> 30	250-500 MG OR 500-875 MG	Q8H Q12H
10-30	250-500 MG	Q12H
< 10	250-500 MG	Q24H†

*****Dosage of Augmentin® is generally expressed in terms of the amoxicillin content
†Hemodialysis patients should be given an additional dose at the end of dialysis.

Both amoxicillin and clavulanic acid have an elimination half-life of about 1 hour. Serum concentrations of Augmentin® are higher and half-lives are prolonged in patients with renal impairment, therefore dosage adjustment is necessary (see above). Peak serum concentrations are achieved within 1-2 hours after oral administration. Peak serum levels following administration of amoxicillin, 250 mg, and clavulanic acid, 125 mg, are 3.7-4.8 µg/ml and 2.2-3.5 µg/ml, respectively.

DRUG INTERACTION

DRUG	INTERACTION	MECHANISM
Methotrexate	↑ methotrexate levels & toxicity	↓ renal tubular secretion of methotrexate

FORMULARY STATUS

Augmentin® is a **CATEGORY I (Formulary)** antibiotic at San Francisco VA Medical Center.

AMPHOTERICIN B

INDICATIONS

- Treatment of patients diagnosed with **progressive and/or potentially fatal fungal infections**
- T**reatment of pulmonary and disseminated infections caused by the following organisms**: *Aspergillus*, *Blastomyces*, *Candida* spp., *Coccidioides*, *Cryptococcus*, *Histoplasma*, and the causative agents of mucormycosis
- As **an addition to empiric treatment** in **febrile, neutropenic cancer patients** who fail to respond to initial antibacterial therapy

SPECTRUM

Amphotericin B is a polyene macrolide antifungal agent with fungistatic and fungicidal activity depending on serum concentration and organism sensitivity. It is active against *Aspergillus spp., Paracoccidioides brasiliensis, Coccidioides immitis, Cryptococcus neoformans, Histoplasma capsulatum, Sporothrix schenckii, Mucor mucedo*, *Rhodotorula* spp., *Candida* spp., and *Blastomyces dermatitidis*. Amphotericin B is also active against some protozoa including *Leishmania* spp. and *Naegleria*.

DOSING/PHARMACOKINETICS

Amphotericin B is administered as a single daily dose infused over 4-6 hours. Daily doses range from 0.25-1.5 mg/kg and are determined by the pathogen being treated and the severity of illness. It is not necessary to administer a test dose or to increase the dose gradually over a prolonged period of time.

The elimination half-life of amphotericin B is approximately 24-48 hours. Following long term administration, the half-life increases to 15 days. The metabolic disposition of amphotericin B is unknown; 2-5% of the drug is excreted unchanged in the urine. Blood levels do not appear to be influenced by renal or hepatic failure; therefore dosage adjustments are usually not necessary. Amphotericin B is highly protein bound and is not removed by hemodialysis. Average peak concentrations of 1.0 µg/ml are achieved with a 30 mg dose.

ADVERSE REACTIONS

Eighty percent of patients experience renal and electrolyte abnormalities, e.g., elevated BUN and serum creatinine (SCr), RTA, nephrocalcinosis, hypomagnesemia, and hypokalemia. If SCr > 3 mg/dl, the amphotericin B dose should be decreased or may be discontinued for 24-48 hours and restarted at half doses. Sodium loading with a liter of normal saline may minimize nephrotoxicity. Nephrotoxic drugs and drugs that cause electrolyte imbalances should be avoided. Nephrotoxicity is usually reversible unless the total dose exceeds 4-6 grams. Dose related headache, fever, chills, malaise, muscle/joint pain, and GI disturbances are also common. Infusion-related reactions begin 1-2 hours after the start of infusion and usually subside with continued treatment. These reactions are believed to be PGE_2 mediated. Ibuprofen 10 mg/kg orally 30 minutes before amphotericin B infusion and hydrocortisone 25 mg IV before infusion are the only agents shown to be effective in preventing infusion reactions. Rigors can be treated with 25-50 mg of parenteral meperidine. The addition of 500-1000 units of heparin to the IV amphotericin B bag may reduce the incidence of phlebitis/thrombophlebitis.

DRUG INTERACTIONS

DRUG	INTERACTION	MECHANISM
Foscarnet	↑ nephrotoxicity & electrolyte abnormalities	Additive effects
Nephrotoxic Drugs	↑ nephrotoxicity	Additive effects

FORMULARY STATUS

Amphotericin B is a **CATEGORY II (restricted)** agent at San Francisco VA Medical Center. This drug will not be dispensed by pharmacy without prior approval by the Infectious Diseases Section.

ATOVAQUONE

INDICATION

•**Treatment of mild to moderate *Pneumocystis jirovecii* pneumonia** (PCP) **(PaO_2 > 60 mm Hg and A-a[DO_2] ≤ 45 mm Hg)** in AIDS patients who are intolerant of trimethoprim-sulfamethoxazole (TMP-SMX), primaquine-clindamycin, and trimethoprim-dapsone.
Note: In the double-blind study that compared atovaquone to oral TMP-SMX, the mortality rate was significantly higher in the atovaquone treated group (8% versus 2%).

•**Prophylaxis of *Pneumocystis carinii* pneumonia** in AIDS patients who are intolerant of trimethoprim-sulfamethoxazole (TMP-SMX), aerosolized pentamidine, and dapsone.

IN VITRO AND IN VIVO ACTIVITY

Atovaquone, a hydroxynaphthoquinone derivative, is an antiprotozoal agent. The drug has in vitro and in vivo activity against *P. jirovecii*, *Toxoplasma gondii*, and *Plasmodium* species. The median inhibitory concentration (IC_{50}) against *P. jirovecii* is 0.5 to 3.0 µg/ml. The exact mechanism of action of atovaquone against *P. jirovecii* is unknown, but it may interfere with electron transport and ATP synthesis.

DOSING/PHARMACOKINETICS

The recommended dose of atovaquone suspension for the treatment of PCP is **750 mg orally with food twice daily (BID) for 21 days**. The recommended dose of atovaquone for the prophylaxis of PCP is 1500 mg orally with food once daily or 750 mg twice daily. The drug **must be administered with food** in order to ensure adequate absorption. **Atovaquone should not be given to patients with gastrointestinal disorders that may limit absorption of orally administered drugs**. Following the oral administration of atovaquone 750 mg twice daily to a group of AIDS patients with PCP, the mean steady state peak serum level was 13.9 µg/ml. Over 99.9% of atovaquone is bound to plasma protein. The drug is eliminated unchanged in the feces. Its elimination half-life is approximately 2 to 3 days. The drug has not been studied in patients with renal or hepatic insufficiency.

ADVERSE REACTIONS

Atovaquone is reasonably well tolerated. Side effects that resulted in the discontinuation of atovaquone occurred in less than ten percent of patients in clinical trials. In the double-blind trial that compared atovaquone to TMP-SMX in the treatment of PCP, the following side effects were reported in patients who received atovaquone: rash (23%), pruritus (5%), fever (14%), nausea (21%), vomiting (14%), diarrhea (19%), abdominal pain (4%), constipation (3%), headache (16%), insomnia (10%), asthenia (8%), dizziness (3%) thrush (5%), anemia (5%), neutropenia (3%), elevated liver function tests (8%), elevated amylase (7%), and hyponatremia (7%). Other adverse reactions reported during atovaquone therapy include cough, pain, anxiety, anorexia, dyspepsia, sinusitis, rhinitis, and elevated creatinine.

DRUG INTERACTIONS

DRUG	INTERACTION	MECHANISM
Efavirenz	↓ atovaquone levels	↑ atovaquone metabolism
Indinavir	↓ indinavir trough levels	Unknown
Metoclopramide	↓ atovaquone levels	↓ atovaquone bioavailability
Rifabutin	↓ atovaquone & rifabutin levels	Unknown
Rifampin	↓ atovaquone levels	Unknown
Ritonavir	↓ atovaquone levels	↑ atovaquone metabolism
Tetracycline	↓ atovaquone levels	Unknown
Zidovudine (AZT)	↑ AZT levels	↓ glucuronidation of AZT

FORMULARY STATUS

Atovaquone is a **CATEGORY II (restricted)** agent at San Francisco VA Medical Center. This drug will not be dispensed by pharmacy without prior approval by the Infectious Diseases Section.

AZTREONAM

INDICATION

- Treatment of serious **aerobic gram-negative** bacillary infections in patients with a history of **severe** (e.g.., anaphylaxis, hives, Stevens-Johnson syndrome) **allergic reactions to other β-lactam antibiotics** with the exception of ceftazidime

SPECTRUM

Aztreonam is a monobactam antibiotic with bactericidal activity against most aerobic gram-negative bacteria. The bactericidal action of aztreonam results from the inhibition of bacterial cell wall synthesis due to a high affinity of aztreonam for penicillin binding protein 3 (PBP3). Susceptible bacteria include *Klebsiella, E. coli, Proteus, Providencia,* and *Salmonella. Enterobacter*, *Serratia marcescens*, and *Citrobacter freundii* tend to be resistant to aztreonam. Resistance to the aforementioned organisms may not be detected by routine susceptibility testing methods; other agents are preferred when infections caused by these bacteria are suspected. Extended-spectrum beta-lactamase (ESBL) producing gram-negative bacilli are also resistant to aztreonam. Most strains of *Pseudomonas aeruginosa* are susceptible. **Aztreonam lacks activity against gram-positive bacteria and anaerobic organisms.** In polymicrobial infections, aztreonam must be given in combination with other antimicrobial agents that are active against these species. Enterobacteriaceae with an MIC $\leq$4 µg/ml are considered sensitive, while enterobacteriaceae with an MIC $\geq$16 µg/ml are considered resistant.

DOSING/PHARMACOKINETICS

CREATININE CLEARANCE (ML/MIN)	DOSAGE*	Frequency
> 30	1-2 gm IV (MAX 8 g/day)	q8h
10 – 30	0.5-1 gm IV	q8h
< 10	0.25-0.5 gm	q8h

*Hemodialysis patients with serious/life threatening infections should receive a supplemental dose of 50% of the maintenance dose after each hemodialysis session.

The elimination half-life of aztreonam ranges from 1.6 to 2.9 hours in patients with normal renal function. Aztreonam is eliminated renally, therefore dosage should be adjusted in patients with renal insufficiency (see above). Aztreonam is 56% to 72% protein bound with a volume of distribution of 0.1 to 0.2 L/kg. Peak serum levels of 204-255 µg/ml are achieved following a 30 minute infusion of a 2 gm dose of aztreonam.

FORMULARLY STATUS

Aztreonam is available for use in patients **with** a history of **severe** allergic reactions to beta-lactam antibiotics at San Francisco VA Medical Center. The use of aztreonam in patients **without** a history of severe allergic reactions to beta-lactam antibiotics requires prior approval from the Infectious Diseases Section.

CEFAZOLIN

INDICATIONS

•Treatment of methicillin susceptible **staphylococcal or streptococcal infections**
•Treatment of **infections caused by gram-negative bacilli that are cefazolin sensitive**
•Empiric treatment of **febrile community-acquired UTIs requiring hospitalization**
•**Antimicrobial prophylaxis for** patients undergoing **cardiac, vascular, orthopedic, head and neck, and upper GI tract surgery**
NOTE: Nafcillin is preferred for staphylococcal endocarditis and meningitis

SPECTRUM

Cefazolin is a first-generation cephalosporin with excellent activity against methicillin susceptible staphylococci and streptococci. Enterococci and nafcillin-resistant staphylococci are resistant to all cephalosporins. Cefazolin's gram-negative spectrum is primarily limited to *E. coli*, *Proteus mirabilis*, and *Klebsiella* sp. Enterobacteriaceae with an MIC $\leq$ 2 µg/ml are considered sensitive, while enterobacteriaceae with an MIC $\geq$ 8 µg/ml are considered resistant.

DOSING/PHARMACOKINETICS

CREATININE CLEARANCE (ML/MIN)	DOSE	FREQUENCY
$\geq$ 55	0.5-2 gm	q8h
35-54	0.5-1 gm	q8h-q12h
11-34	0.25-1 gm	q12h
$\leq$ 10	0.25-1 gm	q24h†

†For hemodialysis patients, give an additional 500 mg dose at the end of dialysis. Alternatively, 2 gm may be administered post-dialysis only to patients on a standard three times weekly dialysis schedule.

The elimination half-life of cefazolin is 1.5-2 hours in patients with normal renal function, which allows for q8h dosing. Cefazolin is eliminated renally, therefore dosage adjustment is required in patients with renal insufficiency (see above). The dose of 1 gm q8h is suitable for all indications except serious staphylococcal or gram-negative infections, e.g., endocarditis, osteomyelitis, bacteremia. When used as surgical prophylaxis, patients should receive a 2 gm doses within an hour prior to the incision and repeat doses every 4 hours during surgery if renal function is normal. Peak serum levels of 75-120 µg/ml are achieved following a 1 gm dose of cefazolin.

FORMULARY STATUS

Cefazolin is a **CATEGORY I (Formulary)** antibiotic at San Francisco VA Medical Center. Cefazolin cannot be dosed more frequently than every 8 hours without prior approval by the Infectious Diseases Section.

CEFEPIME

INDICATION

•Empiric therapy of infection in **febrile neutropenic cancer patients**
•Treatment of ***Pseudomonas aeruginosa* infections in penicillin-allergic patients** (except in patients with a history of penicillin induced anaphylaxis)
•**Infection due to *P. aeruginosa* or other gram-negative bacilli** that are **resistant to** other **formulary antibiotics**
•Empiric therapy of **ventilator-associated pneumonia in penicillin-allergic patients** (except in patients with a history of penicillin induced anaphylaxis)

SPECTRUM

Cefepime is a fourth-generation cephalosporin with a broad gram-negative and gram-positive spectrum. It is active against most gram-positive cocci with the exception of enterococci and methicillin-resistant staphylococci. Cefepime's activity against pneumococci, including penicillin-resistant strains, is comparable to ceftriaxone. Cefepime is also active against anaerobic gram-positive cocci and most *Clostridium* species. *Listeria monocytogenes*, *C. difficile*, and most gram-negative anaerobes are resistant to cefepime. Cefepime has excellent activity against aerobic gram-negative bacilli and *Neisseria* species. Its activity against Enterobacteriaceae that do not produce chromosomally mediated beta-lactamases (e.g., *E. coli, Klebsiella*) is comparable to ceftriaxone. Cefepime is active against many ceftriaxone-resistant organisms that produce chromosomally mediated beta-lactamases including *Enterobacter, Citrobacter freundii*, and *Serratia marcescens*. The anti-pseudomonal activity of cefepime is similar to ceftazidime. Piperacillin/tazobactam with or without an aminoglycoside is the antipseudomonal antibiotic regimen of choice in this institution. Cefepime has variable activity against *Acinetobacter* species. *Stenotrophomonas maltophilia, Burkholderia cepacia*, and *Ps. fluorescens* isolates are usually resistant. Enterobacteriaceae with an MIC $\leq$ 2 µg/ml are considered sensitive, while enterobacteriaceae with an MIC $\geq$ 16 µg/ml are considered resistant.

DOSING/PHARMACOKINETICS

CREATININE CLEARANCE (ML/MIN)	DOSE	DOSE FOR PSEUDOMONAS OR FEBRILE NEUTROPENICS*
> 60	1-2 gm q12h	2 gm q8h
30-60	1-2 gm q24h	2 gm q12h
11-29	0.5-1 gm q24h	2 gm q24h
< 11	0.25-0.5 gm q24h	1 gm q24h
Hemodialysis	1 gm on day 1 then 0.5 mg IV q24h†	1 gm q24h†

*Also for infections caused by enterobacteriaceae with an MIC of 4-8 mcg/ml
†should be administered following dialysis on dialysis days and at the same time each day Alternatively, 2 gm may be administered post-dialysis only to patients on a standard three times weekly dialysis schedule.

The elimination half-life of cefepime is 2 hours in patients with normal renal function. Cefepime is eliminated renally, therefore dosage should be adjusted in patients with renal insufficiency (see above). Peak serum levels of approximately 150 µg/ml are achieved following a 2 gm dose of cefepime.

FORMULARY STATUS

Cefepime is a **CATEGORY II (restricted)** antibiotic at San Francisco VA Medical Center. This drug will not be dispensed by pharmacy without prior approval by the Infectious Diseases Section or Hematology/Oncology Section.

CEFTAZIDIME

INDICATIONS

•Treatment of ***Pseudomonas aeruginosa*** **infections in penicillin-allergic patients** (except in patients with a history of penicillin induced anaphylaxis)
•***Pseudomonas aeruginosa*** **meningitis**

Note: Overuse of third-generation cephalosporins has been associated with an increase in vancomycin-resistant enterococci, *Clostridium difficile* infections, and resistant gram negative rods such as *Enterobacter, Klebsiella, Escherichia coli,* and *Citrobacter*.

SPECTRUM

Ceftazidime is a third-generation cephalosporin with a broad gram-negative spectrum including Enterobacteriaceae*, P. aeruginosa,* and *Hemophilus* species. Gram-positive and anaerobic activity is weaker than most other cephalosporins and penicillins. Enterobacteriaceae with an MIC $\leq$ 4 µg/ml are considered sensitive, while enterobacteriaceae with an MIC $\geq$ 16 µg/ml are considered resistant. Emergence of resistant strains of *P. aeruginosa, Escherichia coli, Enterobacter sp., Klebsiella sp.*, and *Citrobacter sp.* during ceftazidime therapy is a growing concern. The antipseudomonal activity of ceftazidime is similar to piperacillin. Piperacillin/tazobactam with or without an aminoglycoside is the antipseudomonal antibiotic regimen of choice in this institution.

DOSING/PHARMACOKINETICS

CREATININE CLEARANCE (ML/MIN)	DOSE	FREQUENCY
> 50	1-2 gm	q8h - q12h
31-50	1-1.5 gm	q12h
16-30	1-1.5 gm	q24h
6-15	0.5-0.75 gm	q24h
< 5	0.5-0.75 gm	q48h
Hemodialysis	1 gm	post-dialysis

The elimination half-life of ceftazidime is 1.5 to 2 hours in patients with normal renal function. The drug is dosed every 8 to 12 hours in these patients. Ceftazidime is eliminated renally, therefore dosage should be adjusted in patients with renal insufficiency (see above). Peak serum levels of 69-90 µg/ml are achieved following a 1 gm dose of ceftazidime.

FORMULARY STATUS

Ceftazidime is a **CATEGORY II (restricted)** antibiotic at San Francisco VA Medical Center. This drug will <u>not</u> be dispensed by pharmacy without prior approval by the Infectious Diseases Section.

CEFTRIAXONE

INDICATIONS

•Empiric therapy of **meningitis** in combination with vancomycin
•Treatment of **pneumococcal meningitis** caused by isolates that are **penicillin-resistant** and ceftriaxone-susceptible
•Treatment of **spontaneous bacterial peritonitis**
•Empiric therapy of **disseminated gonococcal infection**
•**Single-dose (250 mg) treatment** of urethral, cervical, rectal, or pharyngeal **gonorrhea** in combination with azithromycin 1 gm orally
•Treatment of ***Salmonella* enterocolitis in immunocompromised hosts**
•Empiric therapy of **community-acquired pneumonia (CAP) in patients admitted to medical wards** (in combination with doxycycline).
•Empiric therapy of **community-acquired pneumonia (CAP) in patients admitted to the ICU** (in combination with azithromycin
•**Home intravenous antibiotic therapy** in selected patients

Note: Overuse of third-generation cephalosporins has been associated with an increase in vancomycin-resistant enterococci, *Clostridium difficile* infections, and resistant gram negative rods such as *Enterobacter, Klebsiella, Escherichia coli,* and *Citrobacter*.

SPECTRUM

Ceftriaxone, a third generation cephalosporin, has broad activity against gram-negative bacteria. Susceptible bacteria include *Klebsiella, E. coli, Proteus, Providencia, Salmonella, Haemophilus*, *Moraxella catarrhalis,* and penicillinase-producing *N. gonorrhea. Enterobacter*, *Serratia marcescens*, and *Citrobacter freundii* tend to be resistant to ceftriaxone. Resistance to the aforementioned organisms may not be detected by routine susceptibility testing methods; other agents are preferred when infections caused by these bacteria are suspected. Most strains of *P. aeruginosa* are resistant. Ceftriaxone also has activity against *Streptococcus pneumoniae,* viridans streptococci, *Staphylococcus aureus,* and *Borrelia burgdorferi*. Penicillin-resistant pneumococci are often susceptible to ceftriaxone, but susceptibility should be confirmed for CSF isolates. Most *Bacteroides fragilis* isolates are resistant to ceftriaxone. Enterobacteriaceae with an MIC $\leq$ 1 µg/ml are considered sensitive, while organisms with an MIC $\geq$ 4 µg/ml are considered resistant.

DOSING/PHARMACOKINETICS

TYPE OF INFECTION	DOSE (GM)	FREQUENCY
Community-acquired pneumonia	1	q24h
Disseminated gonococcal infection	1	q24h
Gonorrhea	0.25	IM Once
Meningitis	2	q12h
Salmonella enterocolitis	1-2	q12h - q24h
Spontaneous bacterial peritonitis	1	q24h

The elimination half-life of ceftriaxone is 5-11 hours in patients with normal renal and hepatic function. Thirty-three to 67 percent of a dose is renally eliminated, the remainder is eliminated via the biliary tract. Dosage adjustment in patients with renal insufficiency is unnecessary unless concomitant biliary tract obstruction is present. Following a single 1 gram dose of ceftriaxone given by intravenous injection over 30 minutes, peak serum levels of 123-151 µg/ml are achieved. The serum protein binding of ceftriaxone is inversely proportional to the serum concentration. At a concentration of less than 70 µg/ml 93-96% of the drug is bound to plasma protein versus 84-87% at a concentration of 300 µg/ml.

FORMULARY STATUS

Ceftriaxone is a **CATEGORY I (Formulary)** agent at San Francisco VA Medical Center.

CIDOFOVIR

INDICATION

•Treatment of **cytomegalovirus (CMV) retinitis in patients with AIDS**

ANTIVIRAL ACTIVITY

Cidofovir (HPMPC) is a nucleotide analogue of deoxycytidine monophosphate. Unlike ganciclovir and acyclovir, cidofovir activity is not dependent on phosphorylation by virus-encoded enzymes. Cellular enzymes phosphorylate cidofovir to the active metabolite, cidofovir diphosphate. Cidofovir diphosphate selectively inhibits CMV DNA polymerase, decreasing the rate of viral DNA synthesis. In addition to its anti-CMV activity, cidofovir has *in vitro* and *in vivo* activity against herpes simplex virus type 1 and 2, varicella zoster virus, JC polyomavirus, and Epstein-Barr virus.

DOSING/PHARMACOKINETICS

CREATININE CLEARANCE	DOSAGE REGIMEN	
	INDUCTION	MAINTENANCE
> 55 ml/min	5 mg/kg IV q week x 2 weeks	5.0 mg/kg IV q 2 weeks
≤ 55 ml/min (or serum creatine > 1.5, or urine protein > 100 mg/dL)	**Contraindicated**	

Prehydration with normal saline and concurrent administration of probenecid with cidofovir have been shown to decrease the incidence of nephrotoxicity and must be administered with each cidofovir infusion. Patients should receive at least 1L of normal saline IV over 1-2 hours immediately prior to cidofovir infusion. Adequate fluid volume status must be ensured. If patients are able to tolerate a second liter of normal saline, they should receive a second liter (over 1-3 hours) at the start of or immediately after cidofovir infusion. Probenecid 2 gm PO should be administered three hours prior to cidofovir, then 1 gm PO two hours and eight hours after completion of the one hour cidofovir infusion (4 grams total probenecid). Pre-dose monitoring of creatinine and urinalysis within 48 hours prior to each cidofovir dose is essential. **Patients who experience a significant (0.3-0.4 mg/dL) increase in serum creatinine while receiving cidofovir should have their dose reduced to 3 mg/kg. Therapy must be discontinued in patients in whom there is an increase in serum creatinine of ≥ 0.5 mg/dL above baseline or with ≥ 3+ proteinuria. Cidofovir is contraindicated in patients with impaired renal function**.

The mean terminal half-life after intravenous administration of cidofovir is 2.6 +/- 1.2 hours. This fairly short half-life may not reflect the duration of antiviral activity since the phosphorylated metabolite of cidofovir is the active form of the drug. The intracellular half-life is reported to range from 17 to 65 hours. The steady-state cidofovir volume of distribution is approximately 500 ml/kg. Active tubular secretion appears to play a role in cidofovir clearance, since the mean total clearance of the drug from serum (148 +/- 25 ml/h/kg) is significantly higher than the baseline creatinine clearance (83 +/- 21 ml/h/kg).

ADVERSE REACTIONS

The most common adverse effects include proteinuria (48%), neutropenia (20%), creatinine elevation (≥ 0.4 mg/dL, 15%), fever (15%), and ocular hypotony (12%). Nephrotoxicity is the major dose limiting toxicity. Neutrophil counts should be monitored during cidofovir therapy. Uveitis, iritis, and hearing loss, with or without tinnitus, have also been reported.

DRUG INTERACTIONS

Due to the high incidence of nephrotoxicity, concurrent use of other nephrotoxic agents within 7 days prior to starting therapy should be avoided. Probenecid interferes with the metabolism or renal tubular secretion of many drugs (e.g., acetaminophen, acyclovir, ACE inhibitors, aminosalicylic acid, barbiturates, benzodiazepines, bumetanide, clofibrate, methotrexate, famotidine, furosemide, NSAIDs, theophylline, and zidovudine). Coadministration of these medications should be assessed, since probenecid must always be administered with cidofovir.

FORMULARY STATUS

Cidofovir is a **CATEGORY II (restricted)** antibiotic at San Francisco VA Medical Center. This drug will not be dispensed by pharmacy without prior approval by the Infectious Diseases Section.

CIPROFLOXACIN

INDICATIONS

•Treatment of **UTI's caused by ciprofloxacin-sensitive *Pseudomonas aeruginosa***
•Empiric therapy of **traveler's diarrhea**
•Treatment of chronic bacterial prostatitis
•Treatment of systemic infections caused by ciprofloxacin-susceptible gram-negative bacilli

Note: **Quinolone resistance** in *E. coli* **has dramatically increased**. Quinolones should not be used as empiric therapy for UTIs (see UTI guidelines). Given the risk for disabling and potentially irreversible adverse reactions (e.g., neuropathy, tendinitis), quinolones should not be used for uncomplicated UTIs, acute sinusitis, or acute exacerbations of chronic bronchitis except in patients with no alternatives. **QUINOLONE USE SHOULD BE MINIMIZED WHENEVER POSSIBLE.**

SPECTRUM

Ciprofloxacin is a fluoroquinolone antimicrobial agent with a broad gram-negative spectrum including Enterobacteriaceae*, Pseudomonas aeruginosa,* and *Haemophilus* species. Its gram-negative activity is comparable to levofloxacin. Ciprofloxacin is active against methicillin-susceptible staphylococci, but most methicillin-resistant strains are resistant. In general activity against streptococci and anaerobic organisms is poor and ciprofloxacin should not be used to treat infections caused by these organisms. Emergence of resistance has been reported frequently when ciprofloxacin has been used alone to treat serious infections caused by staphylococci and *Ps. aeruginosa.* Enterobacteriaceae with an MIC ≤ 1 µg/ml are considered sensitive, while Enterobacteriaceae with an MIC ≥ 4 µg/ml are considered resistant.

DOSING/PHARMACOKINETICS

CREATININE CLEARANCE (ML/MIN)	ORAL DOSAGE REGIMEN	PARENTERAL DOSAGE REGIMEN
> 30	250-750 mg q12h	400 mg q8h-q12h
11-29	250-500 mg q12h*	200-400 mg q12h
≤ 10 or Hemodialysis	500 mg q24h	400 mg q24h

The elimination half-life of ciprofloxacin is approximately 4 hours in patients with normal renal function. Accumulation occurs in patients with renal failure, therefore the dose should be adjusted according to the degree of renal insufficiency. Recommended dosing guidelines are listed above. The oral bioavailability of ciprofloxacin is 70 to 80 percent. Peak serum levels of 2.5 µg/ml are achieved following a 500 mg dose of ciprofloxacin, and peak urine levels of ≥ 200 µg/ml are achieved following a 250 mg dose. Following a single 400 mg dose of ciprofloxacin given by intravenous infusion over 60 minutes, peak serum levels of 4.6 µg/ml are achieved.

DRUG INTERACTIONS

DRUG	INTERACTION	MECHANISM
Amiodarone	↑ QT interval	Additive effects
Antacids, enteral nutrition, iron, calcium, sevelamer sucralfate, zinc	↓ ciprofloxacin absorption	
Clozapine	↑ clozapine levels	↓ clozapine metabolism
Corticosteroids	↑ risk of tendon rupture	
Diclofenac	↑ ciprofloxacin levels	Unknown
Dofetilide	↑ risk of arrhythmias	Additive effects
Duloxetine	↑ duloxetine levels	↓ duloxetine metabolism
Erlotinib	↑ erlotinib levels	↓ erlotinib metabolism
Lomitapide	↑ lomitapide levels	↓ lomitapide metabolism
Methadone	↑ methadone levels	↓ methadone metabolism
Methotrexate	↑ methotrexate levels & toxicity	Unknown
Oral hypoglycemic agents	↑ risk of hypoglycemia	Unknown
Phenytoin	↓ phenytoin levels	Unknown
Pomalidomide	↑ pomalidomide levels	↓ pomalidomide metabolism
Rasagiline	↑ rasagiline levels	↓ rasagiline metabolism
Ropinirole	↑ ropinirole levels	↓ ropinirole metabolism
Tizanidine	↑ tizanidine levels and toxicity	↓ tizanidine metabolism
Theophylline	↑ theophylline levels, ↑ risk of seizures	↓ theophylline metabolism, additive effects
Warfarin	↑ anticoagulant effect	↓ warfarin metabolism

FORMULARY STATUS

Oral ciprofloxacin is a **Category I (Formulary)** antibiotic at San Francisco VA Medical Center for outpatients. **Inpatient use** of oral or intravenous ciprofloxacin requires prior approval by the Infectious Diseases or GI Sections.

CLINDAMYCIN

INDICATIONS

•Treatment of **aspiration pneumonia in patients** who are **intolerant of penicillin or** who have **failed penicillin therapy**

•Treatment (in combination with primaquine) of **mild to moderate** *Pneumocystis carinii* pneumonia (**PCP**) (PaO_2 > 60 mm Hg) **in AIDS patients** who are **intolerant of trimethoprim-sulfamethoxazole and trimethoprim-dapsone**

•Treatment of **toxoplasmic encephalitis** (in combination with pyrimethamine and leucovorin) **in AIDS patients** who are **intolerant of sulfadiazine**

•Treatment (in combination with penicillin G) of **necrotizing fascitis or myositis caused by *Streptococcus pyogenes***

•Treatment of **community-acquired skin and soft tissue infections**

Note: Overuse of clindamycin has been associated with an increase in *Clostridium difficile* infections

SPECTRUM

Clindamycin is a bacteriostatic, lincosamide antibiotic that acts by binding to bacterial 50S ribosomal binding sites thereby inhibiting protein synthesis. Clindamycin is active against most non-enterococcal streptococci including pneumococci, *Streptococcus pyogenes*, and viridans streptococci. Most *Staphylococcus aureus* isolates are sensitive to clindamycin, although resistance to both methicillin-susceptible and methicillin resistant isolates is increasing. The drug is active against most anaerobic bacteria including *Prevotella spp.,*peptostreptococci, and *Clostridium perfringens*. Clindamycin is not recommended for serious infections caused by *Bacteroides* spp. because resistance has increased. *Eikenella* sp. and all aerobic gram-negative bacilli are resistant to clindamycin. Organisms with an MIC $\leq$ 0.5 µg/ml are considered sensitive, while organisms with an MIC $\geq$ 8 µg/ml are considered resistant.

DOSING/PHARMACOKINETICS

Clindamycin is principally metabolized by the liver. Only 10% of the drug is eliminated unchanged in the urine. The elimination half-life is 2.4-4 hours in patients with normal renal and hepatic function, but is prolonged to 7-14 hours in patients with severe liver disease. Dosage adjustment is necessary in the presence of concomitant severe renal and hepatic impairment. Clindamycin is not significantly removed by hemodialysis or peritoneal dialysis. Parenteral clindamycin phosphate is an inactive ester that is rapidly hydrolyzed in the blood to the active base. Approximately 90% of an oral clindamycin dose is absorbed. Food delays but does not reduce the absorption of clindamycin. Parenteral doses of 300-600 mg q8h and oral doses of 150-300 mg q8h are adequate to treat most infections caused by susceptible bacteria. A maximum parenteral dosage regimen of 600 mg q8h is recommended because no therapeutic advantage is found with either 600 mg q6h or 900 mg q8h. Peak serum levels following selected doses are listed in the following table:

DOSE	ROUTE	PEAK SERUM LEVEL
600 mg	IV	10-17 µg/ml
300 mg	oral	3-4 µg/ml

DRUG INTERACTIONS

DRUG	INTERACTION	MECHANISM
Kaolin-pectin	↓ peak clindamycin levels	Delayed clindamycin absorption
Neuromuscular-blocking agents	Clindamycin may enhance neuromuscular blockade	Additive effects

FORMULARY STATUS

Oral clindamycin is a **Category I (Formulary)** antibiotic in outpatients at San Francisco VA Medical Center. Inpatient use of oral or intravenous clindamycin by Services other than Oral Surgery and ENT requires prior approval by the Infectious Diseases Section.

DAPSONE

INDICATIONS

•**Treatment** (in combination with trimethoprim) **of mild to moderate *Pneumocystis jirovecii* pneumonia** (PCP) (PaO_2 > 60 mm Hg) **in patients** who are **intolerant of trimethoprim-sulfamethoxazole** [TMP- SMX]
•**Prophylaxis against PCP in patients** who are **intolerant of TMP-SMX**
•**Treatment of paucibacillary leprosy** (in combination with rifampin)
•**Treatment of multibacillary leprosy** (in combination with clofazimine and rifampin)
•**Prophylaxis of close contacts of patients with** multibacillary, lepromatous, or borderline **leprosy**
•Drug of choice for **treatment of dermatitis herpetiformis**

SPECTRUM

Dapsone is a sulfone that usually exerts bacteriostatic activity against susceptible organisms. The mechanism of action of dapsone is probably similar to that of the sulfonamides (inhibition of dihydropteroate synthetase, the enzyme responsible for the conversion of para-aminobenzoic acid [PABA] to dihydropteroate, the immediate precursor of dihydrofolate [folic acid]. Dapsone is active against *Mycobacterium leprae*, *M. tuberculosis*, and several other species of mycobacteria. Dapsone has some activity against *P. jirovecii***,** *Toxoplasma gondii*, **and** *Plasmodium* species. Inhibitory concentrations against susceptible strains of *M*. *leprae* are 1-10 ng/ml.

DOSING/PHARMACOKINETICS

The recommended dose of dapsone for the **treatment or prophylaxis of PCP** is **100 mg daily**. When used to treat PCP, dapsone must be used in combination with TMP (15 mg/kg/day in 3 divided doses) for 21 days. TMP increases dapsone levels by 40% and dapsone increases TMP levels by nearly 50%. Following oral administration, dapsone is completely absorbed. Peak serum levels occur 2 to 8 hours after ingestion. Steady-state peak dapsone levels of 0.9-2.3 µg/ml are achieved following administration of 100 mg daily. Dapsone is distributed widely into most body tissues and fluids; 50-80% is protein bound. The volume of distribution is 1.5-2.5 L/kg. Dapsone undergoes acetylation by liver enzymes; the rate is variable and genetically determined. Almost 50% of blacks and whites are slow-acetylators, whereas over 80% of Chinese, Japanese, and Eskimos are fast-acetylators. Approximately 20% is excreted unchanged in the urine. Small amounts are excreted in breast milk. The elimination half-life ranges from 10-50 hours.

ADVERSE REACTIONS

•**Hemolytic anemia** - Asymptomatic hemolysis occurs in most patients who receive daily dapsone doses ≥ 200 mg. Patients with **G6PD deficiency** are much more susceptible and should not receive the drug.
•**Methemoglobinemia** - Severe methemoglobinemia can occur in people with normal or low G6PD levels, especially when a large dose of dapsone is ingested. Severe methemoglobinemia can cause coma, seizures, circulatory failure, and arrhythmias. Methemoglobin levels should be monitored in patients with symptoms or in patients taking dapsone for PCP treatment; the drug should be discontinued in patients with a methemoglobin concentration > 20%.
•**Sulfone syndrome -** may develop 2-8 weeks after initiation of treatment. Its manifestations include fever, malaise, exfoliative dermatitis, jaundice with hepatic necrosis, lymphadenopathy, and anemia.
•**Other** dapsone-induced side effects include rash, anorexia, nausea, vomiting, headache, dizziness, malaise, agitation, insomnia, blood dyscrasias, nephrotic syndrome, liver damage, and peripheral neuropathy.

DRUG INTERACTIONS

DRUG	INTERACTION	MECHANISM
Probenecid	↑ dapsone levels	↓ elimination of dapsone
Rifampin	↓ dapsone levels by 7-10 fold	↑ metabolism of dapsone
TMP-SMX	↑ TMP & dapsone levels	Inhibition of TMP & dapsone metabolism

FORMULARY STATUS

Dapsone is a **CATEGORY I (formulary)** agent at San Francisco VA Medical Center.

DAPTOMYCIN

INDICATIONS

- Treatment of **complicated skin and skin structure infections** caused by susceptible Gram-positive organisms including methicillin-resistant *Staphylococcus aureus* (MRSA) in patients who have failed, are unable to tolerate, or have resistant isolates to vancomycin
- Treatment of **MRSA bacteremia or endocarditis** in patients who have failed, are unable to tolerate, or have resistant isolates to vancomycin
- Treatment of **bacteremia or endocarditis** caused by **vancomycin-resistant enterococci (VRE)**

Note: Daptomycin is not indicated for the treatment of pneumonia, as it is inhibited by pulmonary surfactants.

SPECTRUM

Daptomycin is a cyclic lipopeptide that binds to bacterial membranes causing rapid depolarization of membrane potential and inhibition of protein, DNA, and RNA synthesis. Daptomycin displays rapid, concentration-dependent bactericidal activity for infections caused by most aerobic Gram-positive bacteria including *Staphylococcus aureus*, *Streptococcus pyogenes, Streptococcus agalactiae,* and *Enterococcus* species. Daptomycin maintains potency *in vitro* against Gram positive isolates that are resistant to methicillin, vancomycin, and linezolid such as MRSA, MRSE, VRE, *Corynebacterium jeikeium* and *Staphylococcus haemolyticus*. Synergistic interactions of daptomycin with aminoglycosides, B-lactams, and rifampin against some isolates of staphylococci and enterococci have been observed *in vitro*. *S. aureus, S. pyogenes,* and *S. agalactiae* with an MIC ≤ 1µg/mL are considered sensitive whereas for *E. faecalis*, an MIC ≤ 4 µg/mL is considered sensitive.

DOSING/PHARMACOKINETICS

Creatinine Clearance (ml/min)	COMPLICATED SKIN & SOFT STRUCTURE INFECTION		BACTEREMIA & INFECTIVE ENDOCARDITIS	
	Dosage Regimen	**Duration**	**Dosage Regimen**	**Duration**
≥ 30	4 mg/kg IV q24h	7-14 days	6 – 10 mg/kg IV q24h†	2 – 6 weeks
< 30 (including hemodialysis)	4 mg/kg IV q48h*	7-14 days	6 – 10 mg/kg IV q48h*†	2 – 6 weeks

* To be given following completion of hemodialysis on hemodialysis days
† Higher doses may be considered for severe infections with close monitoring

The pharmacokinetics of daptomycin is generally linear. Daptomycin is administered by IV infusion as a single daily dose and infused over 30 minutes. The elimination half-life is ~8 hours in patients with normal renal function. Daptomycin is eliminated renally, therefore, dosage adjustment is required in patients with renal insufficiency (see above). Renal function and creatine phosphokinase (CPK) should be monitored. No dose adjustment is required in mild-to-moderate hepatic impairment. Peak serum levels of 57.8 µg/mL and 93.9 µg/mL are achieved at steady state following administration of 4 mg/kg and 6 mg/kg doses. Daptomycin is highly protein bound (90-93%) with a volume of distribution of 0.1 L/kg. Daptomycin has not been shown to be an inhibitor or inducer of CYP P450 enzymes.

ADVERSE REACTIONS

- **Cardiovascular:** atrial fibrillation (<1%), atrial flutter (<1%), cardiac arrest (<1%), hypertension (1.1-5.8%), hypotension (2.4 -5%), edema, chest pain
- **Dermatologic:** injection site reaction (2.5-5.8%), pruritis (2.8-5.8%), rash (4.3-6.7%), eczema, increased sweating, DRESS, Stevens-Johnson syndrome, vesiculobullous rash
- **Endocrine/Metabolic:** hyperkalemia (5%) and hypokalemia (9.2%) observed with 6mg/kg dose, hypomagnesemia**,** increased serum bicarbonate
- **Gastrointestinal:** constipation (6.2-10.8%), diarrhea (5.2-11.7%), indigestion (0.9-4.2%), nausea (5.8-10%), vomiting (3.2-11.7%), *C. difficile*-associated diarrhea, abdominal distention, abdominal pain, stomatitis, taste disturbance, pharyngolaryngeal pain, dry mouth
- **Hematologic:** anemia (2.1-12.5%), elevated INR (<1%), thrombocytopenia (<1%), leukocytosis, thrombocytosis, eosinophilia,
- **Hepatic:** abnormal LFTs (3%), jaundice
- **Hypersensitivity reaction:** anaphylaxis, fever (1.9-6.7%), hives, shortness of breath, difficulty swallowing
- **Musculoskeletal:** arthralgia (0.9-3.3%), elevated CPK (2.8-6.7%), myalgia (<1%), limb pain (1.5-9.2%), rhabdomyolysis, muscle cramps, muscle weakness, increased myoblobin,
  - More frequent CPK elevations observed when daptomycin dosed more than once daily. Monitor for development of muscle pain or weakness, and obtain weekly CPK levels. More frequent monitoring may be required in patients with renal dysfunction or concomitant use of HMG-CoA reductase inhibitors. Consideration should be given to temporarily hold HMG-CoA reductase inhibitors while on daptomycin.
- **Neurologic:** dizziness (2.2-5.8%), headache (5.4-6.7%), insomnia (4.5-9.2%), paraesthesia (<1%), dyskinesia (<1%), peripheral neuropathy, vertigo, mental status changes, hallucinations
- **Renal:** renal failure (2.2-3.3%), proteinuria,
- **Respiratory:** dyspnea (2.1-3.3%), pleural effusion (5.8%), eosinophilic pneumonia (occurred 2-4 weeks after starting daptomycin), cough
- **Other:** gram-negative bacterial infection (8.3%), fungal infection (2.6%), urinary tract infection (2.4-6.7%), fatigue, rigors, flushing, eye irritation, lymphadenopathy, blurred vision

FORMULARY STATUS

Daptomycin is a **CATEGORY II (restricted)** antibiotic at San Francisco VA Medical Center. This drug will not be dispensed by pharmacy without prior approval by the Infectious Diseases Section.

ERTAPENEM

INDICATION

- Treatment of mild to moderate intra-abdominal infections (appendicitis, cholecystitis, diverticulitis)
- Treatment of mild to moderate diabetic foot infections
- Parenteral **antimicrobial prophylaxis for** patients undergoing emergent **colorectal surgery (single dose preoperative use only)**

SPECTRUM

Ertapenem is a carbapenem that has a narrower spectrum than imipenem and meropenem. Ertapenem exerts its antibacterial activity through inhibition of cell-wall synthesis by binding to penicillin-binding proteins (PBPs). Ertapenem has antimicrobial activity against a broad range of microorganisms, including streptococci, staphylococci,, *Moraxella catarrhalis, Haemophilus influenzae*, most anaerobes, and enterobacteriaceae. **It has no activity against *Acinetobacter*, *Pseudomonas aeruginosa*, and *Enterococcus spp.*.** All carbapenems lack activity against *Stenotrophomonas maltophilia* and MRSA. It is highly resistant to degradation by a wide variety of beta-lactamases. It is susceptible to carbapenemases. Staphylococci and enterobacteriaciae with an MIC $\leq$ 0.5 µg/mL are considered sensitive while organisms with an MIC $\geq$ 2 µg/mL are considered resistant.

DOSING/PHARMACOKINETICS

CREATININE CLEARANCE	DOSE
>30 mL/min	1 g daily
≤ 30 mL/min	500 mg daily
Hemodialysis	Avoid administration 6 hours prior to initiation of dialysis

Bioavailability of an IM dose (reconstituted with 1% lidocaine) is approximately 90%. The peak serum concentrations occur approximately 2 hours (67 µg/mL) and 0.5 hours (155 µg/mL) after 1g IM injection and 1g IV (30 minute infusion) of Ertapenem, respectively. Ertapenem is highly bound to human plasma proteins, primarily albumin. Ertapenem displays saturable protein binding, ranging from 85-95% at serum concentrations between 300mcg/ml and less than 100mcg/ml, respectively, resulting in nonlinear pharmacokinetics. Steady state volume of distribution is approximately 8.2L. Ertapenem does not inhibit cytochrome P450-mediated metabolism or P-glycoprotein-mediated drug clearance. Ertapenem is eliminated primarily by the kidneys (approximately 80% is recovered in urine and 10% in feces); therefore dosage adjustment is necessary in patients with renal insufficiency (see above). The mean plasma half-life in healthy young adults is approximately 4 hours and the plasma clearance is approximately 1.8 L/hour.

ADVERSE REACTIONS

•**Hypersensitivity:** Ertapenem is not recommended for patients with a history of IgE-mediated reactions to penicillins or cephalosporins; however, there is no data on the specific incidence of cross-sensitivity of ertapenem with other β-lactams.
•**Gastrointestinal Effects:** DIARRHEA (~9.5%) and NAUSEA (~7.5%). Less commonly, abdominal pain (4%), vomiting (4%), dyspepsia (1%), constipation (4%), and acid regurgitation (1.5%)
•**Hepatic Effects:** Increases in serum transaminases (~ 8%), alkaline phosphatase (~5%), and bilirubin levels (~1%)
•**Hematologic Effects:** Decreases in hemoglobin or hematocrit (~4%), falls in platelet counts (<2%), eosinophilia (<2%), increases in prothrombin time (<2%) were observed, and leukopenia
•**Neurologic Effects:** HEADACHE (~6%) and ALTERED MENTAL STATUS (~4%). SEIZURES (~0.5%) were reported primarily in those with renal insufficiency and/or central nervous system disorders.
•**Other:** Phlebitis/THROMBOPHLEBITIS (2%) and infusion related reactions (6%) were observed.

DRUG INTERACTION

DRUG	INTERACTION	MECHANISM
Valproic acid	↓ valproic acid levels	Unknown

FORMULARY STATUS

Ertapenem is a **CATEGORY I (FORMULARY)** antibiotic at the San Francisco VA Medical Center.

ETHAMBUTOL

INDICATIONS

- **Treatment of tuberculosis** (in combination with other antituberculosis agents, e.g., isoniazid, pyrazinamide, and rifampin)
- **Treatment of infections caused by *Mycobacterium kansasii*** (in combination with other antituberculosis agents, e.g., rifampin and isoniazid)
- **Alternative agent for the treatment of *M. marinum* infection** (in combination with other antimicrobials)
- **Treatment of *M. avium* complex (MAC) disease** (in combination with other agents, e.g., clarithromycin)

SPECTRUM

Ethambutol (EMB) is bacteriostatic at usual doses and is only effective against actively growing mycobacteria. It acts by inhibiting arabinosyl transferases that are involved in arabinogalactan synthesis, a mycobacterial cell wall component. . EMB is active in vitro and in vivo against *M. tuberculosis, M. bovis, M. marinum*, and some strains of *M. kansasii, M. avium, M. fortuitum,* and *M. intracellulare.* The MIC of most *M. tuberculosis* isolates is $\leq$ 8 µg/ml.

DOSING/PHARMACOKINETICS

Dosing is based on estimated lean body weight. The recommended daily dose of EMB for the treatment of tuberculosis is 15-20 mg/kg (up to 1,600 mg). In patients who have received prior antituberculosis therapy, 25 mg/kg EMB may be given once daily for 60 days or until bacteriologic smears and cultures become negative, followed by 15 mg/kg dose once daily. When EMB is administered in a 2 or 3 times per week regimen, it is given at 36-54 mg/kg (up to 4,000 mg) and 27-45 mg/kg (up to 3,000 mg), respectively. EMB is available as 100 mg and 400 mg tablets.

ADJUSTMENT OF DOSAGE REGIMENS IN PATIENTS WITH RENAL INSUFFICIENCY

Creatinine Clearance	Dose	Adjusted Dosing Interval
< 30 ml/min	20-25 mg/kg	3 times weekly

Absorption of EMB is not affected by food. Serum concentrations are undetectable 24 hours after the last dose. EMB is distributed into most body tissues and fluids including inflamed meninges. After a single dose of 15-25 mg/kg EMB, a peak level of 2-5 mcg/ml can be achieved 2-4 hours after administration. The plasma half-life is approximately 3.3 hours in patients with normal renal function and may be 7 hours or longer in patients with renal failure. Following a single oral dose, 50% is excreted unchanged in urine, 8-15% is hepatically metabolized, and 20-22% is excreted unchanged in feces. Plasma protein binding of EMB varies from 8-22%. EMB is removed by peritoneal dialysis and to a lesser extent by hemodialysis.

ADVERSE REACTIONS

- **Ocular** - Optic neuritis with decreases in visual acuity, constriction of visual fields, central and peripheral scotomas, and loss of red-green color discrimination. It is dose and duration dependent (~5% with 25 mg/kg/day given > 2 months; otherwise, ocular complications are infrequent). Testing for visual acuity and green color perception should be performed prior to and during therapy.
- **Gastrointestinal** - Anorexia, nausea, vomiting, GI upset, abdominal pain (1-10%)
- **Nervous system** - Fever, malaise, headache, dizziness, mental confusion, disorientation, hallucinations (< 1%). Peripheral neuritis, with numbness and tingling of the extremities, has been reported infrequently.
- **Hyperuricemia** - EMB decreases the renal excretion of urate. Hyperuricemia occurs frequently, but active gout is uncommon. Joint pain may occur.
- **Allergic** - Rash, pruritus, anaphylactoid reactions, toxic epidermal necrolysis (rare)
- **Other -** Thrombocytopenia and transient increases in liver function tests (<1%)

DRUG INTERACTION

DRUG	INTERACTION	MECHANISM
Aluminum hydroxide gel	↓ ethambutol absorption	

FORMULARY STATUS

Ethambutol is a **CATEGORY I (formulary)** agent at San Francisco VA Medical Center.

FLUCONAZOLE

INDICATIONS

•Treatment of **oropharyngeal candidiasis in patients who have failed topical treatment** (e.g., clotrimazole)
•Treatment of **esophageal candidiasis**
•**Chronic suppressive therapy** of **cryptococcal meningitis in AIDS** patients after initial therapy with amphotericin B
•Treatment of **deep-seated infections** including fungemia **caused by *Candida albicans, C. tropicalis, and C. parapsilloisis***
•Treatment of pulmonary and disseminated **coccidioidomycosis** including meningitis
•Treatment of vaginal candidiasis in patients who have failed topical therapy

SPECTRUM

Fluconazole is a synthetic bis-triazole antifungal agent with fungistatic activity. In vivo susceptibility testing methods indicate that the drug is active against *Candida albicans*, *Cryptococcus neoformans, Coccidioides immitis, Blastomyces dermatitidis,* and *Histoplasma capsulatum*. *Candida* species other than C. albicans are less susceptible and may not respond to fluconazole therapy. *Aspergillus* species and *Candida krusei* are resistant to fluconazole. *Candida albicans, tropicalis, and parapsillosis* isolates with an MIC $\leq$ 2 µg/ml are considered sensitive, while isolates with an MIC $\geq$ 8 µg/ml are considered resistant. *C. glabrata* isolates with and MIC $\leq$ 32 mcg/ml are considered susceptible, dose dependent (SDD). All SDD *glabrata* isolates and other *Candida* species with an MIC of 4 must be treated with maximum fluconazole doses (800 mg or 12mg/kg).*

DOSING/PHARMACOKINETICS

INFECTION	LOADING DOSE	DAILY DOSE
Oropharyngeal candidiasis	200 mg x 1 day	100 mg daily
Esophageal Candidiasis	400 mg x 1 day	200 mg daily
Chronic suppressive therapy of cryptococcal meningitis in AIDS patients (after 14 days of amphotericin B)	400 mg x 1 day	400 mg qd x 8 weeks then 200 mg daily
Deep-seated candidiasis*	800 mg x 1 day	400 mg or 6 mg/kg daily
Vaginal candidiasis (single dose treatment)	150 mg x 1 day	
Coccidioidomycosis	800 mg	400-800 mg daily

Adjustment of dosage regimens in patients with renal insufficiency

CREATININE CLEARANCE	% OF USUAL DOSE
> 50 ml/min	100
< 50 ml/min	50
Hemodialysis	100% after each dialysis and 50% on non-dialysis days

The oral bioavailability of fluconazole is greater than 90 percent. Unlike itraconazole, the gastrointestinal absorption of fluconazole is not affected by gastric acidity. Peak serum levels of 4.5 to 8 µg/ml are achieved following administration of a 100 mg oral dose of fluconazole. Fluconazole is well-distributed to most body tissues and fluids. Its volume of distribution is about 0.8 L/kg. Cerebrospinal fluid levels are 50 to 90 percent of concomitant serum levels and are independent of the degree of meningeal inflammation. The elimination half-life of fluconazole is approximately 30 hours. The drug is primarily eliminated renally; therefore dosage adjustment is required in patients with renal insufficiency (see above).

DRUG INTERACTIONS

DRUG	INTERACTION	MECHANISM
Alfentanil, fentanyl	↑ alfentanil & fentanyl levels	↓ alfentanil & fentanyl metabolism
Alprazolam, midazolam, triazolam	↑ benzodiazepine levels	↓ benzodiazepine metabolism
Amitriptyline, nortriptyline	↑ tricyclic antidepressant levels	↓ tricyclic antidepressant metabolism
Atorvastatin, lovastatin, simvastatin	↑ statin levels	↓ statin metabolism

Avanafil	↑ avanafil levels	↓ avanafil metabolism
Bosentan	↑ bosentan levels	↓ bosentan metabolism
Bosutinib	↑ bosutinib levels	↓ bosutinib metabolism
Carbamazepine	↑ carbamazepine levels	↓ carbamazepine metabolism
Celecoxib	↑ celecoxib levels	↓ celecoxib metabolism
Cisapride	Ventricular arrhythmias	↓ cisapride metabolism
Colchicine	↑ colchicine levels	↓ colchicine metabolism
Cyclosporine	↑ cyclosporine levels	↓ cyclosporine metabolism
Eliglustat	↑ eliglustat levels	↓ eliglustat metabolism
Etravirine	↑ etravirine levels	↓ etravirine metabolism
Everolimus	↑ everolimus levels	↓ everolimus metabolism
Flibanserin	↑ flibanserin levels	↓ flibanserin metabolism
Flurbiprofen, ibuprofen	↑ NSAID levels	↓ NSAID metabolism
Ibrutinib	↑ ibrutinib levels	↓ ibrutinib metabolism
Ivacaftor	↑ ivacaftor levels	↓ ivacaftor metabolism
Losartan	↑ losartan levels	↓ losartan metabolism
Lomitapide	↑ lomitapide levels	↓ lomitapide metabolism
Lurasidone	↑ lurasidone levels	↓ lurasidone metabolism
Methadone	↑ methadone levels	↓ methadone metabolism
Nevirapine	↑ nevirapine levels	↓ nevirapine metabolism
Olaparib	↑ olaparib levels	↓ olaparib metabolism
Oral hypoglycemic agents	↑ risk of hypoglycemia	↓ oral hypoglycemic metabolism
Phenytoin	↑ phenytoin levels	↓ phenytoin metabolism
Pimozide	Ventricular arrhythmias	↓ pimozide metabolism
Ranolazine	↑ ranolazine levels	↓ ranolazine metabolism
Rifabutin	↑ rifabutin levels	↓ rifabutin metabolism
Rifampin	↑ fluconazole clearance	↑ fluconazole metabolism
Rivaroxaban	↑ rivaroxaban levels	↓ rivaroxaban metabolism
Simeprevir	↑ simeprevir levels	↓ simeprevir metabolism
Sirolimus, temsirolimus	↑ sirolimus & temsirolimus levels	↓ sirolimus & temsirolimus metabolism
Tacrolimus	↑ tacrolimus levels	↓ tacrolimus metabolism
Theophylline	↑ theophylline levels	↓ theophylline metabolism
Tipranavir	↑ tipranavir levels	↓ tipranavir metabolism
Tofacitinib	↑ tofacitinib levels	↓ tofacitinib metabolism
Tolvaptan	↑ Tolvaptan levels	↓ Tolvaptan metabolism
Tricyclic antidepressants (TCAs)	↑ TCA levels	↓ TCA metabolism
Warfarin	↑ anticoagulant effect	↓ warfarin metabolism
Zidovudine (AZT)	↑ AZT levels	↓ AZT clearance

FORMULARY STATUS

Oral fluconazole is a **CATEGORY I (Formulary)** antibiotic at San Francisco VA Medical Center for Outpatients.

FOSCARNET

INDICATIONS

1. **Cytomegalovirus (CMV) retinitis**
   - **a.** Patients with CMV retinitis that have failed to respond to a two week course of ganciclovir induction therapy
   - **b.** Patients with a baseline neutrophil count of < 1,000/µl or platelet count of < 75,000/µl
   - **c.** Patients experiencing ganciclovir-induced neutropenia (< 500/µl) or thrombocytopenia (< 25,000/µl)
   - **d.** Patients on other myelosuppressive drugs e.g. (pyrimethamine/sulfadiazine, chemotherapy) in which therapy cannot otherwise be changed
   - **e.** Patients with known hypersensitivity to ganciclovir or acyclovir
2. **Acyclovir-resistant** mucocutaneous **herpes simplex virus** (HSV) **infections**
3. **Acyclovir-resistant varicella-zoster virus infections**

ANTIVIRAL ACTIVITY

Foscarnet is a pyrophosphate analogue with activity against many RNA and DNA viruses including HSV, CMV, varicella-zoster virus, and HIV. Foscarnet acts by inhibiting viral polymerases. The drug has also been shown to inhibit HIV reverse transcriptase *in vitro*. The concentration of foscarnet required to inhibit replication of human CMV by 50% (IC_{50}) is 0.3 µmol/L.

DOSING/PHARMACOKINETICS

The elimination half-life of foscarnet is 3.3-6.8 hours in patients with normal renal function. Foscarnet is eliminated renally, therefore dosage adjustment is required in patients with renal insufficiency. The dose of foscarnet is based on creatinine clearance (CrCl) expressed in ml/min/kg. It is recommended that a baseline 24-hour CrCl be obtained on all patients to allow for accurate dosing (this value must be divided by the patient's body weight (kg) in order to use the tables listed below). Alternatively, CrCl can be estimated with the following formula:

For males: $\frac{140 - \text{age}}{\text{serum creatinine} \times 72}$ (x 0.85 for females)

The two tables that follow list recommended doses for the treatment of CMV retinitis. Induction therapy is continued for two weeks and is followed by maintenance therapy. Foscarnet induction therapy may be dosed on an every 8 hour or every 12 hour schedule. Doses of ≤ 60 mg/kg should be infused over one hour, while doses > 60 mg/kg should be infused over two hours. When a peripheral vein is used to infuse foscarnet, the drug must be diluted to a final concentration of 12 mg/ml or less to avoid local vein irritation.

INDUCTION THERAPY FOR CMV

CrCl (ml/min/kg)	Dose (mg/kg)	Dose (mg/kg)
> 1.4	60 q8h	90 q12h
> 1 to 1.4	45 q8h	70 q12h
> 0.8 to 1	50 q12h	50 q12h
> 0.6 to 0.8	40 q12h	80 q24h
> 0.5 to 0.6	60 q24h	60 q24h
≥ 0.4 to 0.5	50 q24h	50 q24h
< 0.4	Discontinue	Discontinue

MAINTENANCE THERAPY FOR CMV

CrCl (ml/min/kg)	Dose (mg/kg)
> 1.4	90 q24h
> 1 to 1.4	70 q24h
> 0.8 to 1	50 q24h
> 0.6 to 0.8	80 q48h
> 0.5 to 0.6	60 q48h
≥ 0.4 to 0.5	50 q48h
< 0.4	Discontinue

ADVERSE REACTIONS

Foscarnet causes a number of serious adverse reactions, many of which may lead to discontinuation of the drug. **Nephrotoxicity** occurs in over 25% of patients. Foscarnet should be discontinued when CrCl < 0.4 ml/min/kg. Normal saline administered to induce diuresis prior to and during infusion appears to decrease the risk of nephrotoxicity. **Mineral and electrolyte disturbances** include hypocalcemia, hypophosphatemia, hyperphosphatemia, hypomagnesemia, and hypokalemia. Symptomatic hypocalcemia has occurred in patients receiving pentamidine in combination with foscarnet. Nephrotoxic drugs and drugs that cause electrolyte imbalances should be avoided. **Seizures** have occurred in approximately 10% of patients treated with foscarnet. Anemia is another frequent side effect (20-50%). Other common adverse reactions include fever, nausea, vomiting, diarrhea, and genital irritation and ulceration.

DRUG INTERACTIONS

DRUG	INTERACTION	MECHANISM
Amphotericin B	↑ nephrotoxicity & electrolyte abnormalities	Additive effects
Cyclosporine	↑ nephrotoxicity	Additive effects
Nephrotoxic drugs	↑ nephrotoxicity	Additive effects
Pentamidine	Symptomatic hypocalcemia & renal failure	Additive effects

FORMULARY STATUS

Foscarnet is a **CATEGORY II (restricted)** antibiotic at San Francisco VA Medical Center. This drug will not be dispensed by pharmacy without prior approval by the Infectious Diseases Section.

GANCICLOVIR (DHPG)

INDICATION

•Treatment of **cytomegalovirus (CMV) retinitis in immunocompromised patients**

ANTIVIRAL ACTIVITY

Ganciclovir (DHPG) is an acyclic nucleoside analogue of 2'-deoxyguanosine. DHPG is phosphorylated intracellularly to its active triphosphate derivative. DHPG triphosphate is a competitive inhibitor of viral DNA polymerase. The compound is also incorporated into viral DNA, which results in termination of DNA elongation. DHPG has antiviral activity against CMV, herpes simplex virus -1 and -2, Epstein-Barr virus, and varicella-zoster virus. The concentration of DHPG required to inhibit replication of human CMV by 50% (IC_{50}) is 0.5 to 3.0 µmol/L.

DOSING/PHARMACOKINETICS

CREATININE CLEARANCE (ml/min)	INTRAVENOUS DOSAGE REGIMEN	
	INDUCTION (mg/kg)	MAINTENANCE (mg/kg)
≥ 70 ml/min	5.0 q12h	5.0 q24h
50-69 ml/min	2.5 q12h	2.5 q24h
25-49 ml/min	2.5 q24h	1.25 q24h
10-24 ml/min	1.25 q24h	0.625 mg q24h
Hemodialysis	1.25 mg 3 times/week following hemodialysis	0.625 mg 3 times/week following hemodialysis

The elimination half-life of DHPG is 2-4 hours in patients with normal renal function. DHPG is renally eliminated, therefore dosage adjustment is necessary in patients with renal insufficiency. The oral bioavailability of DHPG is < 10%. When DHPG is used to treat CMV retinitis, an initial two week course of induction therapy is followed by maintenance therapy (see above). Ganciclovir should be infused intravenously over one hour.

ADVERSE REACTIONS

Neutropenia is the most common dose-limiting toxicity of DHPG. Neutropenia occurs in approximately 40% of DHPG treated patients and usually develops before a total cumulative dose of 200 mg/kg has been administered. The neutrophil count normally begins to recover within 3-7 days following discontinuation of DHPG. The concomitant use of zidovudine and DHPG results in severe to life-threatening bone marrow suppression in 82% of patients. Myelosuppressive drugs should be avoided in patients treated with DHPG. Thrombocytopenia occurs in approximately 9% of AIDS patients who receive DHPG. Central nervous system side effects occur in 5-17% of DHPG recipients and include confusion, dizziness, headaches, nervousness, psychosis, tremor, coma, and seizures. Seizures may occur more frequently in patients who receive imipenem in combination with DHPG. Other adverse reactions include gastrointestinal complaints, fever, rash, and abnormal liver function tests.

DRUG INTERACTIONS

DRUG	INTERACTION	MECHANISM
Imipenem	↑ risk of seizures	Additive effects
Myelosuppressive drugs	↑ risk of hematologic toxicity	Additive effects
Probenecid	↑ ganciclovir levels	↓ elimination of ganciclovir
Zidovudine (AZT)	↑ neutropenia	Additive effects

FORMULARY STATUS

Ganciclovir is a **CATEGORY II (restricted)** antibiotic at San Francisco VA Medical Center. This drug will not be dispensed by pharmacy without prior approval by the Infectious Diseases Section.

GENTAMICIN/TOBRAMYCIN

INDICATIONS

- **Alternative agent for treatment of** bacteremia, bone and joint infections, skin and soft tissue infections, respiratory tract infections, and intraabdominal infections **caused by susceptible strains of gram negative bacilli**
- Treatment of ***Pseudomonas aeruginosa* infections** (tobramycin is preferred for empiric therapy and for treatment of documented gentamicin-resistant organisms)
- Treatment of **enterococcal endocarditis** in combination with penicillin or ampicillin. In penicillin-allergic patients, vancomycin may be used in combination with gentamicin.

SPECTRUM

Gentamicin and tobramycin are bactericidal agents that are active against most aerobic gram-negative bacilli and gram-positive cocci. Aminoglycosides lack anaerobic activity. Gentamicin is more active than tobramycin against staphylococci, enterococci, and *Serratia marcescens*. However, tobramycin is more active against *P. aeruginosa*. Organisms with an MIC $\leq$ 4 µg/ml are considered sensitive, while organisms with an MIC $\geq$ 16 µg/ml are considered resistant.

DOSING/PHARMACOKINETICS

Traditional dosing

Therapeutic peak and trough gentamicin or tobramycin serum levels are 4-8 µg/ml and 1-2 µg/ml, respectively. In order to obtain the most useful information, serum levels of aminoglycosides should be drawn after the third or fourth dose. Peak serum levels of aminoglycosides should be drawn 30 minutes after the end of infusion, while trough levels should be drawn immediately before the next maintenance dose. The following nomograms may be used to calculate initial loading and maintenance doses for patients receiving gentamicin or tobramycin. The nomograms should **not** be used in hemodialysis patients, obese patients, or patients with significant third-spacing. Serum levels should be used to make further dosage adjustments.

Loading Dose† (mg/kg)	Expected Peak Serum Level (µg/ml)
2.0	6-8
1.75	5-7
1.5	4-6
1.25	3-5
1.0	2-4

†Select loading dose based on ideal body weight (IBW) to provide peak serum level desired.

(Hull JH, Sarubbi FA. *Ann Intern Med.* 1976;85:183-89.)

Maintenance dose as a Percentage of Loading Dose Required for Dosage Interval Selected

CrCl (ml/min)	8 Hours	12 Hours	24 Hours
90	**90%**		
80	**88%**		
70	**84%**		
60	**79%**	91%	
50	**74%**	87%	
40	66%	**80%**	
30	57%	**72%**	92%
25	51%	**66%**	88%
20	45%	**59%**	85%
15	37%	**50%**	75%
10	29%	40%	**64%**
7	24%	33%	**55%**
5	20%	28%	**48%**
2	14%	20%	**35%**
0	9%	13%	**25%**

(**Bold** areas indicate suggested dosage intervals)

Creatinine Clearance (CrCl) (**Males**) = $\frac{(140 - \text{age}) \times \text{IBW}}{72 \times \text{serum creatinine}}$

CrCl (Females) = 0.85 x Male value

The plasma elimination half-life of gentamicin is usually 2-3 hours in patients with normal renal function and ranges from 24-60 hours in adults with severe renal impairment. Significant amounts of tobramycin and gentamicin are removed during hemodialysis, therefore a supplemental dose is necessary after dialysis.

Once-Daily Dosing

Dose-dependent bacterial killing and a relatively long postantibiotic effect against most gram negative rods make once-daily aminoglycoside dosing a viable alternative to traditional aminoglycoside dosing. Most studies have shown similar efficacy with similar to less nephrotoxicity as compared to traditional aminoglycoside therapy. The recommended once-daily dose is 5 mg/kg based on ideal body weight. Obese patients (≥20% over IBW) should be dosed using obese dosing weight [IBW + 0.4(actual body weight-IBW)]. Once-daily, 5 mg/kg dosing should **not** be used for patients with an estimated creatinine clearance < 60 ml/min, treatment of endocarditis, or synergy against gram positive organisms. A serum trough level should be obtained prior to the second dose and should be undetectable. Peak levels are generally not recommended.

FORMULARY STATUS

Gentamicin and **Tobramycin** are **CATEGORY I (Formulary)** antibiotics at San Francisco VA Medical Center.

IMIPENEM/CILASTATIN

INDICATIONS

- Treatment of infections caused by **multidrug-resistant organisms**
- Treatment of **nosocomial infections** in **critically ill patients who have recent exposure to broad-spectrum antibiotic therapy (e.g., cefepime, piperacillin-tazobactam)**

SPECTRUM

Imipenem is a broad-spectrum carbapenem. Imipenem exerts its antibacterial activity through inhibition of cell-wall synthesis by binding to penicillin-binding proteins (PBPs). Imipenem has antimicrobial activity against a broad range of microorganisms, including streptococci, staphylococci, *Moraxella catarrhalis, Haemophilus influenzae*, most anaerobes, and enterobacteriaceae. Unlike ertapenem, it has activity against many isolates of *Acinetobacter* spp. *Pseudomonas aeruginosa*, *Nocardia* spp. and *Enterococcus faecalis..* All carbapenems lack activity against *Stenotrophomonas maltophilia* and MRSA. It is highly resistant to degradation by a wide variety of beta-lactamases. It is susceptible to carbapenemases (the metallo-beta-lactamases) as well as some carbapenemases produced by *Klebsiella pneumoniae* (KPC) and other gram-negative bacilli. Staphylococci and enterobacteriaceae with an MIC $\leq$ 1 µg/mL are considered sensitive while organisms with an MIC $\geq$ 4 µg/mL are considered resistant.

DOSING/PHARMACOKINETICS

Imipenem-Cilastatin IV Dosing Schedule for Adult Patients with Normal and Impaired Renal Function or Body Weight < 70 kg					
Body weight	**≥ 70 kg**	**60 kg**	**50 kg**	**40 kg**	**30 kg**
Clcr (mL/min/ 1.73 m^2)	**Dose (mg)**				
≥ 71	500 every 6 h	500 every 8 h	250 every 6 h	250 every 6 h	250 every 8 h
41 to 70	500 every 8 h	250 every 6 h	250 every 6 h	250 every 8 h	125 every 6 h
21 to 40	250 every 6 h	250 every 8 h	250 every 8 h	250 every 12 h	125 every 8 h
6 to 20	250 every 12 h	250 every 12 h	250 every 12 h	250 every 12 h	125 every 12 h

* Because of high antimicrobial activity, IV dosing should not exceed 50 mg/kg/day or 4 g/day, whichever is lower. There is no evidence that higher doses provide greater efficacy.

Imipenem is extensively metabolized by dehydropeptidase-1 in the brush border of the renal proximal tubule. Because imipenem is inactivated by the renal dipeptidase, this drug is coadministered with the dihydropeptidase inhibitor, cilastatin. Imipenem undergoes 50% to 70% renal elimination and has an elimination half-life of 1 hour. Dosage should be adjusted in patients with renal insufficiency as well as patients who weigh less than 70 kg (see above). Imipenem is 20% protein bound with a volume of distribution of 0.14 to 0.23 L/kg. Peak serum levels of 21 to 58 µg/ml are achieved following intravenous administration of a 500 mg dose of imipenem. Imipenem is dialyzable and supplemental doses should be administered after hemodialysis and at 12-hour intervals timed from the end of that dialysis session.

DRUG INTERACTIONS

DRUG	INTERACTION	MECHANISM
Ganciclovir	↑ risk of seizures	Additive effects
Valproic acid	↓ valproic acid levels	Unknown

FORMULARY STATUS

Imipenem is a **CATEGORY II (restricted)** antibiotic at San Francisco VA Medical Center. This drug will not be dispensed by pharmacy without prior approval by the Infectious Diseases Section.

ISONIAZID

INDICATIONS

•**Treatment of tuberculosis** (in combination with other antituberculosis agents, e.g., rifampin, pyrazinamide, and ethambutol)
•**Treatment of latent tuberculosis** in selected individuals with a significant reaction to the standard Mantoux tuberculin skin test
•**Treatment of infections caused by *Mycobacterium kansasii*** (in combination with other antituberculosis agents, e.g., rifampin and ethambutol)

SPECTRUM

Isoniazid (INH) is bactericidal against rapidly dividing populations of *M. tuberculosis*. Its mechanism of action is unknown. The in vitro activity of INH is limited to *M. kansasii, M. bovis*, and *M. tuberculosis*. Organisms with an MIC $\leq$ 0.2 µg/ml are considered sensitive, while organisms with an MIC $\geq$ 0.8 µg/ml are considered resistant. The development of increasing resistance to INH is of great concern.

DOSING/PHARMACOKINETICS

The recommended daily dose of INH for the treatment or prevention of tuberculosis is 300 mg. When used to treat tuberculosis, INH may be given 2 or 3 times weekly in a dose of 15 mg/kg (up to 900 mg). INH is readily absorbed following oral or intramuscular administration. Peak serum levels of 1-5 µg/ml are achieved 1-2 hours following the oral administration of 300 mg of INH. The absorption of INH is reduced when administered with food. INH is widely distributed into most body tissues and fluids including the cerebrospinal fluid. INH is inactivated in the liver by dehydrazination and acetylation. The rate of acetylation varies and is genetically determined. Almost 50% of blacks and whites are slow-acetylators, whereas over 80% of Chinese, Japanese, and Eskimos are rapid-acetylators. The elimination half-life is 0.5-1.5 hours in rapid-acetylators and 2-4 hours in slow-acetylators.

ADVERSE REACTIONS

•**Hepatic** - Transient increases in transaminases and bilirubin concentration occur in 10-20% of patients, usually during the first 4-6 months of therapy. Hepatitis is uncommon, but the risk is increased in alcoholics and in patients over 34 years of age. INH should be discontinued of signs or symptoms of hepatitis occur.
•**Nervous system** - INH-induced peripheral neuropathy is associated with pyridoxine deficiency. The following patients should receive supplemental pyridoxine (25 mg/d) in order to prevent neuropathy: cancer, uremic, diabetic, malnourished, pregnant, alcoholic and geriatric patients. Pyridoxine should also be given to patients with chronic liver disease or seizure disorders. Optic neuritis, psychosis, confusion, coma, seizures, hallucinations, agitation, insomnia, cerebellar syndrome, muscle twitching, restlessness, urinary retention, memory loss, and dizziness occur rarely. CNS side effects may be decreased by dividing the daily INH dose (100 mg tid) or by administering pyridoxine.
•**Hypersensitivity Reactions** - Fever, rash, urticaria, vasculitis, purpura, Stevens-Johnson syndrome, and interstitial nephritis (<1%)
•**Hematologic** - Agranulocytosis, eosinophilia, thrombocytopenia, methemoglobinemia, hemolytic anemia, aplastic anemia (<1%)
•**Gastrointestinal** - Nausea, vomiting, diarrhea, and epigastric distress (gastrointestinal reactions are uncommon at usual doses)
•**Other** - Systemic lupus erythematosus-like syndrome, arthralgia, glossitis, keratitis, dryness of the mouth, hyperglycemia, metabolic acidosis, and gynecomastia (<1%)

DRUG INTERACTIONS

DRUG	INTERACTION	MECHANISM
Acetaminophen (APAP)	↑ risk of hepatoxicity	↑ metabolism of APAP to toxic metabolites
Aluminum hydroxide gel	↓ INH levels	↓ INH absorption
Carbamazepine	↑ carbamazepine levels	↓ carbamazepine metabolism
Chlorzoxazone	↑ chlorzoxazone levels	↓ chlorzoxazone metabolism
Disulfiram	Coordination difficulty & psychosis	Alteration in dopamine metabolism
Enflurane	↑ risk of nephrotoxicity	Defluorination of enflurane
Itraconazole & ketoconazole	↓ azole levels	Unknown
Lomitapide	↑ lomitapide levels	↓ lomitapide metabolism
Phenytoin	↑ phenytoin levels	↓ phenytoin metabolism
Warfarin	↑ anticoagulant effect	↓ warfarin metabolism

FORMULARY STATUS

Isoniazid is a **CATEGORY I (formulary)** agent at San Francisco VA Medical Center.

ITRACONAZOLE

INDICATIONS

Superficial Infections

- Treatment of **oropharyngeal and cutaneous candidiasis** in patients **failing topicals** (e.g., clotrimazole), and fluconazole
- Treatment of **eosinophilic folliculitis**
- Treatment of **sporotrichosis**
- Treatment of **onychomycosis in patients who have failed treatment with terbinafine**

Systemic Fungal Infections

- Treatment of **aspergillosis** in patients **intolerant to amphotericin B and voriconazole**
- Treatment of **histoplasmosis and blastomycosis**
- Treatment of **coccidioidomycosis and paracoccidioidomycosis**
- **Histoplasmosis prophylaxis**

SPECTRUM

Itraconazole is a synthetic triazole compound that exhibits fungistatic activity by inhibiting ergosterol synthesis in the cell membrane. Itraconazole is active against *Aspergillus* species, *Blastomyces dermatitidis*, *Histoplasma capsulatum*, *Cryptococcus neoformans*, as well as most dermatophytes. Itraconazole has varying activity against *Candida albicans* and other *Candida* species.

DOSING/PHARMACOKINETICS

INDICATION		DOSING (MG), PO ONLY
Aspergillosis		200 tid x 3 days, then 200 bid
Blastomycosis		200 qd-bid x 6-12 months
Histoplasmosis		200 tid x 3 days, then 200 bid x 6-18 months
Eosinophilic folliculitis		200 once or twice daily
Candidiasis (oropharyngeal/cutaneous)		200 daily x 2-3 weeks
Coccidioidomycosis		200 bid x 6-12 months
Onychomycosis		200 bid x 7 days each month x 3 months
Sporotrichosis:	lymphocutaneous extracutaneous pulmonary	200 mg daily x > 3-6 months 200 mg bid x 12 months 200 mg tid x 3 days, then 200 mg bid

Itraconazole capsules require low gastric pH to ensure adequate absorption and should be given after a full meal. Concomitant use of agents that raise gastric pH should be avoided. Oral itraconazole reaches a peak concentration of about 300 ng/ml 4-5 hours after a 200mg dose in healthy adults; its bioavailability is 55%. Itraconazole is 99.8% bound to plasma proteins and is not removed by hemodialysis. Itraconazole is well distributed to most body tissues. CSF and urine penetration are poor. Itraconazole is hepatically metabolized; its half-life is 64 hours. Plasma levels should be monitored in patients with severe hepatic insufficiency. No dosage adjustment is needed in patients with renal impairment.

ADVERSE REACTIONS

Gastrointestinal Tract - Nausea (2-11%), vomiting (1-5%), diarrhea (1-4%), abdominal pain (1-3%), anorexia (≤ 1%), dyspepsia (3-4%), epigastric pain, constipation (2-3%), gastritis (2%), flatulence (4%), increased appetite (2%), gastroenteritis (2%), ulcerative stomatitis (≤3%), gingivitis (≤3%), dysgeusia

Hepatic - Increased aminotransferases (1-4%), hepatitis (rare), acute liver failure

Endocrine- Impotence and decreased libido (1%), adrenal insufficiency, gynecomastia, male breast pain (< 1%) hypertriglyceridemia (1-3%), hair loss in women, menstrual disorder

Hypersensitivity Reactions - Rash (1-9%), pruritus (1-5%), fever (1-3%), urticaria, angioedema, toxic epidermal necrolysis, anaphylaxis, Stevens-Johnson syndrome (rare), vasculitis (1%), anaphylaxis, serum sickness, angioneurotic edema, toxic epidermal necrolysis, exfoliative dermatitis, erythema multiforme, photosensitivity

Nervous System - Headache (1-10%), dizziness (1-4%), somnolence (≤ 1%), insomnia, tinnitus, depression (1-3%), neuropathy (rare), vertigo (1%), tremor (2%), asthenia (2%), pain (2-3%), abnormal dreaming (2%, anxiety (≤3%), paresthesia, hypoesthesia, visual disturbances, hearing loss

Hematologic – Leukopenia, neutropenia, thrombocytopenia

Cardiovascular - Hypertension (1-3%), edema (1-4%), orthostatic hypotension (1%), CHF

Other – Fatigue (1-3%), hypokalemia (1-2%), malaise (1-3%), albuminuria (1%), myalgia (1-3%), rhinitis (5-9%), URI (8%), sinusitis (3-7%), injury (3-7%), UTI (3%), pharyngitis (2%) herpes zoster (2%), bursitis (3%), pulmonary edema, arthralgia, urinary incontinence, pollakiuria

DRUG INTERACTIONS

DRUG	INTERACTION	MECHANISM
Alprazolam, diazepam, midazolam, triazolam	↑ benzodiazepine levels	↓ benzodiazepine metabolism
Apixaban	↑ apixaban levels	↓ apixaban metabolism
Atazanavir	↑ atazanavir levels ↑ itraconazole levels	↓ metabolism
Atorvastatin, lovastatin, simvastatin	↑ statin levels	↓ statin metabolism
Avanafil	↑ avanafil levels	↓ avanafil metabolism
Bosutinib	↑ bosutinib levels	↓ bosutinib metabolism
Buspirone	↑ buspirone levels	
Cabozantinib	↑ cabozantinib toxicity	↓ cabozantinib metabolism
Carbamazepine	↓ itraconazole levels	↑ itraconazole metabolism
Ceritinib	↑ ceritinib levels	↓ ceritinib metabolism

Cilostazol	↑ cilostazol toxicity	↓ cilostazol metabolism
Cisapride	Ventricular arrhythmias	↓ cisapride metabolism
Clarithromycin, erythromycin	Ventricular arrhythmias	↓ macrolide metabolism
Cobimetinib	↑ cobimetinib levels	↓ cobimetinib metabolism
Colchicine	↑ colchicine levels	↓ colchicine metabolism
Conivaptan, tolvaptan	↑ conivaptan/tolvaptan levels	↓ conivaptan/ tolvaptan metabolism
Corticosteroids	↑ corticosteroid levels	↓ corticosteroid metabolism
Crizotinib	↑ crizotinib levels	↓ crizotinib metabolism
Cyclosporine	↑ cyclosporine levels	↓ cyclosporine metabolism
Cyclophosphamide	↑ cyclophosphamide toxicity	↓ cyclophosphamide metabolism
Dabrafenib	↑ dabrafenib levels	↓ dabrafenib metabolism
Darifenacin	↑ darifenacin levels	↓ darifenacin metabolism
Darunavir	↑ itraconazole levels ↑ darunavir levels	↓ itraconazole metabolism ↓ darunavir metabolism
Digoxin	↑ digoxin levels	↓ digoxin metabolism
Docetaxel	↑ docetaxel toxicity	↓ docetaxel metabolism
Dofetilide	Ventricular arrhythmias	↓ drug metabolism
Dronedarone	↑ dronedarone levels	↓ dronedarone metabolism
Drugs that ↑ gastric pH	↓ itraconazole absorption	2^{o} to ↑ gastric pH
Efavirenz	↓ itraconazole levels	↑ itraconazole metabolism
Eliglustat	↑ eliglustat levels	↓ eliglustat metabolism
Eplerenone	↑ eplerenone levels	↓ eplerenone metabolism
Ergot alkaloids	↑ ergot alkaloid levels	↓ ergot alkaloid metabolism
Etravirine	↓ itraconazole levels ↑ etravirine levels	↑ itraconazole metabolism ↓ etravirine metabolism
Felodipine, nifedipine, nisoldipine	↑ calcium channel blocker levels	↓ felodipine metabolism
Fentanyl	↑ fentanyl levels	↓ fentanyl metabolism
Fosamprenavir	↑ itraconazole levels ↑ fosamprenavir levels	↓ itraconazole metabolism ↓ fosamprenavir metabolism
Gefitinib	↑ gefitinib levels	↓ gefitinib metabolism
Haloperidol	↑ haloperidol levels	↓ haloperidol metabolism
Ibrutinib	↑ ibrutinib levels	↓ ibrutinib metabolism
Iloperidone	↑ iloperidone levels	↓ iloperidone metabolism
Indinavir	↑ indinavir levels	↓ indinavir metabolism
Isoniazid	↓ itraconazole levels	↑ itraconazole metabolism
Lomitapide	↑ lomitapide levels	↓ lomitapide metabolism
Lurasidone	↑ lurasidone levels	↓ lurasidone metabolism
Maraviroc	↑ maraviroc levels	↓ maraviroc metabolism
Methadone	↑ methadone levels	↓ methadone metabolism
Nilotinib	↑ nilotinib levels	↓ nilotinib metabolism
Olaparib	↑ olaparib levels	↓ olaparib metabolism
Oral hypoglycemics	↑ hypoglycemic effect	↓ sulfonylurea metabolism
PDE5 Inhibitors (Sildenafil, Tadalafil,Vardenafil)	↑ PDE5 Inhibitor levels	↓ drug metabolism
Phenobarbital	↓ itraconazole levels	↑ itraconazole metabolism
Phenytoin	↑ phenytoin levels ↓ itraconazole levels	↓ phenytoin metabolism ↑ itraconazole metabolism
Pimozide	Ventricular arrhythmias	↓ pimozide metabolism
Pomalidomide	↑ pomalidomide levels	↓ pomalidomide metabolism
Ponatinib	↑ ponatinib levels	↓ ponatinib metabolism
Quinidine	↑ quinidine levels	↓ quinidine metabolism
Ranolazine	↑ ranolazine levels	↓ ranolazine metabolism
Rifabutin, Rifampin	↓ itraconazole levels	↑ itraconazole metabolism
Rivaroxaban	↑ rivaroxaban levels	↓ rivaroxaban metabolism
Simeprevir	↑ simeprevir levels	↓ simeprevir metabolism
Sirolimus, temsirolimus	↑ sirolimus levels	↓ sirolimus metabolism
Tacrolimus	↑ tacrolimus levels	↓ tacrolimus metabolism
Ticagrelor	↑ ticagrelor levels	↓ ticagrelor metabolism
Toremifene	↑ toremifene levels	↓ toremifene metabolism
Tyrosine kinase receptor inhibitors (TKRI)	↑ TKRI levels	↓ TKRI metabolism
Vinblastine, vincristine	↑ neurotoxicity	↓ vinca alkaloid metabolism
Vorapaxar	↑ vorapaxar levels	↓ vorapaxar metabolism
Warfarin	↑ anticoagulant effect	↓ warfarin metabolism

FORMULARY STATUS

Itraconazole is a **CATEGORY II (restricted)** agent at San Francisco VA Medical Center. This drug will not be dispensed by pharmacy without prior approval by the Infectious Diseases Section.

LEVOFLOXACIN

INDICATIONS

•Treatment of **community-acquired pneumonia in patients who have failed standard therapy, including the combination of amoxicillin and doxycycline**

•Treatment of **community-acquired pneumonia** in the following settings:

Medical Ward, severe PCN allergy	Levofloxacin 750 mg PO daily
ICU, *Pseudomonas* risk*	Zosyn 4.5 gm IV q6h & Levofloxacin 750 mg IV q24h
ICU, severe penicillin allergy	Aztreonam 2 gm IV q8h & Levofloxacin 750 mg IV q24 ± Vancomycin 15 mg/kg IV q8h
CA MRSA risk‡	Vancomycin 1 gm IV q12h & Levofloxacin 750 mg IV q24h
NHCU, mild to moderate	Levofloxacin 750 mg PO daily

*Risk factors include advanced HIV, bronchiectasis, and nursing home transfers

‡ Risk factors for community-acquired methicillin-resistant *Staphylococcus aureus* include end-stage renal disease, injection drug abuse, prior influenza, prior respiratory MRSA colonization, and prior antibiotic therapy

Note: Quinolone resistance in *E. coli* **has dramatically increased at SFVAMC**.. Quinolones should not be used as empiric therapy for UTIs (see UTI guidelines in the Guide to Antimicrobials) Given the risk for disabling and potentially irreversible adverse reactions (e.g., neuropathy, tendinitis), quinolones should not be used for uncomplicated UTIs, acute sinusitis, or acute exacerbations of chronic bronchitis except in patients with no alternatives. **QUINOLONE USE SHOULD BE MINIMIZED WHENEVER POSSIBLE**

SPECTRUM

Levofloxacin, the active isomer of ofloxacin, is a fluoroquinolone antimicrobial agent with a broad gram-negative spectrum including Enterobacteriaceae*, Pseudomonas aeruginosa,* and *Haemophilus* species. Increases in resistance of *Escherichia coli* to fluoroquinolones has been reported locally and nationally, susceptibility should be confirmed. Ciprofloxacin is more active than levofloxacin against *P. aeruginosa*. Levofloxacin is more active than ciprofloxacin against pneumococci, staphylococci, and *Chlamydia*. In general activity against anaerobic organisms is poor and levofloxacin should not be used to treat infections caused by anaerobes. Emergence of resistance has been reported frequently when levofloxacin has been used alone to treat serious infections caused by methicillin-resistant staphylococci and *Pseudomonas aeruginosa.* Organisms with an MIC ≤ 2 µg/ml are considered sensitive, while organisms with an MIC > 4 µg/ml are considered resistant.

DOSING/PHARMACOKINETICS

CREATININE CLEARANCE (ML/MIN)	DOSE FOR UTI / PYELONEPHRITIS*	DOSE FOR COMPLICATED SKIN AND SOFT TISSUE INFECTIONS OR PNEUMONIA*	
		LOADING DOSE	MAINTENANCE DOSE
≥ 50	250 mg q24h	750 mg	750 mg q24h
20-49	250 mg q24h	750 mg	750 mg q48h
10-19	250 mg q48h	750 mg	500 mg q48h
CAPD or hemodialysis	250 mg q48h	750 mg	500 mg q48h

CREATININE CLEARANCE (ML/MIN)	DOSE FOR OTHER INFECTIONS	
	LOADING DOSE	MAINTENANCE DOSE
≥ 50	500 mg	500 mg q24h
20-49	500 mg	250 mg q24h
10-19	500 mg	250 mg q48h
CAPD or hemodialysis	500 mg	250 mg q48h

*Oral and intravenous doses are identical. Oral administration is preferable in most patients.

The elimination half-life of levofloxacin is 6 to 8 hours in patients with normal renal function. Accumulation occurs in patients with renal failure, therefore the dose should be adjusted according to the degree of renal insufficiency. Recommended dosing guidelines are listed above. The oral bioavailability of levofloxacin is 99 percent.. Mean levofloxacin serum levels of 5.7 µg/ml and 6.4 µg/ml are achieved following multiple daily 500 mg oral doses and intravenous doses, respectively.

DRUG INTERACTIONS

DRUG	INTERACTION	MECHANISM
Amiodarone	↑ QT interval	Additive effects
Antacids, iron, calcium, sucralfate, zinc	↓ levofloxacin absorption	
Arsenic trioxide	↑ QT interval	Additive effects
Cisapride	↑ QT interval	Additive effects
Corticosteroids	↑ risk of tendon rupture	
Dofetilide	↑ risk of arrhythmias	Additive effects
Oral hypoglycemic agents	↑ risk of hypoglycemia	Additive effects
Toremifene	↑ QT interval	Additive effects
Warfarin	↑ anticoagulant effect	Inhibition of warfarin metabolism

FORMULARY STATUS

Levofloxacin is a **CATEGORY II (restricted)** antibiotic at San Francisco VA Medical Center. This drug will not be dispensed by pharmacy without prior approval by the Infectious Diseases Section except in penicillin-allergic patients with community-acquired pneumonia. Hematology/Oncology may prescribe **oral** levofloxacin without Infectious Diseases Section approval.

LINEZOLID

INDICATIONS

•Proven, serious life-threatening infection or sepsis caused by vancomycin-resistant enterococci
•Complicated skin or skin-structure infections caused by MRSA **AND** one or more of the following:
1) Proven vancomycin resistance
2) Infection in patients who are intolerant of vancomycin
3) Failed treatment with vancomycin
•Nosocomial pneumonia caused by MRSA in patients who failed vancomycin.

SPECTRUM

Linezolid is a synthetic oxazolidinone anti-infective agent. Linezolid exerts its antibacterial activity by binding to a site on the 23S ribosomal RNA of the 50S subunit and inhibiting formation of the 70S initiation complex for protein synthesis. Although generally classified as a bacteriostatic agent, linezolid is bactericidal against pneumococci, *Clostridium perfringens*, and *Bacteroides* species. Linezolid is active against most gram positive bacteria including methicillin-resistant staphylococci, vancomycin-resistant enterococci (VRE), penicillin-resistant pneumococci *Corynebacterium* species, *Rhodococcus equi, Bacillus* species, *Mycobacterium tuberculosis*, *Nocardia* spp., and gram positive anaerobes. Linezolid-resistant VRE have been reported. Linezolid has modest activity against *Bacteroides* species, *Moraxella catarrhalis* and *Pasteurella* species. Most other gram negative bacteria are resistant to linezolid. Staphylococci with an MIC $\leq$ 4 µg/ml are considered sensitive, while enterococci and streptococci with an MIC $\leq$ 2 µg/ml are considered sensitive.

DOSING/PHARMACOKINETICS

The recommended dose of linezolid is 600mg orally or IV every 12 hours. In hemodialysis patients, the dose should be given after dialysis as 30% of dose is cleared during dialysis. Linezolid is rapidly and completely absorbed after oral dose with 100% bioavailability. Its serum peak level is achieved 0.5-2 hours after oral administration of 600mg tablet but high fat meal my delay time to reach the peak level. In healthy adults, linezolid has steady-state volume of distribution of 30-50 L or 0.5-0.6 L/kg. Protein binding is approximately 31% and is not concentration dependent. Linezolid has good tissue penetration including skin blister fluids, bone, muscle, fat, alveolar cells, lung extracellular lining fluids and CSF. Linezolid is primarily metabolized by oxidation into two major metabolites and excreted in urine. No dosage adjustment is necessary in renal or hepatic insufficiency. The elimination half-life of linezolid is approximately 5 hours. Mean peak serum levels of 21.2 µg/ml are achieved following the oral administration of linezolid 600 mg every 12 hours.

ADVERSE REACTIONS

•**Gastrointestinal** - Diarrhea (2.8-11%), nausea (3.4-9.6%), vomiting, constipation, taste alteration, tongue and tooth discoloration, oral candidiasis, dyspepsia, localized abdominal pain, pseudomembranous colitis
•**Hematologic** – Anemia, thrombocytopenia, leukopenia, neutropenia, pancytopenia, bleeding. CBC should be monitored weekly in patients who receive linezolid, especially in patients who receive linezolid for longer than 2 weeks, patients with preexisting myelosuppression, patients receiving concomitant drugs that produce bone marrow suppression, or patients with a chronic infection who have received previous or concomitant antibiotic therapy. Discontinuation of therapy with linezolid should be considered in patients who develop or have worsening myelosuppression.
•**Hypersensitivity Reactions** – Pruritus, fever (1.6%), rash (2%), anaphylaxis, angiodema, bullous skin disorders including Stevens-Johnson syndrome
•**Nervous system** – Headache (0.5-11.3%), dizziness (2%), insomnia (2.5%), peripheral and optic neuropathy, loss of vision, convulsions
•**Other** – Abnormal liver function tests (0.4-1.3%), vaginal candidiasis, hypertension, fungal infection, lactic acidosis

DRUG-DRUG INTERACTIONS

DRUG	INTERACTION	MECHANISM
Adrenergic and dopaminergic agents (e.g., pseudoephedrine, dopamine, epinephrine, tyramine)	↑ pressor response	MAO inhibition
Apraclonidine	Hypertensive crisis	MAO inhibition
Bupropion, Buspirone	Hypertensive crisis	MAO inhibition
CNS stimulants	Hypertensive crisis	MAO inhibition
Cyclobenzaprine	Hypertensive crisis	MAO inhibition
Serotonergic Interactions (e.g., serotonin re-uptake inhibitors, TCAs, triptans, tramadol, meperidine	↑ risk of serotonin syndrome	MAO inhibition
Rifampin	↓ linezolid levels	Unknown

FORMULARY STATUS

Linezolid is a **CATEGORY II (restricted)** agent at San Francisco VA Medical Center. This drug will not be dispensed by pharmacy without prior approval by the Infectious Diseases Section.

MEROPENEM

INDICATIONS

- Treatment of infections caused by **multidrug-resistant organisms**
- Treatment of **nosocomial infections** in **critically ill patients who have recent exposure to broad-spectrum antibiotic therapy (e.g., cefepime, piperacillin-tazobactam)**
- Treatment of **nosocomial, post-operative or post-traumatic meningitis**

SPECTRUM

Meropenem is a broad-spectrum carbapenem. Meropenem exerts its antibacterial activity through inhibition of cell-wall synthesis by binding to penicillin-binding proteins (PBPs). Meropenem has antimicrobial activity against a broad range of microorganisms, including streptococci, staphylococci, *Moraxella catarrhalis, Haemophilus influenzae*, most anaerobes, and enterobacteriaceae. Unlike ertapenem, it has activity against many isolates of *Acinetobacter* spp. *Pseudomonas aeruginosa*, and *Enterococcus faecalis.* All carbapenems lack activity against *Stenotrophomonas maltophilia* and MRSA. It is highly resistant to degradation by a wide variety of beta-lactamases. It is susceptible to carbapenemases (the metallo-beta-lactamases) as well as some carbapenemases produced by *Klebsiella pneumoniae* (KPC) and other gram-negative bacilli. Enterobacteriaceae with an MIC $\leq$ 1 µg/mL are considered sensitive while organisms with an MIC $\geq$ 4 µg/mL are considered resistant.

DOSING/PHARMACOKINETICS

CREATININE CLEARANCE (ML/MIN)	USUAL DOSE	DOSE FOR MENINGITIS OR PSEUDOMONAS INFECTIONS
$\geq$ 50	0.5-1 gm IV q8h	2 gm IV q8h
26-50	0.5-1 gm IV q12h	2 gm IV q12h
10-25	0.5 gm IV q12h	1 gm IV q12h
< 10	0.5 gm IV q24h	1 gm IV q24h
Hemodialysis	0.5 gm IV q24h†	0.5 gm IV q24h†

†should be administered following dialysis on dialysis days and at the same time each day

The elimination half-life of meropenem is approximately 1 hour in patients with normal renal function. Meropenem is eliminated renally, therefore dosage should be adjusted in patients with renal insufficiency (see above). Peak serum levels of 39 to 58 µg/ml are achieved following intravenous administration of a 1 gram dose of meropenem.

DRUG INTERACTION

DRUG	INTERACTION	MECHANISM
Valproic acid	↓ valproic acid levels	Unknown

FORMULARY STATUS

Meropenem is a **CATEGORY II (restricted)** antibiotic at San Francisco VA Medical Center. This drug will not be dispensed by pharmacy without prior approval by the Infectious Diseases Section.

METRONIDAZOLE

INDICATIONS

•Treatment of **serious infections caused by *Bacteroides fragilis***
•Treatment of **anaerobic brain abscesses**
•Treatment of mild to moderate ***Clostridium difficile* associated diarrhea** in outpatients
•Treatment of ***Helicobacter pylori* infection** (in combination with tetracycline, bismuth subsalicylate, and a proton-pump inhitor)
•Treatment of **intestinal or hepatic amebiasis** (metronidazole therapy must be followed by treatment with a luminal agent)
•Drug of choice for treatment of the following **parasitic infections**: ***Entamoeba polecki,* giardiasis, and trichomoniasis**
•Alternative agent for treatment of **infections caused by *Balantidium coli* and *Dientamoeba fragilis***

SPECTRUM

Metronidazole is a nitroimidazole agent that possesses bactericidal activity. Metronidazole is unsurpassed in its activity against most anaerobic bacteria. The drug is active against nearly all gram-negative anaerobes including *Bacteroides* and *Fusobacterium* isolates. Metronidazole is very active against anaerobic gram-positive cocci and *Clostridium* spp. Approximately 50% of *Bifidobacterium* and *Eubacterium* strains are susceptible. Microaerophilic streptococci, *Propionibacterium acnes*, *Actinomyces*, and *Lactobacillus* spp. are usually resistant. Metronidazole also possesses activity against anaerobic protozoa including *Trichomonas vaginalis, Balantidium coli, Giardia lamblia*, and *Entamoeba histolytica*. Organisms with an MIC $\leq$ 16 µg/ml are considered sensitive, while organisms with an MIC $\geq$ 32 µg/ml are considered resistant.

DOSING/PHARMACOKINETICS

Metronidazole is metabolized in the liver to five major metabolites. The hydroxy metabolite has significant anaerobic activity. The elimination half-life is 6-10 hours in patients with normal hepatic function. The long half-life allows for dosing on an every 8 or every 12 hour schedule. Dosage reduction is necessary in patients with hepatic impairment.. Over 80% of an oral metronidazole dose is absorbed. Food delays but does not reduce the absorption of metronidazole. Peak serum levels of 4-6 µg/ml are achieved following a 250 mg oral dose of metronidazole, while peak serum levels of 20-25 µg/ml are achieved following a 500 mg intravenous dose. The following table lists recommended dosage regimens for selected indications:

INDICATION	DOSAGE REGIMEN*	DURATION
Amebiasis	750 mg po or iv q8h	10 days
Anaerobic infections	500 mg po or iv q8h	variable
Clostridium difficile associated diarrhea	500 mg po q8h	10-14 days
Giardiasis.	250 mg po q8h	5 days
Trichomoniasis	2 gm po **or** 250 mg po q8h	Single dose 7 days

*Reduce dose in hepatic impairment

DRUG INTERACTIONS

DRUG	INTERACTION	MECHANISM
Alcohol	Disulfiram-like reaction	Inhibition of aldehyde dehydrogenase
Barbiturates	↓ metronidazole levels	↑ metronidazole metabolism
Busulfan	↑ busulfan levels	↓ busulfan metabolism
Cyclosporine	↑ cyclosporine levels	↓ cyclosporine metabolism
Disulfiram	Psychosis or confusional state	Unknown
Fluorouracil	↑ fluorouracil toxicity	↓ fluorouracil clearance
Lithium	↑ lithium levels	Unknown
Warfarin	↑ anticoagulant effect	↓ warfarin metabolism

FORMULARY STATUS

Metronidazole is a **CATEGORY I (Formulary)** antibiotic at San Francisco VA Medical Center. Metronidazole cannot be dosed more frequently than every 8 hours without prior approval by the Infectious Diseases Section.

MICAFUNGIN SODIUM

INDICATIONS

•Treatment of **esophageal candidiasis in patients refractory to or intolerant to fluconazole, itraconazole, and voriconazole**

•Treatment of **deep-seated infections** including fungemia **caused by *Candida* species**

Treatment of **invasive aspergillosis in patients refractory to or intolerant to other therapies (i.e., amphotericin B, lipid formulations of amphotericin, and voriconazole)**

•As **an addition to empiric treatment** in **febrile, neutropenic cancer patients** who fail to respond to initial antibacterial therapy

SPECTRUM

Micafungin is an echinocandin antifungal agent that works by inhibiting β-(1,3)-D-glucan synthase. Its spectrum of activity is very similar to that of caspofungin. It is fungicidal against most *Candida* spp. including non-albicans strains (MIC_{90} = 0.015-0.25μg/ml), fungistatic against most *Aspergillus spp.* (MIC_{90} ≤ 0.02 μg/ml), and active against the *cysts of Pneumocystis carinii.* Compared to its activity against other *Candida* spp, micafungin has less activity against *Candida parapsilosis* (MIC_{90} = 2 μg/ml), *Candida lusitaniae* (MIC_{90} = 2 μg/ml), and *Candida guillermondii* (MIC_{90} = 0.5 μg/ml). It has poor activity against *Blastomyces* spp., *Histoplasma capsulatum*, and *Coccidiodes immitis*. It lacks activity against *Cryptococcus neoformans* (MIC_{90} ≥ 16 μg/ml), *Fusarium spp*. (MIC_{90} ≥64 μg/ml), *Rhizopus spp. Pseudallescheria boydii*, *Paecilomyces*, and *Sporothrix schenckii*. Candida susceptibility breakpoints vary by species*: glabrata* ≤ 0.06 mcg/ml, *parapsilosis* ≤ 2 mcg/ml, and *ablicans, tropicalis,* and *krusei* ≤ 0.25 mcg/ml.

DOSING/PHARMACOKINETICS

Micafungin is administered as a single daily dose infused slowly over 1 hour. No loading dose is required. When used to treat deep-seated candidal infections, the daily dose is 100 mg. For the treatment of esophageal candidiasis, the daily dose is higher at 150 mg. Dosage reduction is not required for mild to moderate hepatic impairment (Child-Pugh score 5-9). Micafungin pharmacokinetics have not been adequately studied in patients with severe hepatic dysfunction. The CYP 450 pathway does not play a major role in the metabolism of micafungin. Micafungin is not affected by CYP 450 inducers or inhibitors, like rifampin and fluconazole, respectively. Dosage adjustments are also not necessary with concomitant tacrolimus, mycophenolate mofetil, cyclosporine, prednisolone, warfarin, methotrexate, and ritonavir. No dosage adjustments are necessary for patients with renal dysfunction or patients who are elderly. No premedication is necessary.

Micafungin exhibits linear pharmacokinetics. The elimination half-life ranges from 14-15 hours. After a single dose of 100 mg, a trough of about 2 μg/ml is achieved. Micafungin is metabolized by the liver into 3 inactive metabolites. It is minimally metabolized by the CYP 450 system. Less than 1% is excreted unchanged in the urine. Micafungin is highly protein bound (≥99%) and is not dialyzable. Its volume of distribution is about 0.39 L/kg. Micafungin readily distributes into plasma, liver, kidney and lung tissues, but its penetration into CSF is poor.

ADVERSE REACTIONS

Micafungin is well tolerated. There is no evidence of dose- or duration-related toxicities. The most common adverse effects observed are headache, fever, nausea and vomiting, diarrhea, and venous irritation. Infusion-related pain and phlebitis are less commonly observed compared to caspofungin. Elevation of liver function values, manifested by increased serum alkaline phosphatase and transaminase concentrations may occur. Hypokalemia, leukopenia, and eosinophilia may also occur. Possible histamine-related reactions, such as rash, flushing, pruritus, facial edema and isolated cases of anaphylaxis and hemolysis have been reported during administration of micafungin.

DRUG INTERACTIONS

DRUG	INTERACTION	MECHANISM
Cyclosporine	↑ cyclosporine levels, ↑ LFTs	Unknown
Nifedipine	↑ nifedipine AUC by 18% ↑ nifedipine C_{max} by 42%	Unknown
Sirolimus	↑ sirolimus AUC by 21%	Unknown

FORMULARY STATUS

Micafungin is a **CATEGORY I (formulary)** antibiotic at San Francisco VA Medical Center.

NAFCILLIN

INDICATIONS

•Drug of choice for treatment of **meningitis caused by nafcillin-susceptible staphylococci**

•Drug of choice for treatment of **endocarditis caused by nafcillin-susceptible staphylococci**

NOTE: Cefazolin is preferred for other infections caused by nafcillin-susceptible staphylococci because of fewer adverse reactions (e.g., thrombophlebitis, neutropenia) and less frequent dosing.

SPECTRUM

Nafcillin is a penicillinase-resistant penicillin with excellent activity against staphylococci and streptococci. Enterococci, penicillin-resistant pneumococci, nafcillin-resistant staphylococci, and gram-negative bacilli are resistant. Organisms with an MIC $\leq$ 2 µg/ml are considered sensitive, while organisms with an MIC $\geq$ 4 µg/ml are considered resistant.

DOSING/PHARMACOKINETICS

The elimination half-life of Nafcillin is 30 to 60 minutes in patients with normal renal function. Nafcillin is predominately hepatically metabolized; therefore dosage adjustment is unnecessary in patients with renal insufficiency. The recommended dose for the treatment of staphylococcal endocarditis or meningitis is 2 gm IV q4h. Plasma protein binding is 87-90%. Peak serum levels of 20-25 µg/ml are achieved following a 1 gm intravenous dose of nafcillin.

DRUG INTERACTION

DRUG	INTERACTION	MECHANISM
Methotrexate	↑ methotrexate levels & toxicity	↓ renal tubular secretion of methotrexate
Warfarin	↓ anticoagulant effect	↑ warfarin metabolism

FORMULARY STATUS

Nafcillin is a **CATEGORY I (Formulary)** antibiotic at San Francisco VA Medical Center.

NITROFURANTOIN

INDICATIONS

- **Treatment of lower urinary tract infections** (UTI's) caused by susceptible bacteria
- **Prophylaxis of chronic and recurrent UTI's**

SPECTRUM

Nitrofurantoin is a synthetic, nitrofuran-derivative antimicrobial agent. The drug is reduced by bacterial nitroreductases to highly reactive intermediates that inactivate ribosomal proteins and other macromolecules leading to inhibition of protein, DNA, RNA, and cell wall synthesis. The multiple mechanisms of action may account for the rare emergence of resistance seen during nitrofurantoin therapy. Nitrofurantoin is active against staphylococci, enterococci, and streptococci. Its gram-negative spectrum includes *Citrobacter, Klebsiella, Enterobacter*, and *Escherichia coli*. *Proteus, Serratia,* and *Pseudomonas* are generally resistant to nitrofurantoin. Urinary isolates with an MIC $\leq$ 32 µg/ml are considered sensitive, while isolates with an MIC $\geq$ 128 µg/ml are considered resistant.

DOSING/PHARMACOKINETICS

The recommended dose of nitrofurantoin monohydrate/macrocrystals capsules (Macrobid®) for the **treatment of lower urinary tract infections is 100 mg twice daily.** The recommended dose of Macrobid® capsules for the **prophylaxis of chronic and recurrent UTI's 100 mg every evening**. Following oral administration, nitrofurantoin is readily absorbed. Food increases the extent of absorption by increasing the dissolution rate of nitrofurantoin. Twenty-five percent of Macrobid® is macrocrystalline nitrofurantoin. The remaining 75% is nitrofurantoin monohydrate contained in a powder blend which, upon exposure to gastric and intestinal fluids, forms a gel matrix that releases nitrofurantoin over time. Peak nitrofurantoin levels of less than 1 µg/ml are achieved following administration of 100 mg of Macrobid®, urine levels are 50 to 150 µg/ml. Within 24 hours, 20 to 25 percent of an oral dose is excreted as unchanged drug in the urine. Nitrofurantoin is partially metabolized. The elimination half-life is approximately 20 minutes in patients with normal renal function. Nitrofurantoin should **not** be given to patients with creatinine clearances < 40 ml/minute because urinary concentrations of the drug are inadequate for the treatment of UTI's in these patients.

ADVERSE REACTIONS

- **Nervous system** - **Peripheral neuropathy** may be severe and irreversible. Fatalities have been reported. Neuropathy occurs most often in patients with creatinine clearances $\leq$ 60 ml/minute, anemia, diabetes mellitus, electrolyte imbalance, B vitamin deficiency, or a debilitating disease. Other nervous system effects include headache , dizziness, nystagmus, vertigo, asthenia, drowsiness, reversible intracranial hypertension, cerebellar dysfunction, retrobulbar neuritis, and trigeminal neuralgia.
- **Pulmonary - Acute reactions**, which may occur within hours and up to 3 weeks after initiation of therapy, include severe dyspnea, chills, chest pain, fever, cough and eosinophilia. Radiographic findings include alveolar infiltrates or effusions. Resolution of clinical and radiographic abnormalities occurs in 24 to 48 hours following discontinuation of nitrofurantoin. **Subacute/chronic toxicity** is associated with prolonged therapy. Manifestations include dyspnea, nonproductive cough and malaise. Pulmonary function tests show a restrictive pattern and radiographs show interstitial pneumonitis. Resolution of symptoms may take months following drug discontinuation. Pulmonary function may be permanently impaired. Respiratory failure and death have occurred.
- **Gastrointestinal** - include nausea, flatulence, vomiting, anorexia, diarrhea, dyspepsia, constipation, and abdominal pain. Adverse GI effects may be decreased by administering the drug with food or milk or by reducing dosage. Sialadenitis and pancreatitis occur rarely.
- **Hepatic** - Hepatitis, chronic active hepatitis, and cholestatic jaundice has been reported. Hepatotoxicity is usually reversible but permanent liver failure and death has occurred.
- **Hypersensitivity reactions** - include maculopapular, erythematous or eczematous eruptions; pruritus; urticaria, angioedema; exfoliative dermatitis; erythema multiforme; fever; arthralgia; and anaphylaxis.
- **Hematologic reactions** - include hemolytic anemia due to G6PD deficiency, neutropenia, leukopenia, thrombocytopenia, eosinophilia, megaloblastic anemia, and aplastic anemia.

DRUG INTERACTIONS

DRUG	INTERACTION	MECHANISM
Magnesium trisilicate	↓ nitrofurantoin absorption	
Probenecid	↓ nitrofurantoin efficacy ↑ toxicity	Inhibition of nitrofurantoin renal excretion

FORMULARY STATUS

Nitrofurantoin is a **CATEGORY I (formulary)** agent at San Francisco VA Medical Center.

PENTAMIDINE

INDICATIONS

•Treatment of ***Pneumocystis jirovecii*** **pneumonia** (PCP) **in patients who cannot tolerate or** who **fail** to respond to **trimethoprim/sulfamethoxazole**
•**Alternative agent for** treatment of **African trypanosomiasis or leishmaniasis**

SPECTRUM

Pentamidine is an aromatic diamidine-derivative antiprotozoal agent. It is active against *Pneumocystis **jirovecii.*** It is also active against many species of *Trypanosoma* and *Leishmania*.

DOSING/PHARMACOKINETICS

Pentamidine isethionate is administered as a single daily dose infused over at least one hour. The recommended dose for the treatment of PCP is 4 mg/kg once daily. The recommended duration of therapy is 21 days for AIDS patients with PCP, and 14 days for other patients with PCP.

The elimination half-life of pentamidine is 6.4 to 9.5 hours. The drug appears to be extensively distributed or bound to tissues and is eliminated very slowly from its tissue binding sites. Studies suggest that renal clearance accounts for < 5% of the total body clearance of pentamidine. Dosage adjustments are usually not necessary in patients with renal or hepatic insufficiency. Pentamidine is not removed by hemodialysis or peritoneal dialysis.

ADVERSE REACTIONS

Adverse reactions**,** often severe, occur in most patients who receive parenteral pentamidine. **Nephrotoxicity** is the most common adverse reaction associated with pentamidine (≥ 25%). Serum creatinine and BUN increase gradually and usually appears during the second week of therapy. Renal insufficiency is mild to moderate and is reversible following discontinuation of pentamidine. **Electrolyte abnormalities** include hypocalcemia, hyponatremia, hypomagnesemia, and hyperkalemia. Severe hypotension, cardiac arrhythmias, and cardiopulmonary arrest are more likely to occur following rapid intravenous infusion. Pentamidine should be infused over a period of at least one hour to minimize these **cardiovascular reactions**. Severe **hypoglycemia** occurs in 5 to 10% of patients; it usually occurs after 5 to 7 days of therapy. Mild hypoglycemia can be controlled by administration of intravenous glucose. **Hyperglycemia** and insulin-dependent diabetes mellitus may develop during therapy or following discontinuation of pentamidine. **Gastrointestinal side effects** include **acute pancreatitis**, nausea, vomiting, anorexia, and a metallic taste. Liver function tests are elevated in 15 to 70% of patients. **Hematologic toxicity** including neutropenia, thrombocytopenia, and anemia occurs in a high percentage of patients. **Allergic reactions** include fever, rash, urticaria at the injection site, and anaphylaxis. Other side effects include thrombophlebitis, altered mental status, and syncope.

DRUG INTERACTIONS

DRUG	INTERACTION	MECHANISM
Didanosine (ddI)	↑ risk of pancreatitis	Additive effects
Foscarnet	Symptomatic hypocalcemia & renal failure	Additive effects
Nephrotoxic drugs	↑ nephrotoxicity	Additive effects

FORMULARY STATUS

Pentamidine is a **CATEGORY I (formulary)** antibiotic at San Francisco VA Medical Center.

PIPERACILLIN/TAZOBACTAM (ZOSYN®)

INDICATIONS

•**Monotherapy for** suspected or documented **severe polymicrobial infections** (e.g., intraabdominal processes, diabetic foot infections) **involving gram negative rods, *Staphylococcus aureus,*** and **anaerobes**
•Treatment of ***Pseudomonas aeruginosa* infections**
•Empiric therapy of **infection in the neutropenic cancer patient**
•Treatment of **gram-negative hospital-acquired pneumonia**

SPECTRUM

Zosyn® is a fixed combination of piperacillin and the beta-lactamase inhibitor tazobactam. Tazobactam expands the activity of piperacillin against many beta-lactamase producing strains of *S. aureus, Staphylococcus epidermidis, Haemophilus influenzae,* Enterobacteriaceae, *Moraxella catarrhalis* and *Bacteroides* spp. Tazobactam has limited inhibitory activity against the chromosomal beta-lactamases produced by *Enterobacter* species, *Citrobacter freundii, Serratia marcescens*, and *P. aeruginosa;* thus Zosyn® is generally equivalent to piperacillin against the aforementioned organisms. Gram-negative organisms with a piperacillin MIC $\leq$ 16 μg/ml are considered susceptible while organisms with a MIC $\geq$ 128 μg/ml are considered resistant. Staphylococci are considered sensitive if the MIC $\leq$ 8 μg/ml.

DOSING/PHARMACOKINETICS

CREATININE CLEARANCE (ML/MIN)	STANDARD DOSE (GM)*	NOSOCOMIAL PNEUMONIA OR PSEUDOMONAS (GM)
> 40	4.5 q8h or 3.375 q6h	4.5 q6h
20-40	2.25 q6h	4.5 q8h or 3.375 q6h
< 20	2.25 q8h	2.25 q6h
Hemodialysis[#]	2.25 q12h	2.25 q8h

*Zosyn® 4.5 gm contains piperacillin 4 gm and tazobactam 0.5 gm
[#]0.75 g should be administered following each hemodialysis session

The elimination half-life of piperacillin/tazobactam is 0.8-0.9 hour. The drug's clearance is reduced and half-life is prolonged in renally impaired patients; therefore dosage adjustment is necessary (see above). Peak plasma concentrations following a 30-minute infusion of piperacillin/tazobactam 4/0.5 gm are 277/34 μg/ml.

DRUG INTERACTION

DRUG	INTERACTION	MECHANISM
Methotrexate	↑ methotrexate levels & toxicity	↓ renal tubular secretion of methotrexate

FORMULARY STATUS

Zosyn® is a **CATEGORY II (Restricted)** antibiotic at the San Francisco VA Medical Center. This drug will not be dispensed by pharmacy
without prior approval by the Infectious Diseases Section except in ICU and ED patients. ED patients initiated on Zosyn® will need ID approval upon transfer unless they are transferred to the ICU. Single peri-procedural doses do not require ID approval.

POSACONAZOLE

INDICATIONS

•**Prophylaxis against invasive fungal infections** in hematopoietic stem cell transplant recipients with graft-versus-host disease and in patients undergoing chemotherapy for acute myelogenous leukemia

•Treatment of **serious fungal infections** (e.g., zygomycosis, non-meningeal coccidioidomycosis) in patients who are refractory or intolerant to standard antifungal therapy

•Treatment of **oral or esophageal candidiasis** in patients who failed to respond to voriconazole, fluconazole, and itraconazole

SPECTRUM

Posaconazole is a broad-spectrum second-generation triazole that has enhanced inhibition of CYP450-dependent 14α-sterol demethylase, an enzyme involved in ergosterol biosynthesis. It is structurally related to itraconazole Posaconazole has in vitro activity against most yeast, dimorphic fungi, and molds. It has excellent activity against *Cryptococcus* and *Candida* species including many isolates that are resistant to other azoles. Posaconazole also has excellent activity against molds including *Aspergillus* spp., *Fusarium*, spp., and Zygomycetes. Dimorphic fungi including *Coccidiodes* and *Histoplasma* species are inhibited by posaconazole.

DOSING/PHARMACOKINETICS

INDICATION	DOSEtablet
Prophylaxis or treatment of invasive fungal infections	300 mg PO q12h x 2 doses than 300 mg PO daily

Posaconazole was only available as a poorly water- soluble oral suspension when first introduced.. This formulation has rarely been used following the introduction of 100 mg delayed-release tablets Trough serum levels of 0.7 mcg/ml are recommended for prophylaxis and 1.25 mcg/ml are recommended for treatment of invasive fungal infections. **Each dose of posaconazole should be taken with food.** Posaconazole has a large volume of distribution (1774 L) and 98% is bound to plasma protein. Posaconazole is predominately eliminated as unchanged drug in the feces (66%). The elimination half-life ranges from 20-66 hours. Dosage adjustment is not required in patients with hepatic or renal insufficiency.

ADVERSE REACTIONS

Central nervous system –headache, blurred vision, tremors, dizziness, fatigue, weakness, insomnia, anxiety, somnolence, paresthesia

Dermatologic – rash, petechiae, pruritus

Hypersensitivity - fever, rigors

Gastrointestinal – nausea, vomiting, abdominal pain, diarrhea, mucositis, constipation, dyspepsia, anorexia, taster perversion, flatulence, dry mouth

Hepatic – increased aminotransferases, hyperbilirubinemia, increased alkaline phosphatase, hepatitis, hepatomegaly, jaundice

Cardiovascular – hypertension, hypotension, edema, QT prolongation, tachycardia, torsade de pointes (rare)

Renal/Electrolyte –hypokalemia, hypomagnesemia, hypocalcemia, elevated serum creatinine, dehydration, acute renal failure

Hematologic – anemia, neutropenia, thrombocytopenia, hemolytic uremic syndrome (rare), thrombotic thrombocytopenic purpura (rare)

Other – vaginal hemorrhage, hyperglycemia, musculoskeletal pain, arthralgia, back pain, coughing, dyspnea, epistaxis, weight loss, increased sweating, adrenal insufficiency (rare), pulmonary embolus (rare)

DRUG INTERACTIONS

DRUG	INTERACTION	MECHANISM
Alprazolam, midazolam, triazolam	↑ benzodiazepine levels	↓ benzodiazepine metabolism
Apixaban	↑ apixaban levels	↓ apixaban metabolism
Atazanavir	↑ atazanavir levels	↓ atazanavir metabolism
Atorvastatin, lovastatin, simvastatin	↑ statin levels	↓ statin metabolism
Calcium channel blockers (CCB)	↑ CCB levels	↓ CCB metabolism
Cimetidine*	↓ posaconazole levels	↓ posaconazole absorption
Cisapride	Ventricular arrhythmias	↓ cisapride metabolism
Conivaptan, tolvaptan	↑ conivaptan/tolvaptan levels	↓ conivaptan/ tolvaptan metabolism
Cyclosporine	↑ cyclosporine levels	↓ cyclosporine metabolism
Digoxin	↑ digoxin levels	↓ digoxin metabolism
Efavirenz	↓ posaconazole levels	↑ posaconazole metabolism
Ergot alkaloids	↑ ergot alkaloids levels	↓ drug metabolism
Fosamprenavir	↓ posaconazole levels ↓ fosamprenavir levels	↑ posaconazole metabolism ↑ fosamprenavir metabolism
Halofantrine	Ventricular arrhythmias	↓ halofantrine metabolism
Ibrutinib	↑ ibrutinib levels	↓ ibrutinib metabolism
Lomitapide	↑ lomitapide levels	↓ lomitapide metabolism
Metoclopramide*	↓ posaconazole levels	↓ posaconazole absorption
Omeprazole, esomeprazole*	↓ posaconazole levels	↓ posaconazole absorption
Oral hypoglycemics	↑ hypoglycemic effect	↓ sulfonylurea metabolism
Phenytoin	↓ posaconazole levels	↑ posaconazole metabolism
Pimozide	Ventricular arrhythmias	↓ pimozide metabolism
Ponatinib	↑ ponatinib levels	↓ ponatinib metabolism
Quinidine	Ventricular arrhythmias	↓ quinidine metabolism
Rifabutin	↓ posaconazole levels ↑ rifabutin levels	↑ posaconazole metabolism ↓ rifabutin metabolism
Rifampin	↓ posaconazole levels	↑ posaconazole metabolism
Ritonavir	↑ ritonavir levels	↓ ritonavir metabolism
Simeprevir	↑ simeprevir levels	↓ simeprevir metabolism
Sirolimus	↑ sirolimus levels	↓ sirolimus metabolism
Tacrolimus	↑ tacrolimus levels	↓ tacrolimus metabolism
Vinblastine, vincristine	↑ neurotoxicity	↓ vinca alkaloid metabolism
Vorapaxar	↑ vorapaxar levels	↓ vorapaxar metabolism

*interacts with posaconazole suspension but not tablets

FORMULARY STATUS

Posaconazole is a **NON-FORMULARY** antibiotic at San Francisco VA Medical Center. This drug will not be dispensed by pharmacy without prior approval by the Infectious Diseases Section and completion of an electronic non-formulary drug request.

PRIMAQUINE

INDICATIONS

•**Treatment** (in combination with clindamycin) **of mild to moderate** *Pneumocystis jirovecii* pneumonia (**PCP**) (PaO_2 > 60 mm Hg) **in AIDS patients** who are **intolerant of trimethoprim-sulfamethoxazole and trimethoprim-dapsone**

•**Terminal prophylaxis for travelers who are likely to have had a high level of exposure to *Plasmodium vivax* or *P. ovale***

•**Radical cure for malaria caused by *P. vivax* or *P. ovale*** (following completion of chloroquine therapy)

•Alternative agent for **prophylaxis of malaria in travelers to chloroquine resistant areas**

SPECTRUM

Primaquine is an 8-aminoquinolone derivative. Its mechanism of action is unknown, but primaquine or its metabolites may disrupt mitochondrial function and bind to native DNA. Primaquine is the only antimalarial agent with activity against hypnozoites of *P. vivax and P. ovale*. Thus, it prevents relapses of infections from their dormant hepatic stages. The drug is a tissue schizonticidal agent and is active against the preerythrocytic and exoerythrocytic forms of *P. vivax, P. ovale, P. malariae*, and *P. falciparum*. In addition, primaquine is sporonticidal and gametocytocidal but is inactive against the asexual erythrocytic forms of plasmodia. Primaquine resistance has been reported in *P. vivax*. Primaquine has in vitro activity against *Pneumocystis jirovecii*, and synergy is achieved when it is used in combination with clindamycin.

DOSING/PHARMACOKINETICS

INDICATION	DOSAGE REGIMEN*	DURATION OF THERAPY
PCP, mild to moderate†	15 mg daily	21 days
Terminal prophylaxis for high level exposure to *P. vivax* or *P. ovale*	30 mg daily	14 days
Radical cure for malaria caused by *P. vivax* or *P. ovale*	30 mg daily	14 days
Prophylaxis of malaria	30 mg daily	Beginning 1 day prior to travel and continued 3-7 days after return

*****Expressed as primaquine base

†in combination with clindamycin 600 mg IV q6-8h or 300-450 mg PO q6h

Primaquine is well absorbed following oral administration. Peak plasma concentrations are generally attained within six hours and plasma levels are negligible after 24 hours. Considerable inter-individual variation in peak plasma levels has been reported. Primaquine is extensively metabolized in the liver and only a small amount (~1%) is excreted as unchanged drug in the urine. Carboxyprimaquine is the primary metabolite. Carboxyprimaquine and other metabolites have varying degrees of antimalarial activity. The elimination half-life is 3.7-9.6 hours. Primaquine is available as primaquine phosphate tablets containing 26.3 mg of salt, which is equivalent to 15 mg of base.

ADVERSE REACTIONS

•**Hemolytic anemia** - Acute hemolytic anemia may occur, especially in patients with **G6PD deficiency**. Primaquine should not be used in individuals with G6PD deficiency.

•**Methemoglobinemia** - Methemoglobinemia may occur if primaquine is administered to patients with **NADH methemoglobin reductase deficiency** or if the daily dose ≥ 30 mg. Methemoglobin levels should be monitored in patients with symptoms or in patients taking primaquine for PCP treatment; the drug should be discontinued in patients with a methemoglobin concentration > 20%.

•**Other** primaquine-induced side effects include rash, nausea, vomiting, abdominal cramps, headache, impaired visual accommodation, pruritus, and leukopenia. Hypertension and arrhythmias have been reported rarely.

FORMULARY STATUS

Primaquine is a **CATEGORY I (formulary)** agent at San Francisco VA Medical Center.

PYRAZINAMIDE

INDICATIONS

•**Treatment of tuberculosis** (in combination with other antituberculosis agents, e.g., isoniazid, rifampin, and ethambutol)

SPECTRUM

Pyrazinamide (PZA) is a synthetic analogue of nicotinamide. Its exact mechanism of action has not been determined, but appears to depend at least in part on its conversion to pyrazinoic acid (POA). Susceptible strains *Mycobacterium tuberculosis* produce an enzyme, pyrazinamidase, that deaminates PZA to POA. PZA is bactericidal in the acidic intracellular environment of macrophages. The MIC of most *M. tuberculosis* isolates is ≤ 20 µg/ml if tested at a pH of 5.5. When used alone, resistance develops rapidly; however, no cross-reactivity with other anti-tuberculosis agents has been observed.

DOSING/PHARMACOKINETICS

Dosing is based on estimated lean body weight. The recommended daily dose of PZA for the treatment of tuberculosis is 20-25 mg/kg (up to 2 g). When PZA is administered in a 2 or 3 times per week regimen, it is given at 36-54 mg/kg (up to 4,000 mg) and 27-45 mg/kg (up to 3,000 mg), respectively. When used in combination with isoniazid and rifampin as part of a 6 month treatment regimen, PZA is administered during the first two months of therapy only. PZA is available as 500 mg tablets.

PZA is readily absorbed following oral administration. Peak serum levels of 45 µg/ml are achieved 2 hours following the oral administration of 1 g of PZA. The drug is widely distributed into body tissues and fluids including the liver, lungs, and cerebrospinal fluid. PZA is hydrolyzed in the liver to pyrazinoic acid, which is then hydroxylated to the major excretory product, 5-hydroxypyrazinoic acid. About 3-4% of a dose is excreted as unchanged drug in the urine, but its metabolites may accumulate in patients with renal insufficiency. The elimination half-life is 9-10 hours in patients with normal renal and hepatic function. Plasma protein binding is 50%.

ADJUSTMENT OF DOSAGE REGIMENS IN PATIENTS WITH RENAL INSUFFICIENCY

Creatinine Clearance	Dose	Adjusted Dosing Interval
< 30 ml/min	25-35 mg/kg	3 times weekly

ADVERSE DRUG REACTIONS

•**Hepatic** - Transient increases in transaminases, jaundice, hepatitis, and a syndrome of fever anorexia, malaise, liver tenderness, hepatomegaly, and splenomegaly have been reported. Hepatotoxicity is dose related and appears to be rare in patients who receive the recommended dose of 20-25 mg/kg during the initial 2 months of therapy. Many cases of severe hepatotoxicity have been reported in patients who received PZA in combination with rifampin for the treatment of latent tuberculosis infection.

•**Hyperuricemia** - PZA decreases the renal tubular secretion of urate. Hyperuricemia occurs frequently, but active gout is uncommon. Nongouty polyarthralgia occurs in up to 40% of patients.

•**Gastrointestinal** - Anorexia, nausea, vomiting, and diarrhea

•**Other** - Maculopapular rash, fever, urticaria, photosensitivity, pruritus, acne, porphyria, dysuria, thrombocytopenia, and sideroblastic anemia (rare)

FORMULARY STATUS

Pyrazinamide is a **CATEGORY I (formulary)** agent at San Francisco VA Medical Center.

PYRIMETHAMINE

INDICATIONS

•Treatment of **toxoplasmic encephalitis in AIDS** patients (in combination with sulfadiazine 1 to 1.5 gm q6h and leucovorin 10 mg daily)

•**Chronic suppressive therapy** of **toxoplasmic encephalitis in AIDS** patients

SPECTRUM

Pyrimethamine is a folate antagonist. It acts by inhibiting dihydrofolate reductase, the enzyme responsible for the reduction of dihydrofolic acid (folic acid) to tetrahydrofolic acid (folinic acid). Pyrimethamine is active against the replicating trophozoite of *Toxoplasma gondii*. The drug is also active against the asexual erythrocytic forms of susceptible *Plasmodium* species.

DOSING/PHARMACOKINETICS

TABLE I: Pyrimethamine dosage guidelines for treatment of toxoplasmic encephalitis

INDICATION	LOADING DOSE	DAILY DOSE
Active Disease	200 mg in 2 divided doses x 1 day	50 mg (weight < 60 kg) 75 mg (weight ≥ 60 kg)
Suppression	None	25-50 mg

Pyrimethamine is well absorbed following oral administration. Peak serum levels of 1 to 4.5 µg/ml are achieved following 25 to 75 mg oral doses of pyrimethamine. The drug is hepatically metabolized, its elimination half-life is approximately 100 hours. Pyrimethamine's apparent volume of distribution is 3 L/Kg. Cerebrospinal fluid levels are 10 to 25 percent of concomitant serum levels.

ADVERSE REACTIONS

Bone marrow suppression is the major dose limiting toxicity of pyrimethamine. Megaloblastic anemia, leukopenia, neutropenia, and thrombocytopenia occur frequently. Administration of leucovorin may prevent bone marrow suppression. The initial daily dose of **leucovorin** is 10 mg. The daily leucovorin dose may be increased to 50 mg if myelosuppression occurs. Coadministration of trimethoprim/sulfamethoxazole may increase the incidence of megaloblastic anemia. Other myelosuppressive drugs should be avoided if possible. Other adverse reactions include rash, vomiting, abdominal cramps, anorexia, ataxia, and seizures.

DRUG INTERACTIONS

DRUG	INTERACTION	MECHANISM
Myelosuppressive drugs	↑ risk of hematologic toxicity	Additive effects
Trimethoprim-sulfamethoxazole	↑ megaloblastic anemia	Additive effects

FORMULARY STATUS

Pyrimethamine is a **CATEGORY II (restricted)** antibiotic at San Francisco VA Medical Center. This drug will not be dispensed by pharmacy without prior approval by the Infectious Diseases Section.

RIFABUTIN

INDICATIONS

•Alternative to azithromycin for prevention of disseminated *Mycobacterium avium* complex (MAC) disease in AIDS patients with CD4 lymphocyte counts ≤ 50/mm^3

•Treatment of disseminated MAC disease in AIDS patients with moderate to severe disease in combination with other agents including clarithromycin and ethambutol

•Treatment of tuberculosis (in combination with other antituberculosis agents) **in HIV-infected patients who cannot receive rifampin because of drug-drug interactions or adverse effects**

SPECTRUM

Rifabutin is a derivative of rifamycin S and inhibits DNA-dependent RNA polymerase in susceptible bacteria. Rifabutin inhibits DNA-dependent RNA polymerase in susceptible bacteria. . The gram-positive and gram-negative activity of rifabutin is similar to that of rifampin. Emergence of resistance is predictable when rifabutin is used as a single agent to treat bacterial infections. Rifabutin possesses good activity against most mycobacteria including *M. tuberculosis, M. marinum,* and *M. kansasii*. Rifabutin is active against many isolates of *M. tuberculosis* with resistance to low levels of rifampin; however, isolates with resistance to higher levels of rifampin demonstrate cross-resistance to rifabutin. Several studies have demonstrated the good in vitro activity of rifabutin against MAC. Rifabutin is bacteriostatic against MAC when it is used as a single agent. MIC's for MAC strains range from 25 to 2,000 ng/ml. Synergy and bactericidal activity has been demonstrated when rifabutin is used in combination with other drugs active against MAC, e.g., ethambutol and clarithromycin. Rifabutin has been shown to inhibit the replication of HIV-1 and to reduce the cytopathic effect of HIV-1 to CD4 lymphocytes. However, when studied as a single agent in HIV-infected patients, rifabutin lacked beneficial effects.

DOSING/PHARMACOKINETICS

The recommended dose of rifabutin for the prevention of disseminated MAC disease is **300 mg once daily**. The recommended dose of rifabutin for the treatment of tuberculosis in HIV-infected patients is 300 mg daily in the absence of drug-drug interactions. A rifabutin dose of 450 to 600 mg daily or intermittently is recommended in patients receiving efavirenz. Doses of 150 mg daily or intermittently are recommended for patients receiving most protease inhibitors (see Adult and Adolescent Treatment Guidelines at http://aidsinfo.nih.gov/ for specific dosage guidelines). Peak serum levels of about 350 ng/ml are achieved following administration of rifabutin 300 mg. Peak levels occurred 2 to 3 hours after oral administration. Oral bioavailability is 12 to 20 percent; the presence of food decreases the rate of rifabutin absorption but not the extent of absorption. Rifabutin is metabolized in the liver to two major metabolites, hydroxy rifabutin and 25-desacetyl rifabutin. The microbiologic activity of the desacetyl derivative is similar to rifabutin, while the hydroxy metabolite is 4 to 10 fold less active. About 10 percent of rifabutin is excreted as unchanged drug in the urine. The elimination half-life is about 36 hours. **Dosage should be reduced by 50% in patients with creatinine clearances < 30 ml/min.** Rifabutin is widely distributed to all tissues and body fluids. Lung concentrations are 5 to 10 times higher than concomitant serum levels. Plasma protein binding is 71 percent and the volume of distribution is 8 to 9 liters/kg.

ADVERSE REACTIONS

In the double-blind trials that studied rifabutin for the prevention of disseminated MAC infection, side effects that resulted in the discontinuation of rifabutin occurred in 16 percent of patients. Reasons for the discontinuation of rifabutin included rash (4%), gastrointestinal intolerance (3%), neutropenia (2%), myalgias (≤3%), eructation (≤3%), and dysgeusia (≤3%). Side effects reported in at least one

percent of rifabutin recipients include abdominal pain, asthenia, chest pain, fever, headache, anorexia, diarrhea, dyspepsia, eructation, flatulence, nausea, vomiting, myalgia, insomnia, rash, taste perversion, and urine discoloration. Adverse reactions that occurred in less than one percent of patients but appeared to be caused by rifabutin include flu-like syndrome, hepatitis, hemolysis, arthralgia, myositis, chest pressure or pain with dyspnea, and skin discoloration. Laboratory abnormalities associated with rifabutin therapy include liver function test elevations, anemia, eosinophilia, leukopenia, neutropenia, and thrombocytopenia. Dose-related toxicity includes gastrointestinal side effects, head or muscle ache, symmetrical polyarthralgia and arthritis, uveitis, and apthous stomatitis.

DRUG INTERACTIONS*

DRUG	INTERACTION	MECHANISM
Atazanavir	↑ rifabutin levels	↓ rifabutin metabolism
Atovaquone	↓ atovaquone & rifabutin levels	Unknown
Clarithromycin	↑ rifabutin levels ↓ clarithromycin levels	↓ rifabutin metabolism Unknown
Cobicistat	↓ cobicistat levels	↑ cobicistat metabolism
Darunavir	↑ rifabutin levels ↓ darunavir levels	↓ rifabutin metabolism ↑ darunavir metabolism
Delavirdine	↓ delavirdine levels ↑ rifabutin levels	↑ delavirdine metabolism ↓ rifabutin metabolism
Efavirenz	↓ rifabutin levels	↑ rifabutin metabolism
Elvitegravir	↓ elvitegravir levels	↑ elvitegravir metabolism
Etravirine	↓ etravirine levels ↓ rifabutin levels	↑ etravirine metabolism
Fluconazole	↑ rifabutin levels	↓ rifabutin metabolism
Fosamprenavir	↑ rifabutin levels ↓ fosamprenavir levels	↓ rifabutin metabolism ↑ fosamprenavir metabolism
Indinavir	↓ indinavir levels ↑ rifabutin levels	↑ indinavir metabolism ↓ rifabutin metabolism
Itraconazole	↓ itraconazole levels	↑ itraconazole metabolism
Lopinavir / Ritonavir	↑ rifabutin levels	↓ rifabutin metabolism
Nelfinavir	↓ nelfinavir levels ↑ rifabutin levels	↑ nelfinavir metabolism ↓ rifabutin metabolism
Nevirapine	↓ nevirapine levels	↑ nevirapine metabolism
Posaconazole	↓ posaconazole levels ↑ rifabutin levels	↑ posaconazole metabolism ↓ rifabutin metabolism
Rilpivirine	↓ rilpivirine levels	↑ rilpivirine metabolism
Ritonavir	↑ rifabutin levels	↓ rifabutin metabolism
Saquinavir	↓ saquinavir levels	↑ saquinavir metabolism
Tenofovir AF	↓ tenofovir AF levels	↑ tenofovir AF metabolism
Tipranavir	↑ rifabutin levels	↓ rifabutin metabolism
Voriconazole	↓ voriconazole levels ↑ rifabutin levels	↑ voriconazole metabolism ↓ rifabutin metabolism
Zidovudine (AZT)	↓ AZT levels	Unknown

***Overall, P450 induction by rifabutin is less significant than that by rifampin and fewer drugs are contraindicated when coadministered with rifabutin than with rifampin. Dosage adjustment of drugs that are known to interact with rifampin MAY be required if they are given concomitantly with rifabutin,** e.g., atovaquone, anticoagulants, corticosteroids, phenytoin, and dapsone.

FORMULARY STATUS

Rifabutin is a **CATEGORY II (restricted)** antibiotic at San Francisco VA Medical Center. This drug will not be dispensed by pharmacy without prior approval by the Infectious Diseases Section.

RIFAMPIN

INDICATIONS

•**Treatment of tuberculosis** (in combination with other antituberculosis agents, e.g., isoniazid, pyrazinamide, and ethambutol)
•**Alternative** to isoniazid for **treatment of latent tuberculosis infection**
•**Treatment of multibacillary leprosy** (in combination with dapsone and clofazimine)
•**Treatment of dapsone-resistant paucibacillary leprosy** (in combination with clofazimine)
•**Chemoprophylaxis of meningococcal or *Haemophilus influenzae* type b (Hib) infection**
•**Treatment of infection caused by *Mycobacterium kansasii*** (in combination with isoniazid and ethambutol) or ***M. marinum*** (in combination with clarithromycin)
•**Treatment of *Staphylococcus epidermidis* prosthetic valve endocarditis (PVE)** (in combination with vancomycin and gentamicin)
•**Treatment of gram positive prosthetic joint infections with retained prosthesis** (in combination with other appropriate agents)
•**Alternative agent** (in combination with other antimicrobials) **for the treatment of infection caused by *M. avium* complex, *M. fortuitum* complex, *Legionella* species, *S. aureus*, and *Brucella* species**

SPECTRUM

Rifampin is a derivative of rifamycin B and inhibits DNA-dependent RNA polymerase in susceptible bacteria. The drug possesses excellent in vitro activity against most aerobic bacteria, but emergence of resistance is predictable when rifampin is used as a single agent to treat bacterial infections. Rifampin possesses good activity against most mycobacteria including *M. tuberculosis, M. leprae, M. marinum,* and *M. kansasii*. The drug is bactericidal against *M. tuberculosis*. Most strains of *M. tuberculosis* are inhibited by ≤ 0.5 µg/ml.

DOSING/PHARMACOKINETICS

INDICATION	DOSAGE REGIMEN	DURATION OF THERAPY
Tuberculosis	600 mg twice weekly to daily	≥ 4 months
Latent tuberculosis infection	600 mg daily	4 months
Chemoprophylaxis of meningococcal infection	600 mg bid	2 days
Chemoprophylaxis of Hib infection	600 mg daily	4 days
S. epidermidis PVE	300 mg q8h	≥ 6 weeks
Staphylococcal prosthetic joint infections	300-450 mg PO q12h	≥ 6 weeks

Rifampin is readily absorbed following oral administration. Peak serum levels of 4-32 µg/ml are achieved 1.5-2 hours following the oral administration of 600 mg of rifampin. The rate of absorption is reduced when rifampin is administered with food. Rifampin is widely distributed into most body tissues and fluids including the inflamed meninges. The drug is deacetylated in the liver to an active metabolite. Rifampin and its metabolite are eliminated through the biliary tract. Rifampin undergoes enterohepatic recirculation. Three to thirty percent of an oral dose is excreted in the urine as unchanged drug or metabolite. Dosage adjustment is unnecessary in patients with renal failure. Rifampin is not appreciably removed by hemodialysis or by peritoneal dialysis. The elimination half-life is 2-3 hours, and plasma protein binding is 75-91%.

ADVERSE REACTIONS

•**Hepatic** - Transient increases in transaminases and bilirubin concentration occur in ≤ 14% of patients. Hepatitis is uncommon (≤ 1%).
•**Gastrointestinal** - Anorexia, nausea, vomiting, diarrhea, epigastric distress, abdominal pain, cramps, gas, sore mouth and tongue (1-2%); pseudomembranous colitis and pancreatitis (rare)
•**Hypersensitivity Reactions** - Fever, rash, pruritus, flushing (1-5%); urticaria, pemphigoid reaction, and anaphylaxis (rare)
•**Hematologic** - Eosinophilia, thrombocytopenia, hemolytic anemia, and neutropenia (rare)
•**Renal** - Hemoglobinuria, hematuria, interstitial nephritis, renal insufficiency, and acute renal failure
•**Nervous system** - Headache, drowsiness, fatigue, dizziness, inability to concentrated, confusion, numbness, and behavioral changes (uncommon)
•**High dose intermittent therapy** - Associated with an increased frequency of side effects including renal, hematologic, and hypersensitivity reactions. An "influenza-like" syndrome and respiratory syndrome may also be associated with high dose therapy.
•**Other** - **Red orange discoloration of urine, sweat, sputum, feces and tears is common.** Menstrual disturbances, visual disturbances, conjunctivitis, myopathy, muscle weakness, pain in extremities, and osteomalacia.

DRUG INTERACTIONS

DRUG	INTERACTION	MECHANISM
Atovaquone	↓ atovaquone levels	Unknown
Azole antifungal agents	↓ azole levels	↑ azole metabolism
Clarithromycin	↓ clarithromycin levels	Unknown
Cobicistat	↓ cobicistat levels	↑ cobicistat metabolism
Daclatasvir	↓ daclatasvir levels	↑ daclatasvir metabolism
Dapsone	↓ dapsone levels	↑ dapsone metabolism
Delavirdine	↓ delavirdine levels	↑ delavirdine metabolism
Efavirenz	↓ efavirenz levels	↑ efavirenz metabolism
Elbasvir/Grazoprevir	↓ elbasvir/grazoprevir levels	↑ elbasvir/grazoprevir levels
Elvitegravir	↓ elvitegravir levels	↑ elvitegravir metabolism
Etravirine	↓ etravirine levels	↑ etravirine metabolism
HCV & HIV protease inhibitors (PI)	↓ PI levels	↑ PI metabolism
Maraviroc	↓ maraviroc levels	↑ maraviroc metabolism
Nevirapine	↓ nevirapine levels	↑ nevirapine metabolism
Raltegravir	↓ raltegravir levels	↑ raltegravir metabolism
Rilpivirine	↓ rilpivirine levels	↑ rilpivirine metabolism
Sofosbuvir	↓ sofosbuvir levels	↑ sofosbuvir metabolism
Tenofovir AF	↓ tenofovir AF levels	↑ tenofovir AF metabolism
Trimethoprim-sulfamethoxazole (TMP-SMX)	↓ TMP & SMX levels	↑ hepatic metabolism
Zidovudine	↓ zidovudine levels	Unknown
Afatinib, aliskiren, amiodarone, aprepitant, aripiprazole, artemether-lumefantrine, axitinib, barbiturates, bedaquiline, benzodiazepines, bortezomib, bosentan, bosutinib, brentuximab, bupropion, buspirone, cabazitaxel, cabozantinib , canagliflozin, caspofungin, celecoxib, ceritinib, chloramphenicol, clofibrate, clozapine, cobimetinib, corticosteroids, crizotinib, cyclosporine, dabrafenib, dasatinib, dienogest, digoxin, diltiazem, disopyramide, DOACs, doxycycline, eliglustat, enalapril, enzalutamide erlotinib, eszopiclone, estrogens, everolimus, exemestane, fexofenadine, gefitinib, haloperidol, ibrutinib, idelalisib, imatinib, irinotecan, ivacaftor, ixabepilone, ixazomib, lamotrigine, lapatinib, levothyroxine, linezolid, lomitapide, losartan, lurasidone, macitentan, mefloquine, methadone, metoprolol, metronidazole, mexiletine, mifepristone, mycophenolate, narcotics, nifedipine, nilotinib**,** nintedanib, olaparib, ondansetron, osimertinib, oral contraceptives, oral hypoglycemics, palbociclib, panobinostat, perampanel, phenytoin, pomalidomide, ponatinib, praziquantel, progestins, propafenone, propranolol, romidepsin, quetiapine, quinidine, quinine, ramelteon, ranolazine, regorafenib, risperidone, roflumilast, romidepsin, sertraline, sirolimus, sonidegib, sorafenib, statins, sunitinib, tacrolimus, tamoxifen, temsirolimus, terbinafine, theophylline, thiazolidinediones, ticagrelor, tocainide, tofacitinib, tolvaptan, toremifene, trabectedin, tricyclic antidepressants, ulipristal, valproic acid, vandetanib, venetoclax, verapamil, warfarin, zolpidem	↓ drug levels	↑ metabolism

FORMULARY STATUS

Rifampin is a **CATEGORY I (formulary)** agent at San Francisco VA Medical Center.

SULFADIAZINE

INDICATIONS

- Treatment of **toxoplasmic encephalitis in AIDS** patients (in combination with pyrimethamine 75 mg daily and leucovorin 10 mg daily)
- **Chronic suppressive therapy** of **toxoplasmic encephalitis in AIDS** patients (in combination with pyrimethamine 25 to 50 mg daily)

SPECTRUM

Sulfadiazine is a short-acting sulfonamide. It acts by inhibiting dihydropteroate synthetase, the enzyme responsible for the conversion of para-aminobenzoic acid (PABA) to dihydropteroate, the immediate precursor of dihydrofolate (folic acid). Sulfadiazine is active against the replicating trophozoite of *Toxoplasma gondii*. Although sulfadiazine is active against many species of gram-negative and gram-positive bacteria, it is not used to treat infections caused by these pathogens because of the availability of less toxic alternatives.

DOSING/PHARMACOKINETICS

Sulfadiazine dosage guidelines for treatment of toxoplasmic encephalitis

INDICATION	DOSAGE REGIMEN
Active Disease	1 gm PO q6h (weight < 60 kg) 1.5 gm PO q6h (weight ≥ 60 kg)
Suppression	2-4 grams daily in 2-4 divided doses

Sulfadiazine is well absorbed following oral administration. Peak serum levels of 20 to 40 µg/ml are achieved following a 500 mg oral dose of sulfadiazine. The drug is partially metabolized in the liver. Approximately 43 to 60 percent is excreted as unchanged drug in the urine. The elimination half-life of sulfadiazine is 10 to 17 hours in patients with normal renal function, but is prolonged to 34 hours in renal failure patients. The sulfonamide should not be given to patients with renal insufficiency due to the increased risk of crystalluria. Cerebrospinal fluid levels are 40 to 80 percent of concomitant serum levels.

ADVERSE REACTIONS

The most important adverse reactions associated with sulfadiazine are hypersensitivity reactions, hematologic toxicity, and **crystalluria**. Hypersensitivity reactions include fever, rash, and rarely Stevens-Johnson syndrome. Hematologic side effects include, neutropenia, megaloblastic anemia, and thrombocytopenia. **Crystalluria** occurs much more frequently with sulfadiazine therapy than with other sulfonamides. Sulfadiazine and its metabolite acetylsulfadiazine are poorly soluble in acidic urine. Sulfadiazine-induced crystalluria may lead to acute renal failure and death. Predisposing factors include dehydration, acidic urine, hypoalbuminemia, and overdosing in patients with underlying renal insufficiency. Patients receiving sulfadiazine should be well hydrated and their urinalysis should be monitored frequently for crystalluria and hematuria.

DRUG INTERACTIONS

DRUG	INTERACTION	MECHANISM
Cyclosporine (CSA)	↓ CSA levels, ↑ nephrotoxicity	Unknown
Methotrexate (MTX)	↑ methotrexate toxicity	Displacement of MTX from protein binding sites and ↓ MTX renal clearance
Oral hypoglycemic agents	↑ risk of hypoglycemia	Inhibition of oral hypoglycemic agent metabolism
Phenytoin	↑ phenytoin levels	Inhibition of phenytoin metabolism
Vitamin C & other urinary acidifying agents	↑ sulfadiazine crystalluria	↓ sulfadiazine solubility in acidic urine
Warfarin	↑ anticoagulant effect	Inhibition of warfarin metabolism

FORMULARY STATUS

Sulfadiazine is a **CATEGORY II (restricted)** antibiotic at San Francisco VA Medical Center. This drug will not be dispensed by pharmacy without prior approval by the Infectious Diseases Section.

TRIMETHOPRIM-SULFAMETHOXAZOLE (TMP-SMX)

INDICATIONS

- Drug of choice for the **prevention and treatment of *Pneumocystis jiroveci* pneumonia** (PCP)
- Treatment of **urinary tract infections** caused by susceptible bacteria, **empiric therapy is not recommended** as the rate of E. coli resistance is > 20%
- **Prophylaxis against recurrent urinary tract infections**
- Treatment of **acute or chronic prostatitis**
- Alternative agent for treatment of **serious infections** (e.g., bacteremia) **caused by susceptible gram-negative bacilli**
- Treatment of **community-acquired skin and soft tissue infections** of mild to moderate severity suspected to be caused by methicillin-resistant *Staphylococcus. aureus* (when concurrent therapy for group A Streptococcus is not indicated)
- Treatment of **otitis media, sinusitis, bronchitis, and pneumonia caused by *Haemophilus influenzae*, or *Moraxella catarrhalis*.**
- Treatment of **third generation cephalosporin-resistant gram-negative bacillary meningitis**
- **Drug of choice for the treatment of infections caused by** *Nocardia* species, *Moraxella catarrhalis*, *Stenotrophomonas maltophilia*, *Burkholderia cepacia*, *Cyclospora* sp., and *Cystoisospora* (*Isospora) belli.*
- **Alternative agent for the treatment of** cholera, brucellosis, melioidosis, granuloma inguinale, pertussis, toxoplasmosis, listeriosis, Whipple's disease, Wegner's granulomatosis, and *Mycobacterium marinum* infection

SPECTRUM

TMP acts by inhibiting dihydrofolate reductase (DHFR), the enzyme responsible for the reduction of dihydrofolic acid (folic acid) to tetrahydrofolic acid (folinic acid). SMX acts by inhibiting dihydropteroate synthetase, the enzyme responsible for the conversion of para-aminobenzoic acid [PABA] to dihydropteroate, the immediate precursor of dihydrofolic acid. TMP-SMX forms a synergistic bactericidal combination that sequentially inhibits the synthesis of folinic acid, a substrate necessary for nucleic acid synthesis. TMP-SMX has a broad gram negative spectrum including most Enterobacteriaceae, *Haemophilus* species, *Neisseria meningitidis*, *M. catarrhalis*, *Acinetobacter* species, *Yersinia* species, *B. cepacia, Ps. pseudomallei*, *S. maltophilia*, *Vibrio chloerae*, *Brucella* species, *Aeromonas* species, and *Bordetella pertussis*. Resistant gram-negative bacteria include *Ps. aeruginosa* and *Campylobacter* species. The emergence of plasmid-mediated TMP-SMX resistant strains of *Shigella* and *Salmonella* and the overproduction of a resistant DHFR by *Escherichia coli* are of growing concern. TMP/SMX's gram-positive spectrum includes *Listeria monocytogenes*, *S. pneumoniae, and Staph*. *aureus* including most methicillin-resistant isolates. Other susceptible organisms include *Nocardia* species, *Mycobacterium marinum, P. jiroveci*, *Plasmodium* species, and *Cystoisospora belli*. Bacteria with a TMP/SMX MIC of $\leq$ 2/38 µg/ml are considered sensitive, while organisms with an MIC $\geq$ 4/76 µg/ml are considered resistant.

DOSING/PHARMACOKINETICS

INDICATION	DOSAGE REGIMEN	DURATION OF THERAPY
Uncomplicated UTI, female	1 DS* Tablet BID	3 days
Conventional, male or female UTI	1 DS Tablet BID	7-10 days
UTI prophylaxis	1/2 DS Tablet qod	variable
Chronic prostatitis	1 DS Tablet BID	6-12 weeks
Pyelonephritis	1 DS Tablet BID	10-14 days
PCP	5 mg/kg of TMP Q8H	14-21 days
PCP prophylaxis	1 DS Tablet daily or 3x/week	Resolution of PCP risk factor
Skin and soft tissue infection due to MRSA#	2 DS Tablets BID	7-10 days
Upper respiratory tract infections	1 DS Tablet BID	7-10 days
Serious bacterial infections	5 mg/kg of TMP Q12H	variable

*DS = double strength (160 mg TMP & 800 mg SMX)

#Many infections respond to incision and drainage without antimicrobials

USUAL DOSAGE	CREATININE CLEARANCE	ADJUSTED DOSAGE
1 DS Tablet BID	15-30 ml/min	1/2 DS Tablet BID
1 DS Tablet BID	< 15 ml/min*	1/2 DS Tablet daily
5 mg/kg of TMP q12h	10-30 ml/min	2.5-3.75 mg/kg of TMP q12h
5 mg/kg of TMP q12h	< 10 ml/min*	2.5-5 mg/kg of TMP q24h
5 mg/kg of TMP q8h	10-30 ml/min	5 mg/kg of TMP q12h
5 mg/kg of TMP q8h	< 10 ml/min*	5-7.5 mg/kg of TMP q24h

*For hemodialysis patients, give dose at the end of dialysis on dialysis days

TMP-SMX is well absorbed following oral administration. A fixed oral or intravenous combination of 1:5 (TMP:SMX) results in an optimal synergistic bactericidal concentration ratio of 1:20 (TMP:SMX). Mean peak serum concentrations of 3.4 µg/ml TMP and 46.3 µg/ml SMX are achieved after a single intravenous dose of 160 mg TMP and 800 mg SMX. TMP-SMX distributes widely to body fluids and tissues including cerebrospinal fluid and the prostate. TMP and SMX are hepatically metabolized with 80% of TMP and 20% of SMX excreted as unchanged drug in urine. Urinary excretion of SMX is increased by alkalinization of the urine, while urinary excretion of TMP is increased by acidification of the urine. Following oral administration of 160 mg TMP and 800 mg SMX, urine TMP levels of 30-120 µg/ml and SMX levels of 100-500 µg/ml are achieved. In patients with normal renal function, the elimination half-life of TMP and SMX is 8-11 hours and 10-12 hours, respectively. Dosage reduction is necessary in patients with renal insufficiency (see above).

ADVERSE REACTIONS

Dose independent side effects of TMP-SMX include GI upset, drug fever, headache, and rash. Nephrotoxicity, hyperkalemia, hepatitis, and hematologic side effects such as anemia (megaloblastic or hemolytic), thrombocytopenia, and neutropenia are normally dose dependent. AIDS patients have an increased incidence of adverse effects such as rash, fever, neutropenia, and hepatotoxicity.

DRUG INTERACTIONS

DRUG	INTERACTION	MECHANISM
ACE-inhibitors, KCl, Potassium-sparing diuretics	↑ risk of hyperkalemia	Additive effects
Cyclosporine (CSA)	↓ CSA levels, ↑ nephrotoxicity	Unknown
Dapsone	↑ TMP & dapsone levels	↓ TMP & dapsone metabolism
Digoxin	↑ digoxin levels	↓ renal clearance
Dofetilide	Ventricular arrhythmias	↓ dofetilide elimination
Methotrexate (MTX)	↑ megaloblastic anemia, ↑ methotrexate toxicity	Additive effects Displacement of MTX from protein binding sites
Oral hypoglycemics agents	↑ risk of hypoglycemia	↓ oral hypoglycemic agent metabolism or altered plasma protein binding
Phenytoin	↑ phenytoin levels	↓ phenytoin metabolism
Procainamide	↑ procainamide levels	↓ procainamide metabolism
Pyrimethamine	↑ megaloblastic anemia	Additive effects
Rifampin	↓ TMP & SMX levels	↑ hepatic metabolism
Warfarin	↑ anticoagulant effect	↓ warfarin metabolism

FORMULARY STATUS

TMP-SMX is a **CATEGORY I (Formulary)** antibiotic at San Francisco VA Medical Center.

VANCOMYCIN

INDICATIONS

•Treatment of **gram-positive bacterial infections** in patients with **serious allergies to ß-lactam antibiotics**
•Treatment of **documented nafcillin-resistant staphylococcal infections**
•Empiric treatment of **nafcillin-resistant staphylococcal infection** in the **patient at high risk for nafcillin-resistance** (prior documented infection, prior antibiotic therapy, indwelling catheter, prolonged hospitalization, or nursing home or hospital transfer)
•Treatment of **ampicillin-resistant enterococcal infections** caused by vancomycin-susceptible isolates
•Treatment of **infections caused by *Corynebacterium* group JK** (*C. jeikeium*)
•Empiric therapy of **community-acquired bacterial meningitis** (in combination with ceftriaxone) and **post -neurosurgical meningitis** (in combination with cefepime or meropenem)
•**Surgical prophylaxis for procedures involving implantation of prosthetic materials or devices** in patients allergic to cephalosporins

SPECTRUM

Vancomycin has excellent activity against aerobic gram-positive cocci and is bactericidal against staphylococci and non-enterococcal streptococci. (**Note:** systemic infections with *Enterococcus* may necessitate combination therapy with gentamicin). Vancomycin resistant enterococci (VRE) are increasing at an alarming rate. **The use of vancomycin should be limited in order to prevent further increases in VRE and the possible emergence of vancomycin-resistant *Staphylococcus aureus***. Vancomycin is also effective against nafcillin-resistant staphylococci as well as many gram-positive bacilli including diphtheroids, *Clostridium*, and *Bacillus* species. Vancomycin-resistant gram-positive bacteria include *Leuconostoc* spp., *Pediococcus* spp., *Erysipelothrix* spp., and some *Lactobacillus spp. Staphylococcus aureus* isolates with an MIC ≤ 2 µg/ml are considered sensitive, while isolates with an MIC ≥ 16 µg/ml are considered resistant. *S. aureus* isolates with MICs > 1 µg/ml are less likely to respond to vancomycin therapy. Streptococci other than S. pneumoniae with an MIC ≤ 1 µg/ml are considered susceptible. Other organisms with an MIC ≤ 4 µg/ml are considered sensitive, while organisms with an MIC ≥ 32 µg/ml are considered resistant.

DOSING/PHARMACOKINETICS

CREATININE CLEARANCE	DOSE
> 60 ML/MIN	10-15 MG/KG Q12H*
40-60 ML/MIN	10-15 MG/KG Q12H-Q24H
20-40 ML/MIN	5-10 MG/KG Q24H
10-20 ML/MIN	5-10 MG/KG Q24H-Q48H
HEMODIALYSIS	15-20 MG/KG LOAD, THEN 500 MG IV POST HD ONLY

*Dose 15-20 mg/kg q8h-q12h to achieve a trough of 15-20 µg/ml

The elimination half-life of vancomycin is 6-8 hours in adults with normal renal function. In these patients the drug is dosed every 8 to 12 hours. Accumulation occurs in patients with renal failure; therefore the dose should be adjusted according to the degree of renal insufficiency. Recommended dosing guidelines are listed above. Single doses should not exceed 2 grams. Vancomycin is not removed by standard hemodialysis but is removed by high-flux and peritoneal dialysis. Patients who receive high-flux hemodialysis three times weekly, typically require a dose of 500 mg after each dialysis session. Trough serum concentration monitoring has been recommended in the following: 1) dialysis patients, 2) patients requiring higher than usual doses (e.g., pneumococcal meningitis), 3) patients with rapidly changing renal function, 4) intravenous drug users, and 5) patients with extensive burns. A trough serum concentration of 10 -15 µg/ml has been recommended for most patients. Trough levels of 15-20 µg/ml are recommended for central nervous system infections (e.g., meningitis, VP shunt infections), endocarditis, ventilator-associated pneumonia, or osteomyelitis caused by *S. aureus*. Patients with higher trough levels may be at increased risk for the development of nephrotoxicity. In order to minimize the histamine response to vancomycin (flushing, tachycardia, and hypotension; also known as **red-man's syndrome**) one gram doses should be infused slowly over at least one hour.

FORMULARY STATUS

Vancomycin is a **CATEGORY I (Formulary)** antibiotic at San Francisco VA Medical Center.

VORICONAZOLE

INDICATIONS
•Drug of choice for the treatment **of invasive aspergillosis**
•Treatment of serious **infections caused by *Scedosporium apiospermum* and *Fusarium* spp**. **in patients intolerant of or refractory to other therapy**
•Treatment of **esophageal candidiasis in patients who failed to respond to fluconazole and itraconazole**

SPECTRUM
Voriconazole is a second generation triazole derivative of fluconazole that has enhanced inhibition of CYP450-dependent 14α-sterol demethylase, an enzyme involved in ergosterol biosynthesis. It is fungicidal against many *Aspergillus* species, including *Aspergillus terreus*. It is fungistatic against *Scedosporium. apiospermum*, *Fusarium* spp., and all *Candida* spp. Voriconazole has demonstrated fungistatic in vitro activity against *Cryptococcus neoformans*, *Trichosporum* spp., *Coccidiodes immitis*, *Saccharomyces cerevisiae*, and *Geotrichum candidum.* It is fungicidal against many *Blastomyces dermatitidis and Histoplasma capsulatum* isolates. Voriconazole has variable activity against *Rhizopus* spp. and *Sporothrix schenckii*. It is inactive against *Apophysomyces elegans* and *Rhizomucor pusillus* isolates. Fungal isolates that exhibit reduced susceptibility to fluconazole or itraconazole may also show reduced susceptibility to voriconazole, suggesting cross resistance among azole antifungals. *Candida albicans, tropicalis, and parapsillosis* isolates with an MIC ≤ 0.12 µg/ml are considered sensitive, while isolates with an MIC ≥ 1 µg/ml are considered resistant. C. krusei isolates with an MIC ≤ 0.5 µg/ml are considered sensitive and isolates with an MIC ≥ 2 are considered resistant.

DOSING/PHARMACOKINETICS
Administration from either the oral or intravenous route results in the same pharmacokinetic profile. The oral bioavailability of voriconazole is 96%. It can be given as an oral loading dose of 400 mg every 12 hours on day 1, followed by 200 mg oral dose twice daily. A high-fat meal decreases the drug's bioavailability to ~80%. Voriconazole should be taken 1 hour before or 1 hour after a meal. Its absorption is not affected by drugs known to increase gastric pH (i.e., ranitidine, cimetidine, or omeprazole). Patients who weigh less than 40 kg should receive 100 mg of oral voriconazole every 12 hours. Patients who are unable to take oral voriconazole should receive an IV loading dose of 6 mg/kg every 12 hours for 2 doses, followed by an IV maintenance dose of 4 mg/kg every 12 hours. Voriconazole should be infused over 1-2 hours at a concentration of ≤5 mg/ml, or the rate should not exceed 3 mg/kg/hour. Patients with mild to moderate hepatic cirrhosis (Child-Pugh Class A and B) should receive a normal loading dose and 50% of the maintenance dose. Data are not available for patients with severe hepatic cirrhosis (Child-Pugh Class C), chronic hepatitis B, or chronic hepatitis C. In patients with mild to moderate renal insufficiency (CrCl = 30-50 ml/min), the intravenous vehicle, SBECD, can accumulate. Therefore, intravenous voriconazole should be avoided in patients with ClCr < 50 ml/min. Voriconazole and SBECD are not significantly removed by dialysis, so dosage adjustment is not required. If patient response is inadequate, he maintenance dose of voriconazole may be increased to 300 mg orally every 12 hours or 150 mg orally every 12 hours (≤40 kg). When phenytoin is given, the maintenance dose of voriconazole should be increased to 5 mg/kg intravenously every 12 hours, or to 400 mg orally every 12 hours (>40 kg) or 200 mg orally every 12 hours (≤40 kg).

Voriconazole is distributed rapidly and extensively throughout tissues. Plasma protein binding is approximately 58%. Peak serum levels of 2.12-4.8 mcg/ml are achieved following administration of a 200 mg oral dose twice daily. Voriconazole has non-linear pharmacokinetics due to saturation of its metabolism. Increasing the oral dose from 200 mg every 12 hours to 300 mg every 12 hours results in a 2.5-fold increase in the AUC, while increasing the intravenous dose from 3 mg/kg every 12 hours to 4 mg/kg every 12 hours produces a 2.3-fold increase in the AUC. Cerebrospinal fluid levels are 29% and 68% of concomitant serum levels. Its volume of distribution is 2-4.6 L/kg. The elimination half-life is approximately 6 hours. Voriconazole is a substrate of the CYP2C9, CYP2C19, and CYP3A4 hepatic isoenzymes, with the greatest affinity for CYP2C19 and the least affinity for CYP3A4. Its major metabolite, voriconazole *N*-oxide, inhibits CYP2C9 and CYP3A4 to a greater extent than CYP2C19. Less than 2% is eliminated renally as unchanged drug. Trough serum levels below 1 mcg/ml may be associated with therapeutic failure while levels greater than 5.5 mcg/ml may be associated with higher rates of toxicity such as visual disturbances and transaminitis.

ADVERSE REACTIONS
Ocular – visual changes (photophobia, color changes, increased or decreased visual acuity (usually reversible with discontinuation of therapy), or blurred vision in 21-30%), eye hemorrhage (rare), optic neuritis, papilledema, blepharitis, conjunctivitis, corneal opacity, eye pain, dry eyes, keratitis, keratoconjunctivitis, mydriasis, night blindness, optic atrophy, uveitis, scleritis, retinitis, visual field defect. Patients should NOT drive at night and should avoid potentially hazardous tasks
Nervous system –hallucinations (≤5.1%), dizziness (1-2.6%), headache (≤3.6%), cerebral hemorrhage, cerebral ischemia, cerebrovascular accident, abnormal dreams, acute brain syndrome, agitation, akathisia, amnesia, anxiety, ataxia, brain edema, coma, confusion, convulsion, delirium, dementia, depersonalization, depression, diplopia, encephalitis, encephalopathy, euphoria, EPS, grand mal convulsion, Guillain-Barré syndrome, hypertonia, hypesthesia, insomnia, intracranial hypertension, libido decreased, neuralgia, neuropathy, nystagmus, oculogyric crisis, paresthesia, psychosis, somnolence, suicidal ideation, tremor, vertigo, tinnitus
Dermatologic – rash (1.5-7%), pruritus (1%), photosensitivity, squamous cell carcinoma, melanoma, serious reactions (including Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme, urticaria) (rare), cellulitis, alopecia, contact dermatitis, discoid lupus erythematosis, eczema, fixed drug eruption, furunculosis, exfoliative dermatitis, herpes simplex, melanosis, pruritus, pseudoporphyria, psoriasis, skin discoloration, skin disorder, skin dry, sweating
Hypersensitivity - fever (≤ 6%), chills (≤ 4%), infusion related reactions (flushing, sweating, dyspnea, chest tightness), anaphylactoid reaction, facial edema, flu syndrome, angioedema
Gastrointestinal – nausea (1-7%), vomiting (1-5.6%), abdominal pain (2%), diarrhea (≤1.5%), xerostoma (≤1.5%), peritonitis, anorexia, cheilitis, cholecystitis, cholelithiasis, constipation, ulcer, perforation, duodenitis, dyspepsia, dysphagia, dry mouth, esophagitis, flatulence, gastroenteritis, gastrointestinal hemorrhage, gingivitis, glossitis, gum hemorrhage, gum hyperplasia, hematemesis, melena, mouth ulceration, pancreatitis, parotid gland enlargement, periodontitis, proctitis, pseudomembranous colitis, rectal disorder, rectal hemorrhage, stomatitis, tongue edema, taste loss, taste perversion
Hepatic – increased alkaline phosphatase (3-5%), increased serum transaminases (≤4%), cholestatic jaundice (1-2%), ascites (rare), bilirubinemia (< 1%), hepatic coma, hepatic failure, hepatitis, hepatomegaly
Cardiovascular – tachycardia (2.5%), hypertension (0.5-1.9%), hypotension (0.5-1.7%), vasodilatation (≤ 1.5%), peripheral edema (1%), chest pain (≤ 2%), arrhythmias, syncope, CHF, cardiomegaly, cardiomyopathy, MI, palpitation
Renal/Electrolyte – acute renal failure (rare) abnormal renal function (≤2%), hypokalemia (≤1.6%), hypomagnesemia (≤1%), albuminuria, uremia, BUN increased, anuria, dysuria, glycosuria, hemorrhagic cystitis, hematuria, hydronephrosis, nephritis, nephrosis, oliguria, urinary retention, UTI,

incontinence, kidney pain, tubular necrosis, hypercalcemia, hyperkalemia, hypermagnesemia, hypernatremia, hypocalcemia, hyponatremia, hypophosphatemia

Hematologic/Lymphatic – thrombocytopenia (0.5-1%), leukopenia (0.3-0.5%), anemia (rare), agranulocytosis, aplastic anemia, hemolytic anemia, bleeding time increased, cyanosis, DIC, ecchymosis, eosinophilia, hypervolemia, lymphadenopathy, lymphangitis, marrow depression, pancytopenia, petechia, purpura, enlarged spleen, TTP

Musculoskeletal – arthralgia, arthritis, bone necrosis, bone pain, leg cramps, myalgia, myasthenia, myopathy, osteomalacia, osteoporosis

Respiratory System – cough increased, dyspnea, epistaxis, hemoptysis, hypoxia, lung edema, pharyngitis, pleural effusion, pneumonia, respiratory disorder, respiratory distress syndrome, respiratory tract infection, rhinitis, sinusitis, voice alteration

Other – asthenia, sepsis, pain, infection, graft versus host reaction, granuloma, injection site pain, multi-organ failure, adrenal insufficiency, diabetes insipidus, hyperthyroidism, hypothyroidism, decreased glucose tolerance, CPK increased, hypercholesteremia, hyperuricemia, hypoglycemia, deafness, ear pain, hypoacusis, otitis externa, blighted ovum, dysmenorrhea, epididymitis, impotence,, metrorrhagia, scrotal edema, uterine hemorrhage, vaginal hemorrhage

DRUG INTERACTIONS

DRUG	INTERACTION	MECHANISM
Alfentanil, fentanyl	↑ alfentanil & fentanyl levels	↓ alfentanil & fentanyl metabolism
Alprazolam, midazolam, triazolam	↑ benzodiazepine levels	↓ benzodiazepine metabolism
Apixaban	↑ apixaban levels	↓ apixaban metabolism
Atazanavir		
Atorvastatin, lovastatin, simvastatin	↑ statin levels	↓ statin metabolism
Barbiturates (long-acting)	↓ voriconazole levels	↑ voriconazole metabolism
Bosutinib	↑ bosutinib levels	↓ bosutinib metabolism
Cabozantinib	↑ cabozantinib levels	↓ cabozantinib metabolism
Carbamazepine	↓ voriconazole levels	↑ voriconazole metabolism
Cisapride	Ventricular arrhythmias	↓ cisapride metabolism
Crizotinib	↑ crizotinib levels	↓ crizotinib metabolism
Cyclosporine	↑ cyclosporine levels	↓ cyclosporine metabolism
Docetaxel	↑ docetaxel levels	↓ docetaxel metabolism
Dronedarone	↑ dronedarone levels	↓ dronedarone metabolism
Efavirenz	↓ voriconazole levels ↑ efavirenz levels	↑ voriconazole metabolism ↓ efavirenz metabolism
Eplerenone	↑ eplerenone levels	↓ eplerenone metabolism
Ergot alkaloids	↑ ergot alkaloids levels	↓ drug metabolism
Erythromycin	↑ erythromycin levels	↓ erythromycin metabolism
Fosamprenavir	↓ voriconazole levels	↑ voriconazole metabolism
Ibrutinib	↑ ibrutinib levels	↓ ibrutinib metabolism
Lomitapide	↑ lomitapide levels	↓ lomitapide metabolism
Maraviroc	↑ maraviroc levels	↓ maraviroc metabolism
Methadone	↑ methadone levels	↓ methadone metabolism
Nilotinib	↑ nilotinib levels	↓ nilotinib metabolism
Omeprazole	↑ voriconazole and omeprazole levels	↓ drug metabolism
Oral contraceptives (OC)	↑ voriconazole levels ↑ OC levels	↓ voriconazole metabolism ↓ OC metabolism
Oxycodone	↑ oxycodone levels	↓ oxycodone metabolism
Phenytoin	↓ voriconazole levels ↑ phenytoin levels	↑ voriconazole metabolism ↓ phenytoin metabolism
Pimozide	Ventricular arrhythmias	↓ pimozide metabolism
Ponatinib	↑ ponatinib levels	↓ ponatinib metabolism
Quinidine	↑ quinidine levels	↓ quinidine metabolism
Rifabutin	↓ voriconazole levels ↑ rifabutin levels	↑ voriconazole metabolism ↓ rifabutin metabolism
Rifampin	↓ voriconazole levels	↑ voriconazole metabolism
Ritonavir	↓ voriconazole levels	↑ voriconazole metabolism
Saquinavir	↓ voriconazole levels	↑ voriconazole metabolism
Sirolimus	↑ sirolimus levels	↓ sirolimus metabolism
St. John's Wort	↓ voriconazole levels	↑ voriconazole metabolism
Tacrolimus	↑ tacrolimus levels	↓ tacrolimus metabolism
Tipranavir	↓ voriconazole levels	↑ voriconazole metabolism
Ticagrelor	↑ ticagrelor levels	↓ ticagrelor metabolism
Toremifene	↑ toremifene levels	↓ toremifene metabolism
Vinblastine, vincristine	↑ neurotoxicity	↓ vinca alkaloid metabolism
Warfarin	↑ anticoagulant effect	↓ warfarin metabolism

FORMULARY STATUS

Voriconazole is a **NON-FORMULARY** antibiotic at San Francisco VA Medical Center. This drug will not be dispensed by pharmacy without prior approval by the Infectious Diseases Section and completion of an electronic non-formulary drug request.

ADVERSE EFFECTS OF BETA-LACTAM ANTIBIOTICS

	Hematologic	Allergic	Gastrointestinal	Hepatic	Renal/ Electrolyte	CNS/ Neurologic	Miscellaneous
Penicillins	Eosinophilia Hemolytic anemia Neutropenia (esp nafcillin & liver dz) Platelet dysfunction (antipseudomonal PCNs) Thrombocytopenia	Anaphylactic reactions Exfoliative dermatitis Fever Pruritus Rash (more common with amp & amox) Serum sickness Stevens-Johnson syndrome Urticaria Vasculitis	Abdominal pain Anorexia *C. difficile* colitis (esp amp & amox) Diarrhea (esp. Augmentin®) N/V Thrush	Cholestatic hepatitis (esp Augmentin®) Elevated LFT's (esp antistaph pcn's) Hepatitis	Hyperkalemia (K PCN) Hypernatremia Hypokalemic alkalosis (ticarcillin/nafcillin) Interstitial nephritis (esp methicillin)	Hallucinations Headache Herxheimer reaction (syphilis) Insomnia Lethargy Neuromuscular hyperirritability Seizures (esp PCN)	Pain at injection site Thrombophlebitis Tissue damage with nafcillin extravasation Vaginal candidiasis
Cephalosporins	**All of the above** Hypoprothrombin-emia (n-MTT side chain) Thrombocytosis	**All of the above** Serum sickness (esp cefaclor)	**All of the above** *C. difficile* colitis (esp. 3rd generation cephs) Diarrhea (esp oral 2nd gen cephs & ceftriaxone) Pseudocholelithiasis (ceftriaxone)	Elevated LFT's	Interstitial nephritis	**All of the above** Seizures (esp cefazolin & cefepime) Encephalopathy (esp. cefepime)	Disulfiram-like reaction (MTT side chain) Pain at injection site Superinfections Thrombophlebitis Vaginal candidiasis
Carbapenems	Eosinophilia Hemolytic anemia Neutropenia Thrombocytopenia Thrombocytosis	**All of the above**	**See penicillins** Diarrhea (dose related)	Elevated LFT's Hepatitis		**All of the above** Seizures (esp imipenem)	Hypotension during infusion Pain at injection site Superinfections Thrombophlebitis
Aztreonam	Anemia Eosinophilia Neutropenia Thrombocytopenia Thrombocytosis	**All of the above**	**See penicillins**	Elevated LFT's		Confusion Dizziness Hallucinations Insomnia Paresthesia Seizures Vertigo	Pain at injection site Thrombophlebitis Vaginal candidiasis

ANTIRETROVIRAL AGENT DOSING GUIDELINES

NUCLEOSIDE/TIDE REVERSE TRANSCRIPTASE INHIBITORS (N(t)RTIs)

Drug	Dosage Forms	Dose	Excretory Route	Dosage Adjustment in Renal Insufficiency and Hemodialysis
Abacavir (Ziagen®)	Tablet: 300 mg Oral solution: 20 mg/mL	300 mg PO BID or 600mg once daily	Hepatic and renal	None but dosage adjustment is recommended with hepatic insufficiency. Child-Pugh Score — Dose 5-6 — 200mg PO BID (use oral soln) >6 — Contraindicated
Didanosine (Videx®)	EC Capsules: 125 mg, 200 mg, 250 mg, 400 mg Tablets for oral suspension: 100 mg, 150 mg, 200 mg Powder for suspension: 10 mg/mL	**< 60 kg**: 250 mg once daily *; with Tenofovir, 250mg once daily **≥ 60 kg**: 400 mg once daily*; with Tenofovir 200mg once daily *Preferred dosing with oral soln is BID (total daily dose divided into 2 doses)	Renal and non-renal	See table below

CrCl (ml/min)	<60kg Capsule	<60kg Soln	≥60kg Capsule	≥60kg Soln
30-59	125mg QD	150 mg QD	200mg QD	200mg QD
10-29	125mg QD	100mg QD	125mg QD	150mg QD
<10	Use oral soln	75 mg QD	125mg QD	100mg QD
HD/CAPD	Use oral soln	75mg QD	125mg QD	100mg QD

Drug	Dosage Forms	Dose	Excretory Route	Dosage Adjustment in Renal Insufficiency and Hemodialysis
Emtricitabine (Emtriva™)	Capsule: 200 Oral solution: 10mg/mL	200 mg once daily or 240mg (24mL) oral soln once daily	Renal	Dose CrCl (ml/min) — Capsule — Soln 30-49 — 200 mg q48h — 124mg q24h 15-29 — 200 mg q72h — 80mg q24h <15 — 200 mg q96h — 60mg q24h HD — 200 mg q96h# — 60mg q24h# #Take dose after HD session on dialysis days
Lamivudine (Epivir®)	Tablets: 100 mg, 150 mg, 300 mg Oral solution: 5 mg/mL, 10 mg/mL	150 mg PO BID or 300 mg once daily	Renal	CrCl (ml/min) — Dose 30-49 — 150 mg Q24h 15-29 — 150 mg x1, then 100mg q24h 5-14 — 150 mg x1, then 50mg q24h <5 — 50 mg x1, then 25mg q24h HD — 50 mg x1, then 25mg q24h post HD session on dialysis days

Stavudine (Zerit®)	Capsules: 15 mg, 20 mg30 mg, 40 mg Powder for oral solution: 1mg/mL	**< 60 kg**: 30 mg PO BID **≥ 60 kg**: 40 mg PO BID	Renal	Dose CrCl (ml/min) <60kg >60kg 26-50 15 mg q12h 20 mg q12h 10-25 15 mg q24h 20 mg q24h HD 15 mg q24h 20 mg q24h after HD session on dialysis days
Tenofovir disoproxil fumarate (DF) (Viread®)	Tablets: 150 mg, 200 mg, 250 mg, 300 mg Oral powder: 40 mg/g	300 mg once daily	Renal	CrCl (ml/min) Dose 30-49 300 mg q48h 10-29 300 mg BIW (i.e., q 3-4 days) <10 not on HD no recommendation HD 300 mg Q wk
Zidovudine (Retrovir®)	Capsule :100 mg Tablet: 300 mg Oral syrup: 10mg/ml Injection solution: 10mg/ml	200 mg PO TID or 300 mg PO BID	Hepatic and renal	CrCl (ml/min) Dose < 15 100 mg TID or 300mg once daily HD 100 mg TID or 300mg once daily

NUCLEOSIDE/TIDE REVERSE TRANSCRIPTASE INHIBITORS CO-FORMULATIONS

Drug	Dosage Forms	Dose	Excretory Route	Dosage Adjustment in Renal Insufficiency and Drug Interactions
Zidovudine / Lamivudine (Combivir®)	Tablet: 300 mg zidovudine/ 150 mg lamivudine	1 tablet BID	Hepatic and renal	Not recommended in patients with CrCL < 50 ml/min
Abacavir / Lamivudine (Epzicom®)	Tablet: 600 mg abacavir/ 300 mg lamivudine	1 tablet once daily	Renal	Not recommended in patients with CrCL < 50 ml/min Contraindicated in hepatic impairment

Zidovudine / Lamivudine / Abacavir (Trizivir®)	Tablet: 300 mg zidovudine/ 150 mg lamivudine/ 300 mg abacavir	1 tablet BID	Hepatic and renal	Not recommended in patients with CrCL < 50 ml/min Contraindicated in hepatic impairment
Tenofovir disoproxil fumarate (DF) / Emtricitabine (Truvada®)	Tablet: 300 mg tenofovir DF/ 200 mg emtricitabine	1 tablet once daily	Renal	ClCr (ml/min) Dose 30-49 1 tablet q48h < 30 Not recommended
Tenofovir alafenamide (AF)/ Emtricitabine (Descovy®)	Tablet: 25 mg tenofovir AF/ 200mg emtricitabine	1 tablet once daily	Renal	Not recommended in patients with CrCL < 30 ml/min Concomitant administration with: Rifamycins Not recommended

NON-NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS (NNRTIs)

Drug	Dosage Forms	Dose	Excretory Route	Dosage Adjustment Renal or Hepatic Impairment and Drug Interactions
Efavirenz (Sustiva®)	Capsules: 50 mg, 200 mg Tablet: 600 mg	600 mg PO QHS	Hepatic and renal	No dosage adjustment necessary in renal impairment. Caution with impaired hepatic function
Etravirine (Intelence®)	Tablets: 25 mg, 100 mg, 200mg	200 mg PO BID	Hepatic	No dosage adjustment necessary in renal impairment. No dosage adjustment necessary in hepatic impairment. Concomitant administration with: Rifampin Do not coadminister Rifapentine Do not coadminister

Nevirapine (Viramune®)	Tablet: 200 mg Extended release tablet: 100 mg, 400 mg Oral suspension: 10 mg/mL	200 mg PO once daily for 2 weeks, then 200 mg PO BID thereafter	Hepatic and renal	Pts on hemodialysis, an additional 200mg dose following each dialysis treatment is recommended Nevirapine should be discontinued in moderate to severe liver function test (LFT) abnormalities until LFT's have returned to baseline. Restart at half the previous dose. If moderate or severe LFT abnormalities recur, discontinue permanently. Nevirapine should not be administered in patients with moderate or severe hepatic impairment (Child-Pugh Class B or C). <u>Concomitant administration with</u>: Rifampin Do not coadminister Rifapentine Do not coadminister
Rilpivirine (Edurant®)	Tablet: 25 mg	25 mg once daily	Hepatic	No dosage adjustment necessary for mild or moderate renal impairment. No dosage adjustment necessary for mild or moderate hepatic impairment. <u>Concomitant administration with</u>: Rifabutin Rilpivirine 50mg once daily Rifampin Contraindicated Rifapentine Do not coadminister

FIXED-DOSE COMBINATIONS CONTAINING NRTI Pair plus NNRTI

Drug	Dosage Forms	Dose	Excretory Route	Dosage Adjustment Renal or Hepatic Impairment
Efavirenz/ Emtricitabine/ Tenofovir DF (Atripla®)	Tablet: 600 mg efavirenz/ 200 mg emtricitabine/ 300 mg tenofovir DF	1 tablet once daily	Hepatic and renal	Not recommended in patients with CrCL <50 ml/min Not recommended Child-Pugh Class B or C
Rilpivirine/ Emtricitabine/ Tenofovir DF (Complera®)	Tablet: 25 mg rilpivirine/ 200 mg emtricitabine/ 300 mg tenofovir DF	1 tablet once daily	Hepatic and renal	Not recommended CrCL <50 ml/min No dosage adjustment necessary in mild-moderate hepatic impairment; no data in severe impairment
Rilpivirine/ Emtricitabine/ Tenofovir AF (Odefsey®)	Tablet: 25 mg rilpivirine/ 200 mg emtricitabine/ 25 mg tenofovir AF	1 tablet once daily	Hepatic and renal	Not recommended CrCL <30 ml/min No dosage adjustment necessary for Child-Pugh A or B No dosing data for Child-Pugh C

PROTEASE INHIBITORS

Drug	Dosage Forms	Dose	Excretory Route	Dosage Adjustment in Hepatic Impairment, Hemodialysis and Drug Interactions
Atazanavir (Reyataz®) **Atazanavir/ Cobicistat (Evotaz®)**	Capsules: 150 mg, 200 mg, 300 mg Pediatric powder: 50 mg packet Tablet: 300mg co-formulated with cobicistat 150 mg	400 mg once daily or 300 mg once daily + 100 mg Ritonavir (RTV) once daily or 150 mg cobicistat once daily or Atazanavir/cobi one tablet once daily	Hepatic (CYP-450 3A4)	Child-Pugh Score / Dose B — 300 mg once daily C — not recommended RTV boosting is not recommended in patients with Child-Pugh Score ≥7. Treatment-experienced pts receiving hemodialysis not recommended to get Atazanavir (boosted or unboosted) Concomitant administration with: Efavirenz — RTV 100 mg once daily + Atazanavir 400 mg once daily Tenofovir — RTV 100 mg once daily + Atazanavir 300 mg once daily
Darunavir (Prezista®) **Darunavir/ Cobicistat (Prezcobix®)**	Tablets: 75 mg, 150 mg, 400 mg, 600 mg, 800 mg Oral suspension: 100 mg/mL Tablet: 800mg co-formulated with cobicistat 150 mg	ARV-naïve: 800 mg once daily + 100 mg RTV once daily or 150mg cobicistat once daily or Darunavir/cobi one tablet once daily PI-experienced with ≥1 darunavir mutations 600 mg PO BID + 100 mg RTV PO BID	Hepatic (CYP-450 3A4)	No renal dose adjustment required; Darunavir/cobi plus Tenofovir should not be administered if CrCL < 70 mL/min No dosage recommendation for mild to moderate hepatic impairment Not recommended in severe hepatic impairment

Fosamprenavir (Lexiva®)	Tablet: 700 mg Oral suspension: 50 mg/mL	<u>ARV-naïve:</u> 1400 mg PO BID or 1400 mg PO once daily + 100mg to 200mg RTV once daily or 700 mg PO BID + 100mg RTV PO BID <u>PI-experienced:</u> 700 mg PO BID + 100 mg RTV PO BID	Hepatic (CYP-450 3A4)	<u>Child-Pugh Score Dose</u> PI naïve only: 5-9 700 mg BID 10-15 350mg BID PI naïve or PI experienced: 5-6 700mg BID + RTV 100mg once daily 7-9 450mg BID + RTV 100mg once daily 10-15 300mg BID + RTV 100mg once daily <u>Concomitant administration with</u>: Efavirenz Fosamprenavir 700 mg BID + RTV 100 mg BID or Fosamprenavir 1400 mg once daily + RTV 300 mg once daily
Indinavir (Crixivan®)	Capsules: 100mg, 200 mg, 400 mg	800 mg PO Q8h or 800 mg PO BID + 100mg to200mg RTV PO BID	Hepatic and renal (CYP-450 3A4)	Mild to moderate hepatic insufficiency due to cirrhosis: 600 mg Q8H
Lopinavir/Ritonavir (Kaletra®)	Each tablet contains 200 mg lopinavir + 50 mg RTV or 100 mg lopinavir + 25mg RTV Oral solution- each ml contains 80 mg lopinavir + 20 mg RTV	<u>ARV-naïve:</u> 400mg/100mg PO BID or 800mg/200mg once daily <u>PI-experienced:</u> 400mg/100mg PO BID	Hepatic (CYP-450 3A4)	Caution with hepatic impairment Once daily dosing not recommended if receiving hemodialyis <u>Concomitant administration with</u>: Efavirenz or Nevirapine: 533 lopinavir + 133mg RTV BID (3 tablets PO BID)

Nelfinavir (Viracept®)	Tablets: 250 mg, 625 mg Oral powder: 50 mg/g	750 mg PO TID or 1250 mg PO BID	Hepatic (CYP-450 3A4)	No dosage adjustment in mild hepatic impairment Not recommended in moderate to severe hepatic impairment
Ritonavir (Norvir®)	Capsule: 100 mg (soft gelatin) Tablet: 100 mg Oral solution: 80 mg/mL	Primarily used for "boosting" and in combination with other PI's 100 mg to 400 mg per day in 1 to 2 divided doses (refer to other PIs for specific dosing recommendations)	Hepatic (CYP-450 3A4 & CYP-450 2D6)	Refer to recommendations for the primary PI for hepatic dose adjustment
Saquinavir (Invirase®)	Capsule: 200 mg Tablet: 500 mg	1000 mg PO BID + 100 mg Ritonavir PO BID	Hepatic (CYP-450 3A4)	Use with caution in mild to moderate hepatic impairment Contraindicated in severe hepatic impairment
Tipranavir (Aptivus®)	Capsule: 250 mg Oral solution: 100mg/mL (with 116IU vitamin E/mL)	500 mg PO BID + 200 mg Ritonavir PO BID	Hepatic (CYP-450 3A4)	Child-Pugh Class A: use with caution Child-Pugh Class B or C: contraindicated

FUSION INHIBITOR

Drug	Dosage Forms	Dose	Excretory Route	Dosage Adjustment in Renal or Hepatic Impairment
Enfurvitide (Fuzeon®)	Lyophilized powder Each single-use vial contains 108 mg of enfurvitide to be reconstituted with 1.1 ml of Sterile Water for injection.	90 mg SQ Q12H	Catabolism to constituent amino acids, with subsequent recycling of amino acids in the body pool	No dosage adjustment necessary in renal insufficiency. No dosage recommendation in hepatic impairment.

CHEMOKINE CO-RECEPTOR ANTAGONIST

Drug	Dosage Forms	Dose	Excretory Route	Dosage Adjustment in Renal or Hepatic Impairment
Maraviroc (Selzentry®)	Tablets: 150 mg, 300 mg	Depends on presence of concomitantly administered medications: • 150 mg BID with strong CYP3A inhibitors (with or without CYP3A inducers)including PIs (except TPV/rit) • 300mg BID with NRTIs, T-20, TPV/rit, NVP, and other drugs not strong CYP3A inhibitors or inducers • 600mg BID with CYP3A inducers, including EFV, ETR, etc. (without a CYP3A inhibitor)	Hepatic and renal	No dosage recommendation in hepatic impairment. Use with caution. Maraviroc concentrations may be increased in patients with renal impairment, especially when CYP3A inhibitors are coadministered. Use only if potential benefits outweigh the risk. Not recommended with severe renal impairment or end-stage renal disease (CrCl <30ml/min) and taking a potent CYP3A4 inducer or inhibitor.

INTEGRASE STRAND TRANSFER INHIBITORS (INSTI)

Drug	Dosage Forms	Dose	Excretory Route	Dosage Adjustment in Renal or Hepatic Impairment, and Drug Interactions
Dolutegravir (Tivicay®)	Tablet: 10 mg, 25 mg, 50 mg	ARV-naïve or treatment-experienced but integrase strand inhibitor-naïve (INSTI-naïve): 50 mg PO once daily INSTI-experienced with certain known or suspected INSTI-associated resistance: 50 mg PO BID	Hepatic and renal	Mild to severe renal impairment and ARV-naïve or treatment-experienced and INSTI-naïve: no dosage adjustment necessary Mild to moderate renal impairment and INSTI-experienced with known or suspected resistance: no dosage adjustment necessary Severe renal impairment and INSTI-experienced with known or suspected resistance: use with caution Mild to moderate hepatic insufficiency: no dosage adjustment necessary Severe hepatic insufficiency: use not recommended Concomitant administration with: Efavirenz — Dolutegravir 50 mg BID FPV/rit — Dolutegravir 50 mg BID TPV/rit — Dolutegravir 50 mg BID Rifampin — Dolutegravir 50 mg BID (only if no INSTI mutation) Rifapentine — Do not co-administer

Elvitegravir (Vitekta®)	Tablet: 85 mg, 150 mg	Unboosted elvitegravir is not recommended. With once daily ATV/r or BID LPV/r: 85 mg PO once daily With BID DRV/r, FPV/r, or TPV/r: 150 mg PO once daily •	Hepatic	No dosage adjustment necessary in renal insufficiency. No dosage adjustment in mild to moderate hepatic insufficiency Not recommended in severe hepatic insufficiency
Raltegravir (Isentress®)	Tablet: 400 mg Chewable tablets: 25 mg, 100 mg Powder for oral suspension: 100 mg packets	400 mg PO BID	Hepatic	No dosage adjustment necessary in renal insufficiency. No dosage adjustment in mild to moderate hepatic insufficiency No recommendation in severe hepatic insufficiency <u>Concomitant administration with</u>: Rifampin — Raltegravir 800mg BID Rifapentine — Do not coadminister with once-daily Rifapentine

FIXED-DOSE COMBINATIONS CONTAINING NRTI Pair plus INTEGRASE STRAND TRANSFER INHIBITORS

Drug	Dosage Forms	Dose	Excretory Route	Dosage Adjustment Renal or Hepatic Impairment
Elvitegravir/ cobicistat/ Emtricitabine/ Tenofovir DF (Stribild®)	Tablet: 150 mg elvitegravir/ 150 mg cobicistat/ 200 mg emtricitabine/ 300 mg tenofovir DF	1 tablet once daily	Hepatic and renal	Initial use not recommended with CrCL < 70 ml/min Continued use not recommended with CrCl < 50 ml/min No dosage adjustment necessary in mild-moderate hepatic impairment Not recommended in severe hepatic impairment
Elvitegravir/ cobicistat/ Emtricitabine/ Tenofovir AF (Genvoya®)	Tablet: 150 mg elvitegravir/ 150 mg cobicistat/ 200 mg emtricitabine/ 10 mg tenofovir AF	1 tablet once daily	Hepatic and renal	Not recommended CrCL <30 ml/min No dosage adjustment necessary in mild-moderate hepatic impairment Not recommended in severe hepatic impairment
Dolutegravir/ Abacavir/ Lamivudine (Triumeq®)	Tablet: 50 mg dolutegravir/ 600mg abacavir/ 300 mg lamivudine	1 tablet once daily	Hepatic and renal	Not recommended CrCL <50 ml/min Not recommended if for Child-Pugh A or higher