Guide to ANTIMICROBIALS

San Francisco VA Medical Center (SFVAMC)
2021 Edition

Guide to Antimicrobials
2021

Theora Canonica, Pharm.D.
Harry Lampiris, M.D.
Jennifer Mulliken, M.D.
Mai Vu, Pharm.D.

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,

Current antimicrobial sensitivity patterns and *SFVAMC Guidelines for Antimicrobial Use in Adults* available on the Antibiotic Stewardship Program page on SharePoint: https://dvagov.sharepoint.com/sites/SFC/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 edition of the SFVA Guide to Antimicrobials is dedicated to Daniel Maddix, Pharm.D.

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

Table of Contents

Resources

SFVA Specific Guidelines on SFVA Intranet

- Isolation Instructions (type of isolation by organism), interpreting C. Diff testing results, rule out TB algorithm:
  - Infection Control - Algorithms - All Documents (sharepoint.com)
- SFVAMC Antibiogram: LINK
  - SFVAMC SharePoint: Antibiograms
- Infection Control Manual:
  - Infection Control - IC Manual - All Documents (sharepoint.com)

UCSF IDMP:

- Guidelines for Empiric Antimicrobial Therapy
  - https://idmp.ucsf.edu/guidelines-empiric-antimicrobial-therapy
- Antimicrobial Dosing Guidelines
  - https://idmp.ucsf.edu/antimicrobial-dosing-guidelines

SFVA Specific Guidelines under Hospital Specific Guidelines on IDMP:

- VASF Guide to Antimicrobials and Restricted Antibiotics
  - Guidelines At VASF | Infectious Diseases Management Program at UCSF

Phone/Pager Numbers

ID Pharmacist	Pager (415) 223 – 8046 or EXT 25269
ID Fellow	Pager (415) 443 – 5151
HIV Pharmacist	EXT 24793
Outpatient Pharmacy	EXT 22708
Inpatient Order Processing Pharmacist	EXT 22935 or EXT 22934
Infection Control (6AM – 4:30PM)	ASCOM # 26269
Needle Stick:	Phone (415) 469 – 4411
Occupational Health (8AM – 4:30PM)	

Antibiogram: Non-Urine Isolates

Sensitivity Patterns of NON-URINE Isolates (First isolate per patient per organism)
San Francisco VA Medical Center **January-December 2020**
Confidential: For official use by San Francisco VA Medical Center Employees and Students only

Percent Sensitive						Percent Sensitive				
ORGANISM	**TOTAL #ISO***	**AMP**	**TZP**	**ETP**	**CIP**	**SXT**	**CRO**	**FEP**	**GEN**	
***Escherichia coli*†** ESBL (6%)	65	58	97	100	74	69	94	94	92	
***Klebsiella pneumoniae*†** ESBL (0%	39	NA	95	100	100	100	100	100	100	
Proteus mirabilis	32	75	100	100	69	75	75	75	88	
Pseudomonas aeruginosa	44	NA	89	NA	89	NA	NA	93	98	
		DAP	**LZD**	**VAN**	**OXA**	**SXT**	**ERY**	**CLI**	**TET**	**AMP**
Enterococcus faecalis VRE (10%	29	100	97	90	NA	NA	7	79	24	97
Staphylococcus aureus	215	100	100	100	70	97	57	77	91	NA
MRSA (30%)	65	100	100	100	0	92	NA	52	80	NA
MSSA (70%)	150	100	100	100	100	100	NA	87	96	NA
***Staphylococcus* coag neg**	132	100	99	98	53	83	52	77	80	NA
Methicillin Resistant (47%)										

NA = not available
AMP - ampicillin, TZP piperacillin/tazobactam, ETP - ertapenem, CIP - ciprofloxacin, SXT - SXT - trimethoprim/sulfamethoxazole
CRO - ceftriaxone, FEP - cefepime, GEN - gentamicin, VAN - vancomycin, OXA - oxacillin, ERY - erythromycin, CLI - clindamycin, TET - tetracycline
*Statistical validity of % susceptible is decreased if fewer than 30 isolates are tested.
33% (27/72) of all *enterococcal spp*. isolates recovered via culture were vancomycin-resistant
†Extended-Spectrum Beta-Lactamase (ESBL) Positive - *E. coli - 6%; K. pneumoniae - 0%*

Prepared by Theora Canonica, Pharm.D. 1/12/2021

Antibiogram: Urine Isolates

Sensitivity Patterns of URINE Isolates (First isolate per patient per organism)
San Francisco VA Medical Center **January-December 2020**
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Percent Sensitive						Percent Sensitive			
ORGANISM	**TOTAL #ISO***	**AMP**	**AMC**	**CRO**	**CIP**	**GEN**	**NIT**	**TET**	**SXT**
Enterobacter cloacae	30	NA	NA	NA	NA	100	87	93	77
***Escherichia coli*†** ESBL (12%	234	50	92	88	74	88	98	74	74
***Klebsiella oxytoca*†** ESBL (7%	28	NA	93	93	96	100	100	93	89
***Klebsiella pneumoniae*†** ESBL (8%	88	NA	99	92	92	92	92	92	93
Proteus mirabilis	63	75	95	76	65	95	NA	NA	75
Pseudomonas aeruginosa	48	NA	NA	NA	90	100	NA	NA	NA
					OXA	**VAN**	**NIT**	**TET**	**SXT**
Staphylococcus aureus	42				67	100	95	93	98
***Staphylococcus* coag neg**	122				50	100	100	85	97

NA = not available
AMP - ampicillin, AMC - amoxicillin/clavulanate, CRO - ceftriaxone, CIP - ciprofloxacin, GEN - gentamicin,
NIT - nitrofurantoin, TET - tetracycline, SXT - trimethoprim/sulfamethoxazole, OXA - oxacillin, VAN - vancomycin
*Statistical validity of % susceptible is decreased if fewer than 30 isolates are tested.
33% (27/72) of all *enterococcal spp*. isolates recovered via culture were vancomycin-resistant
†Extended-Spectrum Beta-Lactamase (ESBL) Positive - *E. coli - 12%; K. oxytoca - 7%; K. pneumoniae - 8%*

Prepared by Theora Canonica, Pharm.D. 1/12/2021

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

	Recommended	Duration
Able to tolerate PO	Ciprofloxacin[#] 500 mg PO twice daily	3 – 7 days
Unable to tolerate PO (i.e. bleeding, NG tube, intubated, etc.)	Ciprofloxacin[#] 400 mg IV every 12 hours	Same total duration as above, but transition to PO Ciprofloxacin once able to tolerate PO

[#]Infectious Diseases Section approval required

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

	Recommended	**Alternative**
Primary Prophylaxis in patients with: • Cirrhosis and low ascites protein (< 1.5 g/L) who have either advanced liver failure or renal dysfunction	Ciprofloxacin[#] 250mg PO daily	
Secondary Prophylaxis	Ciprofloxacin[#] 250mg PO daily	TMP/SMX 1DS tablet PO daily

[#]Infectious Diseases Section approval required

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, intravenous drug use, 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 ertapenem 1 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 < 40 mL/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	**Obtain urine culture to rule out other uropathogens** **Check GC, *Chlamydia* LCR** **Consider: Doxycycline 100 mg PO BID x 7 days + Ceftriaxone IM** • **Weighs < 150 kg: Ceftriaxone 500 mg IM once** • **Weighs > 150 kg: Ceftriaxone 1 gm IM once**
Chronic bacterial prostatitis	**Ciprofloxacin 500 mg PO bid for 4 weeks (if possible based upon results of antimicrobial sensitivities)**

#Infectious Diseases Section approval required

San Francisco VA Medical Center Guidelines for the Empiric Therapy of Hospital Acquired and Ventilator Associated Pneumonia

Risk Factors for MRSA	Risk Factors for Pseudomonas
• Prior intravenous antibiotic use within 90 days • Hospitalization in a unit • End stage renal disease • IVDU • Prior respiratory MRSA colonizer	• Prior intravenous antibiotic use within 90 days • Bronchiectasis • HIV • Nursing homes

I. Ventilator Associated Pneumonia (VAP): pneumonia occurring > 48 hours after endotracheal intubation

Likely Pathogens	Therapy
P. aeruginosa ***Methicillin-resistant S. aureus* (MRSA)** ***S. pneumoniae*, *H. influenzae*, β-hemolytic *streptococcus* spp.** **MSSA** **Enteric gram negative bacilli (i.e. *E. coli*; *Klebsiella* spp.; *Enterobacter* spp.; *Proteus* spp.; *Serratia* spp.)**	**Zosyn# 4.5 gm IV q6h** **(Penicillin Allergy: Aztreonam# 2 gm IV q8h + Metronidazole 500 mg IV q8h)** **AND** **Vancomycin 15mg/kg IV q8h – 12h (consider a loading dose of 25 – 30mg/kg x 1 for severe illness)**

#Infectious Diseases Section approval required

Duration of Therapy: Patients with VAP should be treated for 7 days. Shorter or longer duration of antibiotics may be indicated, depending upon the rate of improvement of clinical, radiologic, and laboratory parameters.

II. Hospital Acquired Pneumonia (HAP): pneumonia not incubating at the time of hospital admission and occurring 48 hours or more after admission

Likely Pathogens	Therapy
Patients not at high risk of mortality (not requiring ventilation because of pneumonia, not in septic shock) and without IV antibiotic use in the past 90 days, and low - no MRSA risk	
P. aeruginosa ***S. pneumoniae*, *H. influenzae*, β-hemolytic *streptococcus* spp.** **MSSA** **Enteric gram negative bacilli (i.e. *E. coli*; *Klebsiella* spp.; *Enterobacter* spp.; *Proteus* spp.; *Serratia* spp.)**	**Zosyn# 4.5 gm IV q6h** **(Penicillin Allergy: Aztreonam# 2 gm IV q8h + Metronidazole 500 mg IV q8h)**
Patients at high risk of mortality (requiring ventilation or in septic shock), receipt of IV antibiotic in the past 90 days, structural lung disease, and has risk factors for MRSA	
P. aeruginosa ***S. pneumoniae*, *H. influenzae*, β-hemolytic *streptococcus* spp.** ***Methicillin-resistant S. aureus* (MRSA)** **MSSA** **Enteric gram negative bacilli (i.e. *E. coli*; *Klebsiella* spp.; *Enterobacter* spp.; *Proteus* spp.; *Serratia* spp.)**	**Zosyn# 4.5 gm IV q6h** **(Penicillin Allergy: Aztreonam# 2 gm IV q8h + Metronidazole 500 mg IV q8h)** **AND** **Vancomycin 15mg/kg IV q8h – 12h (consider a loading dose of 25 – 30mg/kg x 1 for severe illness)**

#Infectious Diseases Section approval required

Duration of Therapy: Patients with HAP should be treated for 7 days. Shorter or longer duration of antibiotics may be indicated, depending upon the rate of improvement of clinical, radiologic, and laboratory parameters.

San Francisco VA Medical Center Guidelines for the Treatment of Diarrhea Associated with *Clostridioides difficile* Infection (CDI)

Diagnosis

- Presence of diarrhea defined as 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 and take the shape of the collection container, NOT formed stool.
    - 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 ≤ 15,000 **&** SrCr < 1.5 mg/dL
Severe	WBC > 15,000 **OR** SrCr ≥ 1.5 mg/dL
Fulminant	Presence of hypotension, shock, ileus, or megacolon

Interpreting Lab Results

Probable C-Diff Colonization: Infection Control: Place in Enhanced Contact Precautions if > 3 bowel movements in the past 24 hours. Duration of Enhanced Precautions is for 48 hours after diarrhea resolves. Consider treatment if high clinical suspicion of active C-diff disease

Test	Result / Status	Flag	Units	Ref Range
CDIFF TOX-B GENE PCR	POSITIVE			Ref: Negative
027-NAP1-BI	PRESUMPTIVE NEGATIVE			
C.DIFF GDH ANTIGEN	POSITIVE			Ref: Negative
C.DIFF TOXIN A/B	Negative			Ref: Negative

C. Diff PCR: Positive
C. Diff GDH Antigen: Positive
C. Diff Toxin A/B: **Negative**
Enter Comment:
C. DIFF COLONIZATION LIKELY.

C. Diff PCR: Positive
C. Diff GDH Antigen: Negative
C. Diff Toxin A/B: **Negative**
Enter Comment:
C. DIFF COLONIZATION LIKELY.

Probable C-Diff Infection: Same precautions as above. Treat if high clinical suspicion of active C-diff disease

Test	Result / Status	Flag	Units	Ref Range
CDIFF TOX-B GENE PCR	POSITIVE			Ref: Negative
027-NAP1-BI	PRESUMPTIVE NEGATIVE			
C.DIFF GDH ANTIGEN	POSITIVE			Ref: Negative
C.DIFF TOXIN A/B	POSITIVE			Ref: Negative

C. Diff PCR: Positive
C. Diff GDH Antigen: Positive
C. Diff Toxin A/B: Positive
Enter Comment:
C. DIFF INFECTION LIKELY

Treatment Regimens - as determined by severity of disease

Mild/Moderate/Severe	Vancomycin 125 mg PO q6h x10 days
Fulminant	Vancomycin oral solution 500mg PO Q6H. If ileus is present, add metronidazole 500mg IV Q8H and 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

*Notes:
-If an inciting antimicrobial is suspected (most commonly clindamycin, aminopenicillins, third-generation cephalosporins, and fluoroquinolones), discontinue the agent as soon as possible.
-The use of antimotility agents (loperamide, etc.) should be avoided.
-If severe or fulminant 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, 3) patients with history of life-threatening vancomycin allergy, 4) second recurrence. 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.
-Consider prophylaxis (vancomycin 125 mg PO BID) in inpatients who have had a prior episode of *C. difficile* and will be receiving antibacterials (beta-lactams, quinolones, or clindamycin).

-Patients with recurrent CDI who are currently not hospitalized may be eligible for FMT (fecal microbiota transplant) via capsules from ID Clinic.
Criteria for FMT are:

1. Patients who have had at least 3 relapses of CDI and have failed a 6-week vancomycin taper and a 10 day course of fidaxomicin
2. Patients who have had at least 2 relapses of CDI with any episodes requiring hospitalization

Adapted from: McDonald LC, et al. Clinical practice guidelines for *Clostridium difficile* infection in adults and children: 2017 update by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA). Clin Infect Dis 2018.

San Francisco VA Medical Center Beta-Lactam Test Dosing Protocol

WHAT IS BETA-LACTAM TEST DOING?

A formalized process for evaluating patients with reported beta-lactam allergies. Those that are determined as low risk for an adverse reaction with a different beta-lactam antibiotic from their initial allergy, will receive a one-time test dose (10% of their full treatment dose) of an alternative beta-lactam under observation. If the patient tolerates this, they will receive a full dose (100% of treatment dose) 30 minutes later. If the patient tolerates both doses, they will continue on this antibiotic to treat their infection.

WHY ARE WE DOING THIS?

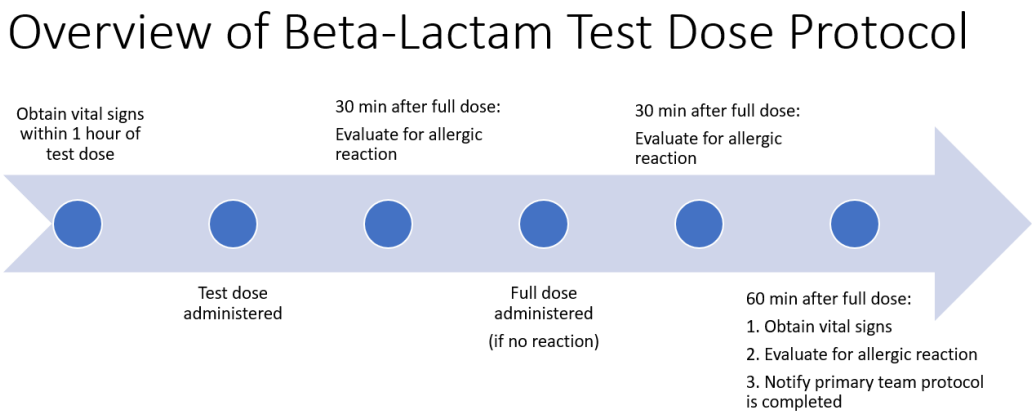
- Cross-Reactivity rates between different beta-lactam antibiotics are low. Therefore, patients with true penicillin or cephalosporin allergies can still receive many other cephalosporins and carbapenems
- By evaluating patients through a thorough allergy assessment, we can identify patients at low risk of having an adverse reaction with alternative beta-lactams which will allow the patient to receive a more effective, less toxic, and/or less costly antibiotics to treat their infections.

HOW ARE WE DOING THIS?

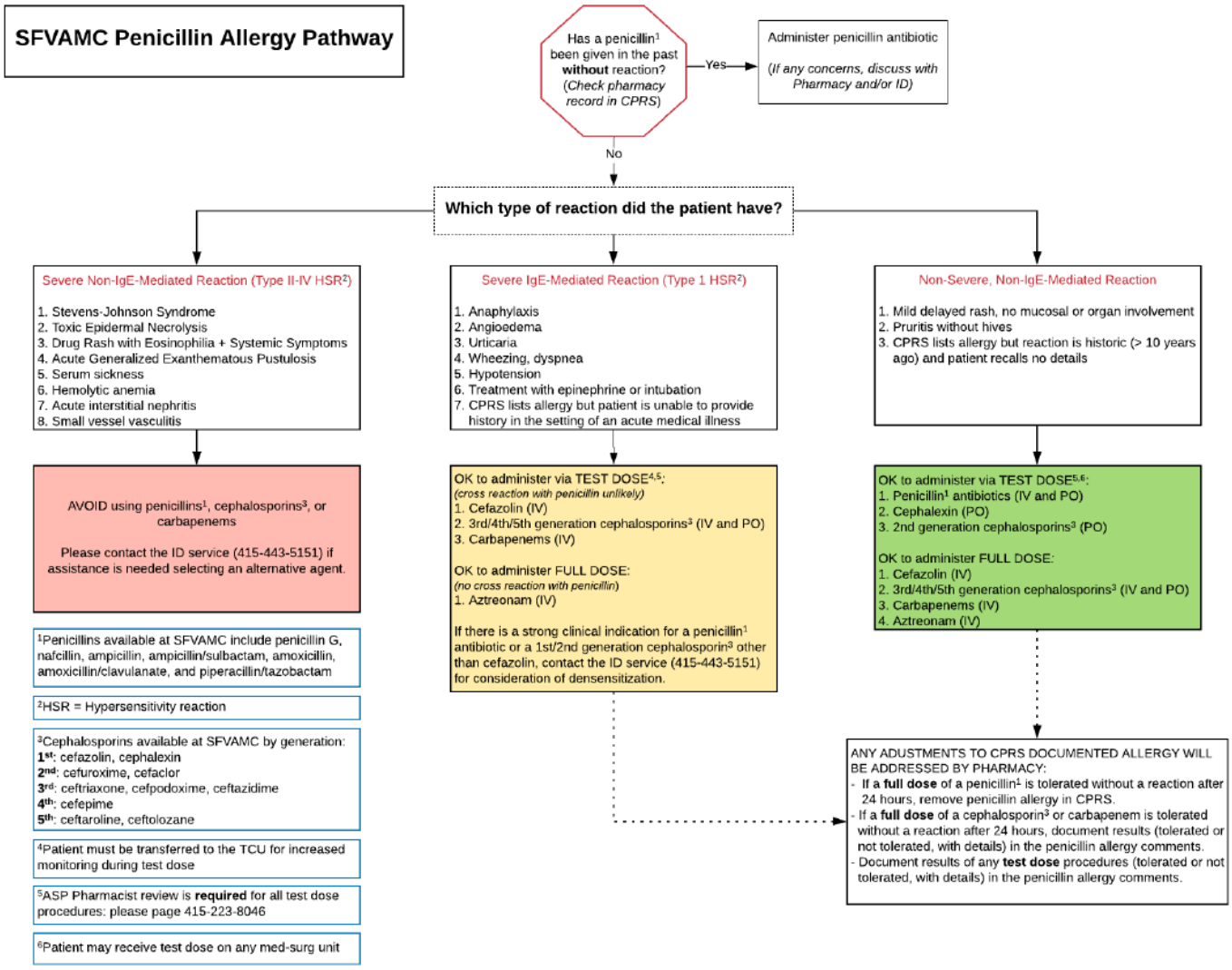
- A new order set is available to standardize the test dose, full dose, assessment, and monitoring
- Primary team can order Beta-Lactam Test Doses via the order set for eligible inpatients with a reported beta-lactam allergy AND an active infection in which a beta-lactam is indicated for treatment
- Case will be review by ID Pharmacist (415-223-8046) prior to proceeding
- Test doses will be conducted Monday through Friday from 10:00 to 14:00
- For patients with a history of severe, IgE mediated reactions, test doses should be administered in the TCU. All other patients may undergo this protocol outside of the TCU.
- If possible, systemic beta-blocker doses should be held for 24 hours prior to test dose
- Monitoring nurse will use new CPRS template to document vital signs obtained after doses

WHAT MEDICATIONS ARE NEEDED FOR THIS PROCESS?

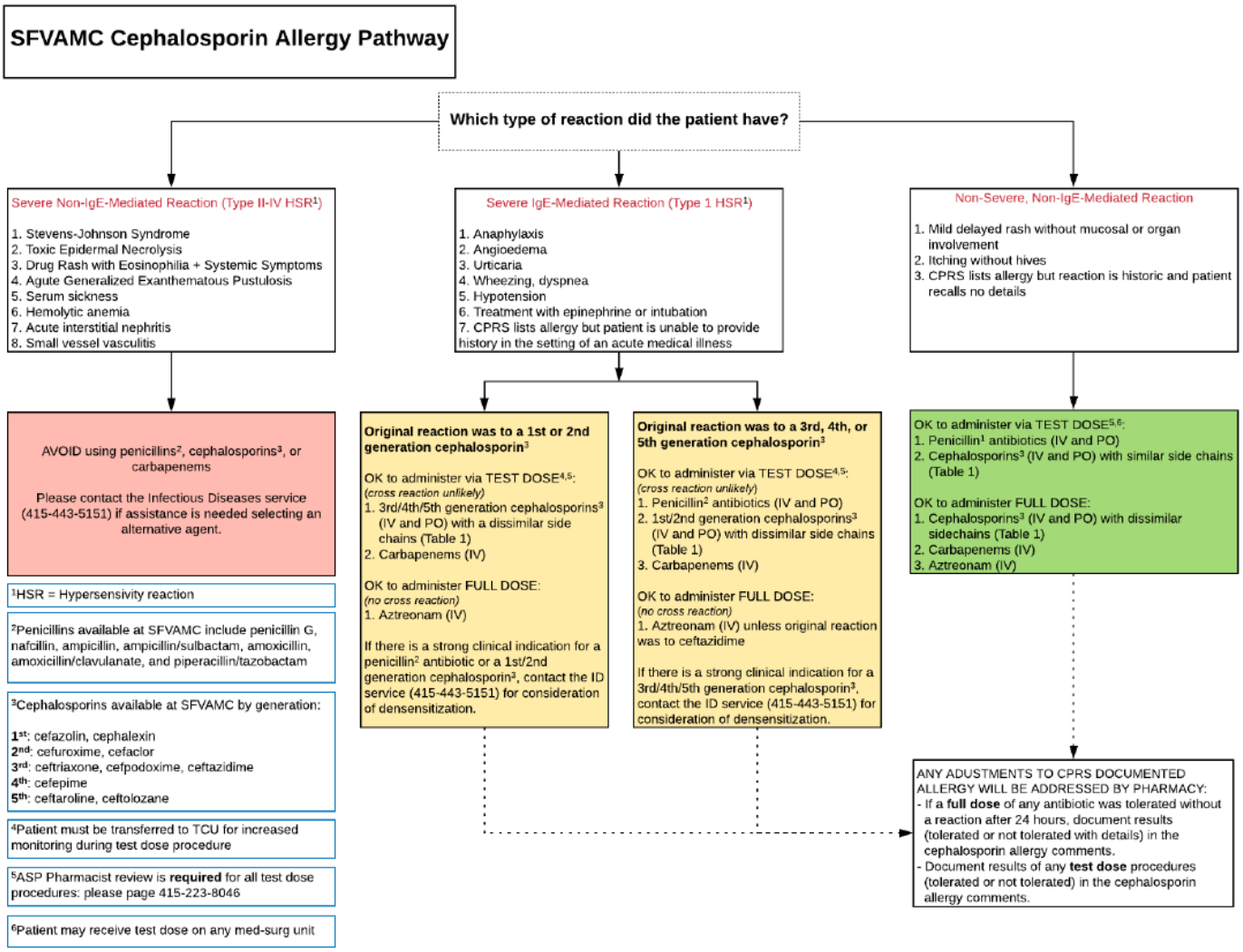
- Pharmacy will send the antibiotic test dose and the Rescue Medication Kit that will include:
    - Epinephrine 0.3 mg pen x1
    - 0.9% NS 1 L bag x1
    - Diphenhydramine 50 mg vial x1
    - Methylprednisolone 125 mg vial x1
    - Glucagon 1 mg vial x1
    - Albuterol 0.0083% 3 mL vials x2
- The full dose may be located in the pyxis machine or will be delivered by pharmacy depending on which antibiotic is selected



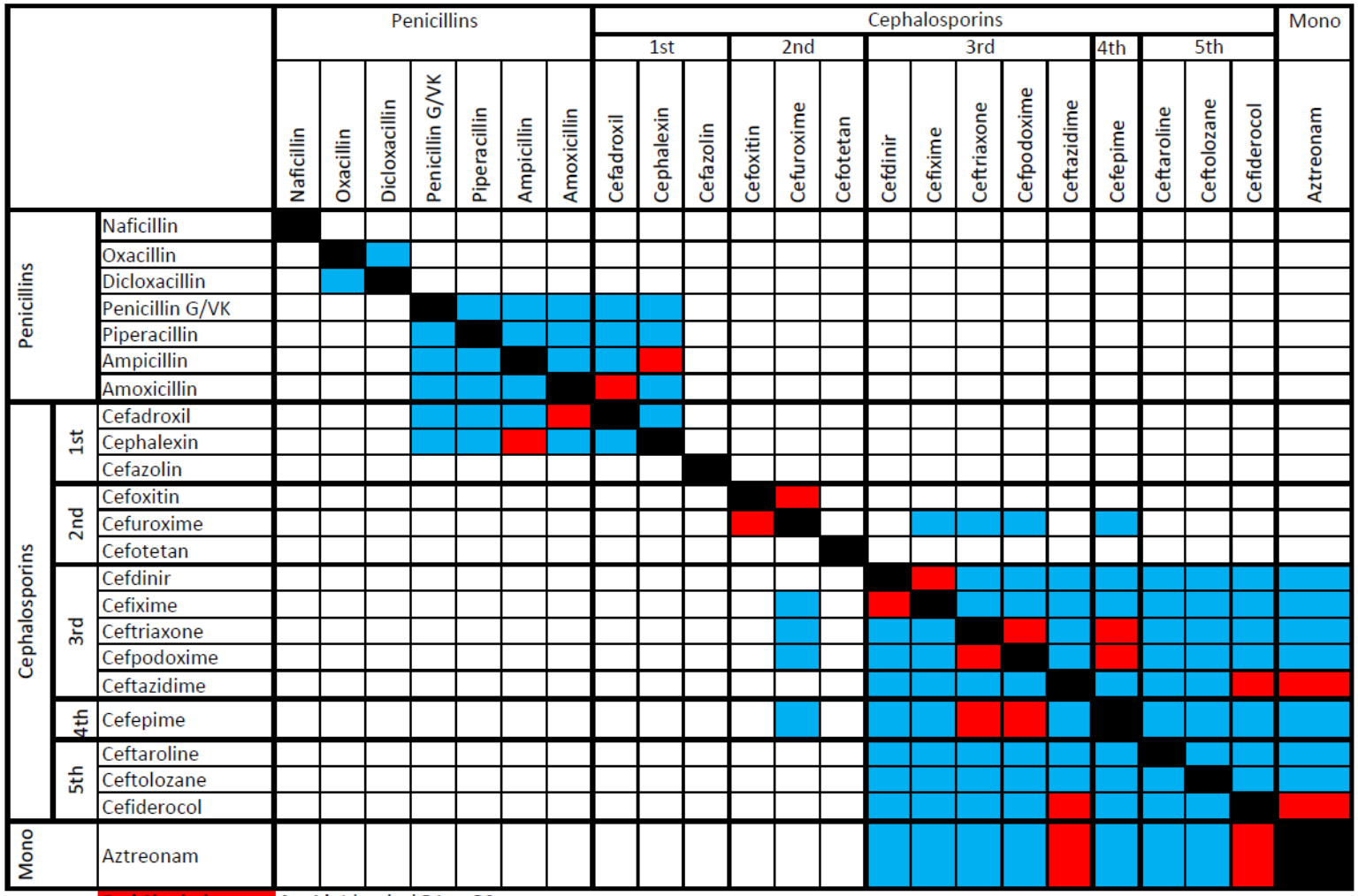
San Francisco VA Medical Center Penicillin Allergy Pathway



San Francisco VA Medical Center Cephalosporin Allergy Pathway

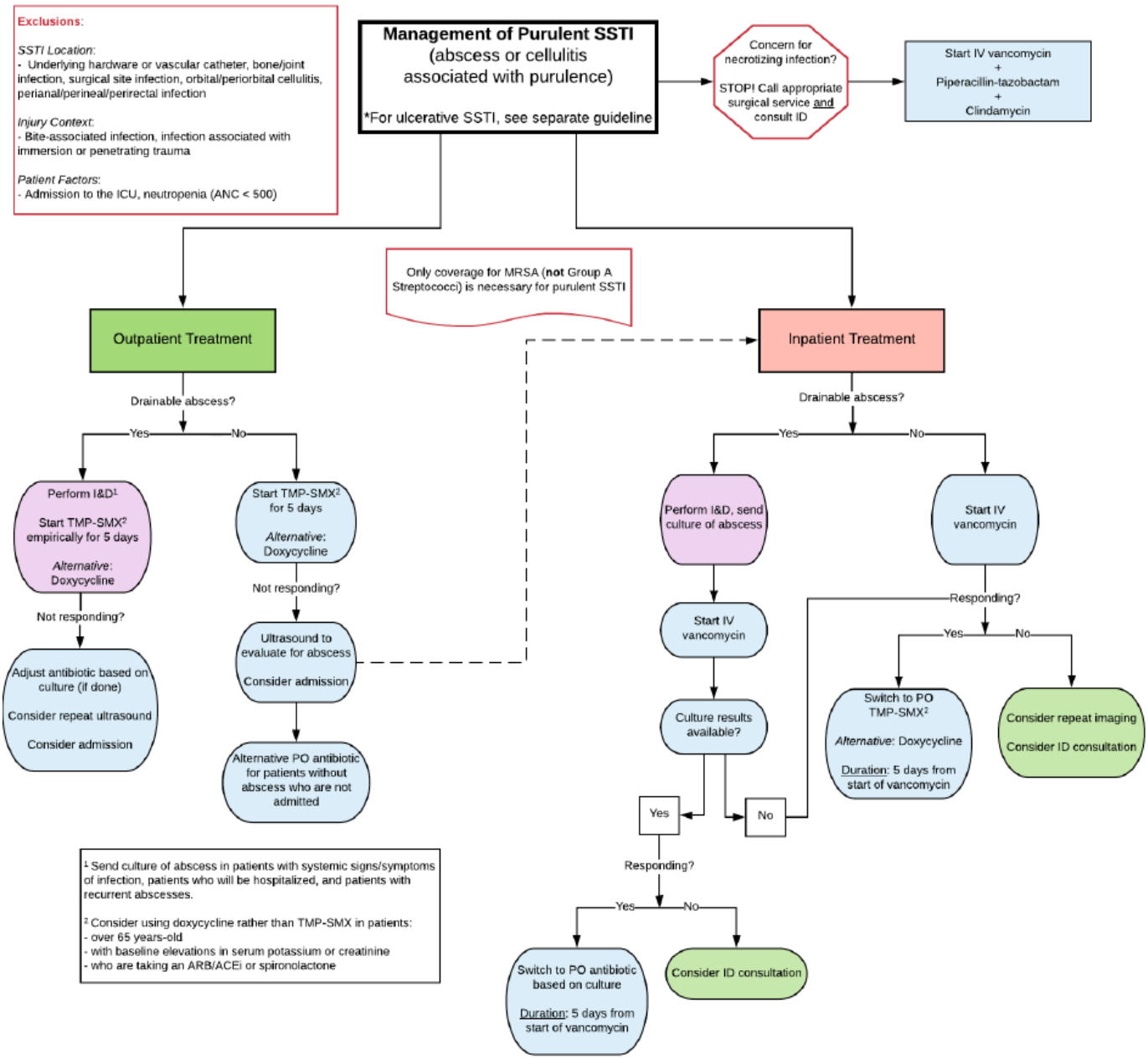


San Francisco VA Medical Center Beta-Lactam Cross Reactivity Table

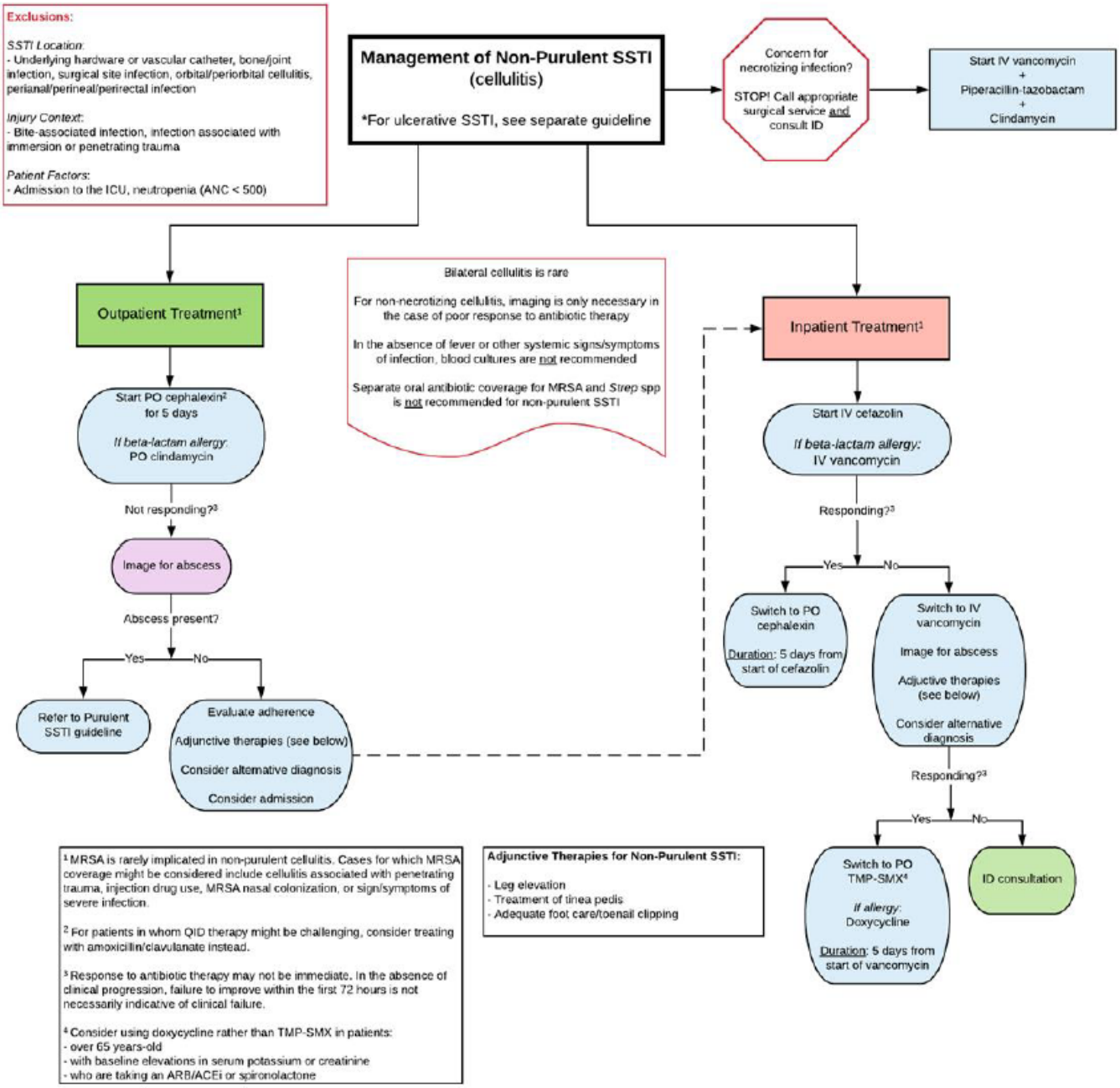


Adapted from Zagursky RJ et al. Allergy Clin Immunol Pract (2017)6: 72-81

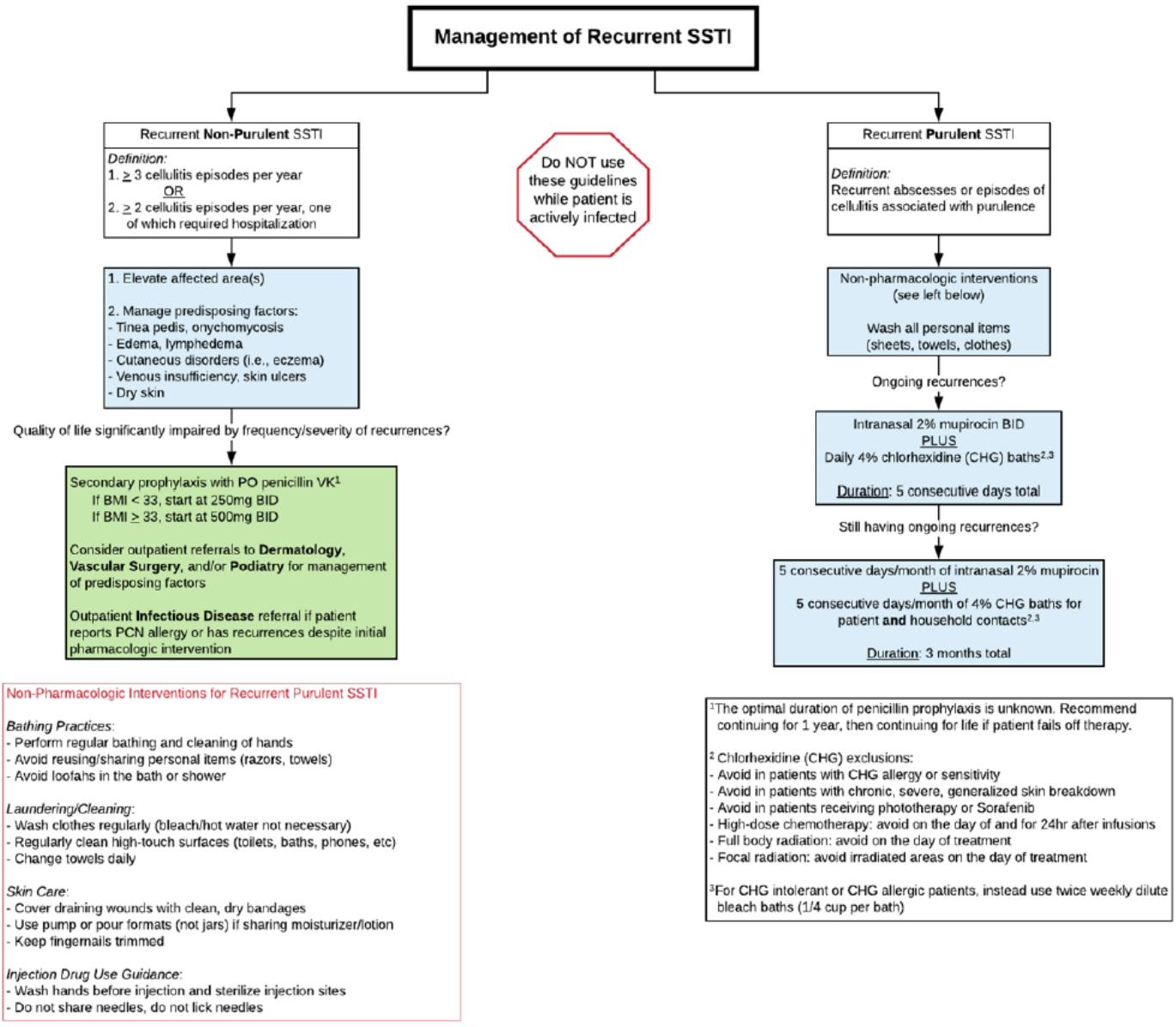
San Francisco VA Medical Center Guidelines for the Empiric Therapy of Purulent Skin and Soft Tissue Infections (SSTI)



San Francisco VA Medical Center Guidelines for the Empiric Therapy of Non- Purulent Skin and Soft Tissue Infections (SSTI)



San Francisco VA Medical Center Guidelines for the Empiric Therapy of Recurrent Skin and Soft Tissue Infections (SSTI)



Non-Pharmacologic Interventions for Recurrent Purulent SSTI

Bathing Practices:
- Perform regular bathing and cleaning of hands
- Avoid reusing/sharing personal items (razors, towels)
- Avoid loofahs in the bath or shower

Laundering/Cleaning:
- Wash clothes regularly (bleach/hot water not necessary)
- Regularly clean high-touch surfaces (toilets, baths, phones, etc)
- Change towels daily

Skin Care:
- Cover draining wounds with clean, dry bandages
- Use pump or pour formats (not jars) if sharing moisturizer/lotion
- Keep fingernails trimmed

Injection Drug Use Guidance:
- Wash hands before injection and sterilize injection sites
- Do not share needles, do not lick needles

[1]The optimal duration of penicillin prophylaxis is unknown. Recommend continuing for 1 year, then continuing for life if patient fails off therapy.

[2] Chlorhexidine (CHG) exclusions:
- Avoid in patients with CHG allergy or sensitivity
- Avoid in patients with chronic, severe, generalized skin breakdown
- Avoid in patients receiving phototherapy or Sorafenib
- High-dose chemotherapy: avoid on the day of and for 24hr after infusions
- Full body radiation: avoid on the day of treatment
- Focal radiation: avoid irradiated areas on the day of treatment

[3]For CHG intolerant or CHG allergic patients, instead use twice weekly dilute bleach baths (1/4 cup per bath)

San Francisco VA Medical Center Antibiotic Dosing for Skin and Soft Tissue Infections

Drug	CrCl > 50 mL/min	CrCl 10 – 50 mL/min	CrCl <10 mL/min	Dialysis (HD)
Cephalexin (Keflex)	500 mg PO q6h	500 mg PO q12h	250 mg PO q24h	500 mg PO q24h (on dialysis days, administer dose after completion of dialysis session)
Clindamycin	<u>Weight-Based (using total body weight):</u> 60 – 90kg: 300mg PO q8h 90 – 120kg: 450mg PO q8h 120 – 180kg: 450mg PO q6h >180 kg: 600mg PO q6h			
TMP/SMX (Bactrim or Septra) *Weight based dosing (using total body weight) *	<u>≥30 mL/min</u> <u>(Ideally ≥5mg/kg/day)</u> 60 – 90kg: 1 DS tablet PO q8h 90 – 120kg: 2 DS tablets PO q12h 120 – 180kg: 2 DS tablets PO q8h >180kg: 2 DS tablets PO q6h	<u>15 – 29 mL/min:</u> <u>(Ideally ≥2.5mg/kg/day)</u> 60 – 90kg: ½ DS tablet PO q8h 90 – 120kg: 1 DS tablets PO q12h 120 – 180kg: 1 DS tablets PO q8h >180: 1 DS tablets PO q6h	Not Recommended	
Doxycycline	100mg PO q12h			
Amoxicillin/Clavulanic Acid (Augmentin)	<u>≥30 mL/min</u> 875 mg PO q12h	<u>10 – 30 mL/min:</u> 500 mg PO q12h	500 mg PO q24h	500 mg PO q24h (administer after HD on dialysis days

<u>References</u>

1. Sanford Guide. Cephalexin.
2. Cox KK, Alexander B, Llvorsi DJ, et. al. Clinical outcomes in patients hospitalized with cellulitis treated with oral clindamycin and trimethoprim/sulfamethoxazole: The role of weight-based dosing. *Journal of Infection.* 2017; 75(6):486 – 492
3. UpToDate. Doxycycline.
4. UpToDate. Amoxicillin and clavulanate.
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San Francisco VA Medical Center Guidelines for Procalcitonin Use

WHAT IS PROCALCITONIN

- Procalcitonin is a biomarker that has been used to aid in diagnosis of bacterial infection or sepsis
- May be used to guide antibiotic treatment decisions but **should be used in conjunction with laboratory findings** and **should not overrule clinical judgement**

INDICATIONS

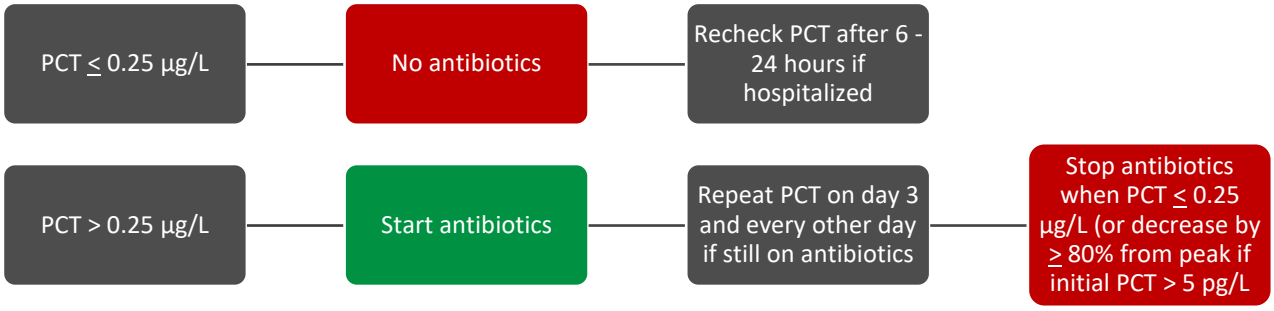
WHEN IS PROCALCITONIN RECOMMENDED	WHEN IS PROCALCITONIN NOT RECOMMENDED

• Decision making about discontinuation of antimicrobials in:
  ○ Non-critically ill ICU patients
  ○ Hospitalized for lower respiratory tract infections
	• Severely immunocompromised (solid organ transplant patients, BMT patients, cancer patients receiving active treatment, HIV positive patients with CD4 <200, patients receiving immunosuppressive drugs other than prednisone)

HOW DO YOU USE PROCALCITONIN?

SUSPECTED RESPIRATORY INFECTION IN STABLE PATIENTS

- Not critically ill or high-risk (e.g. CAP PSI $\geq$ IV / CURB 65 $\geq$ 2, COPD GOLD > 111)
- Not severely immunocompromised (other than corticosteroids)
- No other concomitant infection requiring antibiotics



SUSPECTED SEPSIS IN CRITICALLY ILL PATIENTS

- Not severely immunocompromised (other than corticosteroids)
- Not on antibiotics for chronic bacterial infection (e.g. endocarditis, osteomyelitis)

LIMITATIONS

- Serum procalcitonin may be elevated due to non-infectious causes based on various patient factors
- The time course of bacterial infection and type of infectious process may impact the serum procalcitonin level

FALSE POSITIVES	FALSE NEGATIVES
• Major stressors: recent surgery, severe trauma or burns, prolonged cardiogenic shock • Fungal and malarial infections • Patients taking certain immunomodulating agents that stimulate cytokine release (e.g. OKT3, antilymphocyte globulins, alemtuzumab, IL-2 and granulocyte transfusion) • Patients with paraneoplastic syndromes due to medullary thyroid or small cell lung carcinomas • CKD with or without dialysis (generally higher procalcitonin levels in patients not yet on dialysis)	• Procalcitonin drawn in the first 6 – 12 hours of a bacterial infection • Localized infections (empyema, osteomyelitis, cellulitis, appendicitis)

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3. Kamat, Ishan S et al. "Procalcitonin to Distinguish Viral From Bacterial Pneumonia: A Systematic Review and Meta-analysis." *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America* vol. 70,3 (2020): 538-542. doi:10.1093/cid/ciz545
4. Daubin, Cédric et al. "Procalcitonin algorithm to guide initial antibiotic therapy in acute exacerbations of COPD admitted to the ICU: a randomized multicenter study." *Intensive care medicine* vol. 44,4 (2018): 428-437. doi:10.1007/s00134-018-5141-9

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.

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 ≤ 8/4 µg/ml are considered sensitive, while organisms with an MIC ≥ 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.

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. Enterobacteriaceaewith an MIC ≤ 4 µg/ml are considered sensitive, while enterobacteriaceaewith an MIC ≥ 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 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.

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 ≤ 2 µg/ml are considered sensitive, while enterobacteriaceae with an MIC ≥ 8 µg/ml are considered resistant.

DOSING/PHARMACOKINETICS

CREATININE CLEARANCE (ML/MIN)	DOSE	FREQUENCY
≥ 55	0.5-2 gm	q8h
35-54	0.5-1 gm	q8h-q12h
11-34	0.25-1 gm	q12h
≤ 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 <120kg should receive a 2 gm dose and patients >120kg should receive a 3 gm dose 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** (except in patients with a history of penicillin induced anaphylaxis)
•Treatment of gram-negative hospital-acquired or ventilator-associated pneumonia (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 <u>not</u> be dispensed by pharmacy without prior approval by the Hematology/Oncology Section or the Infectious Diseases Section except in ICU and ED patients. ED patients initiated on cefepime will need ID approval upon transfer unless they are transferred to the ICU.

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	0.5 - 1	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.

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. Staphylococci with an MIC $\leq$ 0.5 µg/ml are considered sensitive, while isolates with an MIC $\geq$ 4 µg/ml are considered resistant. Streptococci with an MIC $\leq$ 0.25 µg/ml are considered sensitive while isolates with an MIC $\geq$ 1 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 MIC ≤ 1µg/mL are considered sensitive whereas for *E. faecalis*, 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:** a. fib (<1%), a. 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, SJS, 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 ≤ 0.5 µg/mL are considered sensitive while organisms with an MIC ≥ 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.

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 ≤ 2 µg/ml are considered sensitive, while isolates with an MIC ≥ 8 µg/ml are considered resistant. *C. glabrata* isolates with and MIC ≤ 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.

FOSFOMYCIN (PO)

INDICATIONS

• Treatment of acute uncomplicated cystitis in women caused by susceptible bacteria
• [Off-label] Treatment of acute simple cystitis (mild infection limited to the bladder in women or men) caused by susceptible bacteria
• [Off-label] Treatment of multidrug-resistant simple cystitis

SPECTRUM

Fosfomycin is a synthetic, broad spectrum, bactericidal antibiotic. The drug is rapidly absorbed following oral administration and converted to the active drug, which inhibits pyruvyl transferase, a critical enzyme in the synthesis of bacterial cell walls. Fosfomycin is active against *E. faecalis* and *E. coli*, and has shown *in vitro* activity against *E. faecium, C. diversus, C. freundii, E. aerogenes, K. oxytoca, K. pneumoniae, P. aeruginosa, P. mirabilis, P. vulgaris, and S. marcescens.* Urinary isolates with an MIC $\leq$ 64 mg/L are considered susceptible for the treatment of UTIs.

DOSING/PHARMACOKINETICS

The recommended dose of fosfomycin for the **treatment of both acute uncomplicated and simple cystitis is 3 g as a single dose;** however, multidose regimens **(3 g every 2-3 days x 3 doses) have been described for multidrug-resistant lower UTIs.** Following oral administration, fosfomycin is rapidly absorbed. Taking this medication under fed conditions reduces the oral bioavailability of fosfomycin from 37% to 30% and reduces the C_{max} from 26.1 mcg/mL to 17.6 mcg/mL. The drug is well distributed through the kidneys, bladder wall, prostate, and seminal vesicles. Fosfomycin is excreted unchanged in both urine and feces. The mean urine fosfomycin concentration 2-4 hours was 706 mcg/mL after a 3 gm dose of fosfomycin under fasting conditions. The mean urine fosfomycin concentration 6-8 hours was 537 mcg/mL after a 3 gm dose under fed conditions. However, because the cumulative amount of fosfomycin excreted in the urine was the same 1118 mg (fed) vs. 1140 (fasting) and furthermore, urinary concentrations greater than or equal to 100 mcg/mL were maintained for the same duration of 26 hours indicates that fosfomycin can be taken without regard to food. The mean half-life for elimination is 5.7 hours.

No renal adjustments are provided in the manufacturer's labeling. In patients with varying degrees of renal impairment (creatinine clearances ranging from 54 mL/min to 7 ml/min), the half-life for elimination increased from 11 hours to 50 hours, and the percent of fosfomycin recovered in urine decreased from 32% to 11%, respectively.

ADVERSE REACTIONS

•**Hepatic effects –** Hepatic injury, including steatosis and hepatitis, has been reported; usually reversible upon discontinuation.
•**Superinfection –** Prolonged use may result in fungal or bacterial superinfection, including *Clostridioides difficile*-associated diarrhea (CDAD) and pseudomembranous colitis; CDAD has been observed > 2 months post-antibiotic treatment.
•**Hypersensitivity –** Hypersensitivity reactions, including anaphylactic shock, have been reported (rare). Discontinue use and institute supportive measures at the first sign(s) of a hypersensitivity reaction.

DRUG INTERACTIONS

DRUG	INTERACTION	MECHANISM
Metoclopramide	↓ fosfomycin absorption	↑ gastric motility

FORMULARY STATUS

Fosfomycin is a **CATEGORY II (restricted)** antibiotic at San Francisco VA Medical Center.

GANCICLOVIR

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 mg/kg q12h	5 mg/kg q24h
50-69 ml/min	2.5 mg/kg q12h	2.5 mg/kg q24h
25-49 ml/min	2.5 mg/kg q24h	1.25 mg/kg q24h
10-24 ml/min	1.25 mg/kg q24h	0.625 mg/kg q24h
Hemodialysis	1.25 mg/kg 3 times/week following hemodialysis	0.625 mg/kg 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 ≤ 4 µg/ml are considered sensitive, while organisms with an MIC ≥ 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.)

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

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	55%	**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%**

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.

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.

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 ***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 INTERACTIONS

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 ≤ 32 µg/ml are considered sensitive, while isolates with an MIC 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 ≤ 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.

OSELTAMIVIR

INDICATIONS

- **Treatment of acute, uncomplicated influenza A and B in outpatients who have been symptomatic for no more than 48 hours and hospitalized patient regardless of symptom onset.**
- **Post-exposure prophylaxis of influenza A and B in patients 1 year and older within 48 hours following close contact with an infected individual**
- **Pre-exposure prophylaxis of influenza A and B during a community outbreak**

ANTIVIRAL ACTIVITY

Oseltamivir phosphate is an ethyl ester prodrug requiring ester hydrolysis for conversion to the active form, oseltamivir carboxylate. The active drug inhibits influenza virus neuraminidase, affecting the release of viral particles. The concentrations of oseltamivir carboxylate required for inhibition of influenza virus were highly variable depending on the assay method used and the virus tested. The 50% and 90% effective concentrations (EC50 and EC90) were in the range of 0.0008 μM to >35 μM and 0.004 μM to >100 μM (1 μM=0.284 μg/mL) respectively. The relationship between the antiviral activity in cell culture and the inhibition of influenza virus replication in humans has not been established.

LIMITATIONS OF USE

- Not a substitute for annual influenza vaccination
- Influenza viruses change over time. Emergence of resistance substitutions could decrease drug effectiveness. Other factors (for example, changes in viral virulence) might also diminish clinical benefit of antiviral drugs. Prescribers should consider available information on influenza drug susceptibility patterns and treatment effects when deciding whether to use oseltamivir.

DOSING/PHARMACOKINETICS

INFECTION	DOSAGE REGIMEN	DURATION OF THERAPY
Prophylaxis	75 mg PO daily	At least 10 days (Community outbreak: up to 6 weeks)
Treatment	75 mg PO BID	5 days (longer duration can be considered in severely ill or immunocompromised patients)

ADJUSTMENT OF ORAL DOSAGE REGIMENS IN PATIENTS WITH RENAL INSUFFICIENCY

USUAL DOSAGE	CREATININE CLEARANCE	ADJUSTED DOSAGE
75 mg PO BID	31-60 ml/min	30 mg PO BID
	11-30 ml/min	30 mg PO daily
	0-10 ml/min	Use is not recommended
	IHD	30 mg immediately and then 30 mg after every hemodialysis cycle
75 mg PO daily	31-60 ml/min	30 mg PO daily
	11-30 ml/min	30 mg every other day
	0-10 ml/min	Use is not recommended
	IHD	30 mg immediately and then 30 mg after every other HD sessions for the recommended prophylaxis duration

Oseltamivir phosphate is readily absorbed from the GI tract and is extensively converted predominantly by hepatic esterases to oseltamivir carboxylate. At least 75% of an oral dose reaches the systemic circulation as oseltamivir carboxylate. The elimination half-life of oseltamivir phosphate is 1 to 3 hours. The elimination half-life of oseltamivir carboxylate is 6 to 10 hours. Oseltamivir is renally eliminated as oseltamivir carboxylate; therefore dose adjustment for renal insufficiency is required (see above).

DRUG INTERACTIONS

Live attenuated influenza vaccine (LAIV): avoid administration of LAIV within 2 weeks before or 48 hours after Tamiflu use unless medically indicated

FORMULARY STATUS

Oseltamivir is a **CATEGORY I (Formulary)** agent 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	4.5 q6h
20-40	2.25 q6h	4.5 q8h
< 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 INTERACTIONS

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	DOSE (tablet)
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
Fosaprenavir	↓ 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	↑ simeprevir levels	↓ simeprevir 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, unless ordered by Heme/Onc, and completion of an electronic non-formulary drug request.

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.

SULFAMETHOXAZOLE-TRIMETHOPRIM (SMX-TMP)

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. SMX-TMP 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 SMX-TMP resistant strains of *Shigella* and *Salmonella* and the overproduction of a resistant DHFR by *Escherichia coli* are of growing concern. SMX-TMP'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 SMX-TMP 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

SMX-TMP 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. SMX-TMP 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 SMX-TMP 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

SMX-TMP 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.

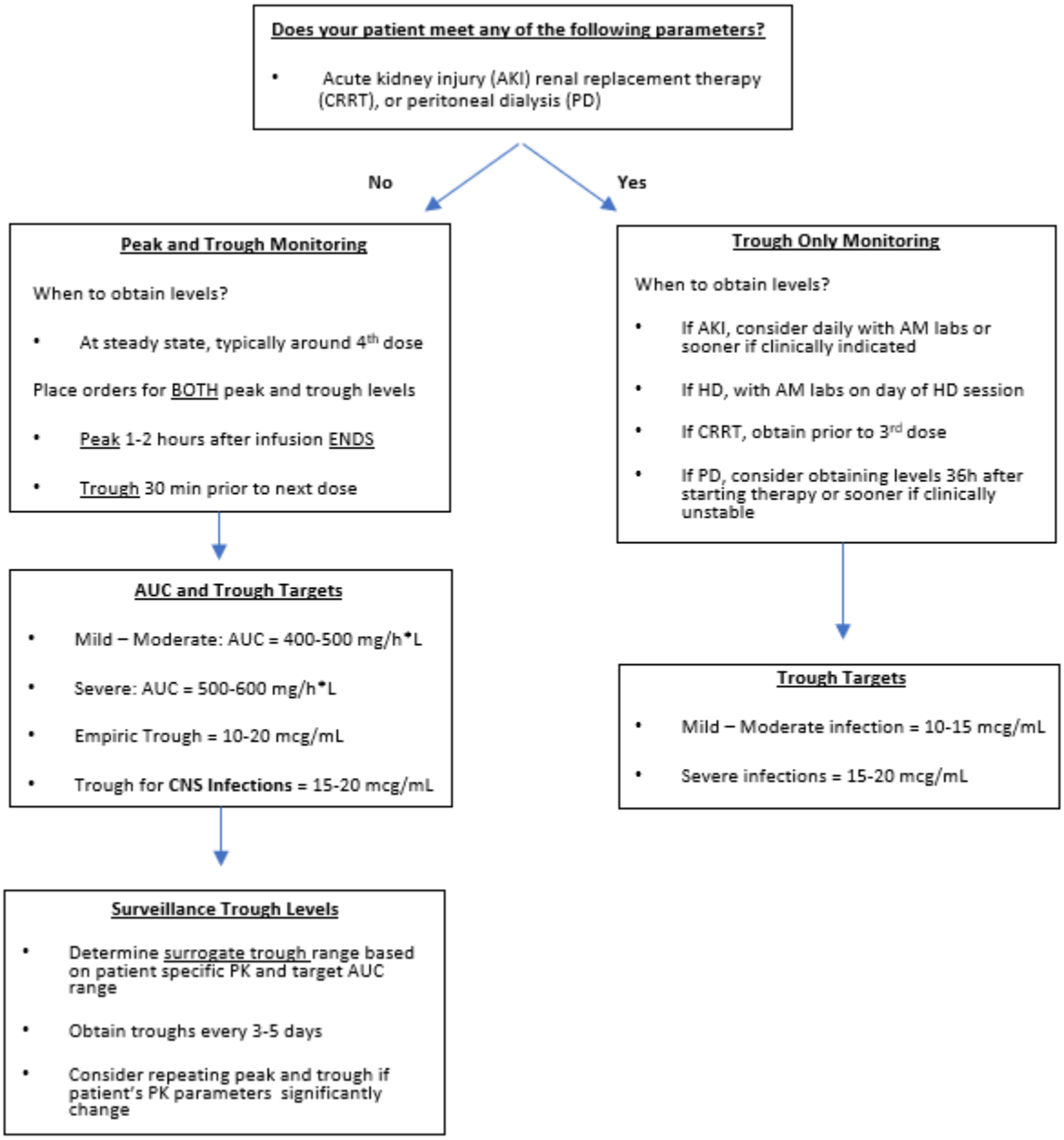
DOSING/PHARMACOKINETICS

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 total body weight q8h-q12h to achieve an AUC 400-600 mg/L*h or 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. Therapeutic drug 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 target AUC of 400-600 mg/L*h has been recommended for most patients. Higher AUC target of 500-600 mg/L*h may be considered for severe infections such as endocarditis, ventilator-associated pneumonia, or osteomyelitis caused by *S. aureus*. Trough levels of 15-20 µg/ml are recommended for central nervous system infections (e.g., meningitis, VP shunt infections) as there is a paucity of data with regards to optimal AUC target. Patients with higher AUC levels (> 550 mg/L*h) and higher trough levels (> 15 mg/L) 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.

VANCOMYCIN MONITORING ALGORITHM



Prioritize trough range of 15-20 mcg/L as efficacy parameter in patients with CNS infections such as meningitis or patients with enterococcal endocarditis. Consider consulting the infectious diseases service for assistance in managing these patients.

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 IV 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
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.

San Francisco VA Medical Center Antiretroviral Agent Dosing Guidelines

Nucleoside/tide Reverse Transcriptase Inhibitors (NRTIs)

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 PO once daily	Hepatic and renal	No dosage adjustment in renal insufficiency Child-Pugh Class — Dose A — 200mg PO BID (use oral soln) B or C — Contraindicated
Emtricitabine **(Emtriva™)**	Capsule: 200 mg Oral solution: 10mg/mL	200 mg PO once daily or 240mg (24mL) oral soln once daily	Renal	Dose CrCl (mL/min) — Capsule — Soln 30-49 — 200 mg q48h — 120mg q24h 15-29 — 200 mg q72h — 80mg q24h <15 — 200 mg q96h — 60mg q24h HD — 200 mg q24h# — 240mg 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 PO 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
Tenofovir Alafenamide (TAF) **(Vemlidy®)**	Tablet: 25mg	25 mg PO daily	Renal	CrCl (mL/min) Dose <15 and not on HD Not recommeded HD 25 mg q24h post HD session on dialysis days Child-Pugh Class Dose B or C Not recommended

Tenofovir disoproxil fumarate (TDF) **(Viread®)**	Tablets: 150 mg, 200 mg, 250 mg, 300 mg Oral powder: 40 mg/1 gm	300 mg PO 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 every 7 days post HD
Zidovudine **(Retrovir®)**	Capsule :100 mg Tablet: 300 mg Oral syrup: 50 mg/ 5mL Injection solution: 10mg/mL	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# #Take dose after HD session on dialysis days

NRTI Co-Formulations

Drug	Dosage Forms	Dose	Excretory Route	Dosage Adjustment in Renal Insufficiency and Drug Interactions
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
Tenofovir alafenamide (TAF)/ Emtricitabine (Descovy®)	Tablet: 25 mg tenofovir AF/ 200mg emtricitabine	1 tablet once daily	Renal	ClCr (mL/min) Dose < 30 and not on HD Not recommended < 30 and on HD 1 tablet once daily Concomitant administration with: Rifamycins Not recommended
Tenofovir disoproxil fumarate (TDF) / 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 or on HD Not recommended

Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)

Drug	Dosage Forms	Dose	Excretory Route	Dosage Adjustment Renal or Hepatic Impairment and Drug Interactions
Doravirine **(Pifeltro®)**	Tablet: 100 mg	100mg PO once daily	Hepatic	No dosage adjustment with renal impairment. Has not been studied in ESRD or on HD Child-Pugh Class — Dose A or B — No dosage adjustment C — Not studied Concomitant administration with: Rifampin — Contraindicated Rifabutin — Doravirine 100mg PO BID Rifapentine — Contraindicated

Efavirenz **(Sustiva®)**	Capsules: 50 mg, 200 mg Tablet: 600 mg	600 mg PO once daily, at or before bedtime	Hepatic and renal	No dosage adjustment necessary in renal impairment. Caution with impaired hepatic function <u>Concomitant administration with</u>: Rifampin — No dosage adjustment Rifabutin — ↑ Rifabutin dose 450-600 mg per day Rifapentine — No dosage adjustment
Etravirine **(Intelence®)**	Tablets: 25 mg, 100 mg, 200mg	200 mg PO BID Take following a meal	Hepatic	No dose adjustment necessary in renal impairment <u>Child-Pugh Class</u> — <u>Dose</u> A or B — No dosage adjustment C — No dose recommendation <u>Concomitant administration with</u>: Rifampin — Do not coadminister Rifabutin — Do not coadminister if with PI/r If without PI/r, use rifabutin 300mg once daily Rifapentine — Do not coadminister

Nevirapine **(Viramune®)**	Tablet: 200 mg Extended release tablet: 400 mg Oral suspension: 10 mg/mL	200 mg PO once daily for 2 weeks, then 200 mg PO BID thereafter* or 400 mg XR once daily *Repeat lead-in period if therapy is discontinued for >7 days	Hepatic and renal	On hemodialysis, an additional 200mg dose following each dialysis treatment is recommended <u>Child-Pugh Class</u> — <u>Dose</u> A — No dosage adjustment B or C — Contraindicated <u>Concomitant administration with</u>: Rifampin — Do not coadminister Rifabutin — No dosage adjustment Rifapentine — Do not coadminister

Rilpivirine **(Edurant®)**	Tablet: 25 mg	25 mg PO once daily	Hepatic	No dosage adjustment necessary in renal impairment <u>Child-Pugh Class</u> <u>Dose</u> A or B No dosage adjustment C No dose recommendation <u>Concomitant administration with</u>: Rifampin Contraindicated Rifabutin Rilpivirine 50mg once daily Rifapentine Contraindicated

Fixed-dose Combinations Containing NRTI Pair Plus NNRTI

Drug	Dosage Forms	Dose	Excretory Route	Dosage Adjustment Renal or Hepatic Impairment
Doravirine/ Lamivudine/ Tenofovir DF (Delstrigo®)	Tablet: 100 mg doravirine/ 300 mg lamivudine/ 300 mg tenofovir DF	1 tablet once daily	Hepatic and renal	Not recommended if CrCl <50 mL/min Child-Pugh Class — Dose A or B — No dosage adjustment C — Not studied
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 if CrCl <50 mL/min Caution with impaired hepatic function
Efavirenz/ Lamivudine/ Tenofovir DF (Symfi®)	Tablet: 600 mg efavirenz/ 300mg lamivudine/ 300 mg tenofovir DF	1 tablet once daily on an empty stomach, preferably at bedtime	Hepatic and renal	Not recommended if CrCl <50 mL/min Not recommended with moderate to severe hepatic impairment. Caution with mild hepatic impairment

Efavirenz/ **Lamivudine/** **Tenofovir DF** **(Symfi Lo®)**	Tablet: 400 mg efavirenz/ 300mg lamivudine/ 300 mg tenofovir DF	1 tablet once daily on an empty stomach, preferably at bedtime	Hepatic and renal	Not recommended if CrCl <50 mL/min Not recommended with moderate to severe hepatic impairment. Caution with mild hepatic impairment
Rilpivirine/ **Emtricitabine/** **Tenofovir DF** **(Complera®)**	Tablet: 25 mg rilpivirine/ 200 mg emtricitabine/ 300 mg tenofovir DF	1 tablet once daily with a meal	Hepatic and renal	Not recommended CrCl <50 mL/min <u>Child-Pugh Class</u> — <u>Dose</u> A or B — No dosage adjustment C — No dose recommendation
Rilpivirine/ **Emtricitabine/** **Tenofovir AF** **(Odefsey®)**	Tablet: 25 mg rilpivirine/ 200 mg emtricitabine/ 25 mg tenofovir AF	1 tablet once daily with a meal	Hepatic and renal	Not recommended CrCL <30 mL/min who are not receiving chronic HD On Chronic HD: 1 tablet once daily. On HD days, take after dialysis <u>Child-Pugh Class</u> — <u>Dose</u> A or B — No dosage adjustment C — No dose recommendation

Protease Inhibitors (PI)

Drug	Dosage Forms	Dose	Excretory Route	Dosage Adjustment With Hepatic Impairment, Hemodialysis and Drug Interactions
Atazanavir (Reyataz®)	Capsules: 100mg, 150 mg, 200 mg, 300 mg Pediatric powder: 50 mg packet	ARV-naive: Atazanavir 300mg plus ritonavir 100mg once daily or Atazanavir 400mg once daily ARV-experienced: Atazanavir 300mg plus ritonavir 100mg once daily	Hepatic	Reyataz ARV-naïve on HD; Atazanavir 300mg plus ritonavir 100mg once daily ARV-experienced on HD: ATV and ATV/ritonavir not recommended Child-Pugh Class Dose A No dosage adjustment B ATV 300mg un-boosted for naive C Not recommended Concomitant administration with: Efavirenz Atazanavir 400 mg plus ritonavir 100mg once daily Tenofovir Atazanavir 300 mg plus ritonavir 100mg once daily

Atazanavir/ **Cobicistat** **(Evotaz®)**	Tablet: 300mg co-formulated with cobicistat 150 mg	One tablet once daily	Hepatic and renal	<u>If used with Tenofovir DF:</u> Not recommended if CrCl < 70mL/min Not recommended with hepatic impairment
Darunavir **(Prezista®)**	Tablets: 75 mg, 150 mg, 600 mg, 800 mg Oral suspension: 100 mg/mL	<u>ARV-naïve or no DRV mutations:</u> 800 mg plus 100 mg RTV once daiy <u>ARV-experienced with one or more DRV mutations</u>: 600 mg plus 100 mg RTV twice daily	Hepatic	Mild to moderate hepatic impairment: No dose adjustment Severe hepatic impairment: Not recommended

Darunavir/ Cobicistat **(Prezcobix®)**	Tablet: 800 mg darunavir/ 150 mg cobicistat	One tablet once daily <u>ARV-experienced with one or more DRV mutations</u>: not recommended	Hepatic and renal	<u>If used with Tenofovir DF:</u> Not recommended if CrCl < 70mL/min <u>Child-Pugh Class</u> — <u>Dose</u> A or B — No dosage adjustment C — Not recommended
Ritonavir **(Norvir®)**	Capsule: 100 mg (soft gelatin) Tablet: 100 mg Oral solution: 80 mg/mL Oral powder: 100mg single packet	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	Refer to recommendations for the primary PI for hepatic dose adjustment

Fixed-Dose Combinations Containing NRTI Pair plus PI

Drug	Dosage Forms	Dose	Excretory Route	Dosage Adjustment Renal or Hepatic Impairment
Darunavir/ Cobicistat/ Emtricitabine/ Tenofovir AF (Symtuza®)	Tablet: 800 mg darunavir/ 150 mg cobicistat/ 200 mg emtricitabine/ 10 mg tenofovir AF	1 tablet once daily	Hepatic and renal	CrCl <30 mL/min – not recommended On chronic HD: 1 tablet PO once daily. On HD days, administer after dialysis Not recommended in severe hepatic impairment Concomitant administration with: Rifampin Contraindicated Rifabutin No data Rifapentine Contraindicated

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/r) • 300mg BID with NRTIs, T-20, TPV/r, NVP, and non-strong CYP3A inhibitors or inducers • 600mg BID with CYP3A inducers, including EFV, ETR, etc. (without a CYP3A inhibitor) •	Hepatic and renal	No dosage recommendation with hepatic impairment. Maraviroc concentrations will likely be increased <u>CrCl <30 mL/min or on HD:</u> • Without potent CYP3A4 inhibitors or inducers: Maraviroc 300mg twice daily; if postural hypotension occurs, reduce to maraviroc 150 mg twice daily • With potent CYP3A4 inhibitors or inducers: Not recommended

CD4 Post-Attachment Inhibitor

Drug	Dosage Forms	Dose	Excretory Route	Dosage Adjustment in Renal or Hepatic Impairment
Ibalizumab (Trogarzo®)	Single dose 2 mL vial containing 200 mg/ 1.33 mL (150 mg/mL) of ibalizumab	• Administer a single loading dose of ibalizumab 2,000 mg IV infusion over 30 minutes, followed by a maintenance dose of 800mg IV infusion over 15 minutes every 2 weeks	Not well defined	No dosage recommendation in renal or hepatic impairment

GP-120-Directed Attachment Inhibitor

Drug	Dosage Forms	Dose	Excretory Route	Dosage Adjustment in Renal or Hepatic Impairment
Fostemsavir (Rukobia®)	Tablet: 600mg XR	600mg PO BID	Hepatic and renal	No dosage adjustment required with renal impairment or those on HD No dosage adjustment required with mild to severe hepatic impairment

Integrase Strand Transfer Inhibitors (INSTI)

Drug	Dosage Forms	Dose	Excretory Route	Dosage Adjustment in Renal or Hepatic Impairment, and Drug Interactions
Bictegravir	Only available as a component of fixed-dose combination **BIKTARVY®**	BIKTARVY: One tablet PO once daily	Hepatic	Refer to BIKTARVY for details

Dolutegravir **(Tivicay®)**	Tablet: 10 mg, 25 mg, 50 mg Tablet for suspension: 5 mg	<u>ARV-naïve or treatment-experienced but integrase strand inhibitor-naïve (INSTI-naïve):</u> 50 mg PO once daily <u>INSTI-experienced with certain known or clinically suspected INSTI-resistance:</u> 50 mg PO BID	Hepatic and renal	No dosage adjustment necessary with renal impairment. <u>Child-Pugh Class</u> — <u>Dose</u> A or B — No dosage adjustment C — Not recommended <u>ARV- or INSTI- naïve and concomitant administration with</u>: 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) Rifabutin — No dosage adjustment Rifapentine — Do not co-administer

Elvitegravir	Only available as a component of a fixed-dose combination known as either **Genvoya®** (elvitegravir/cobicistat/emtricitabine/TAF) or **Stribild®** (elvitegravir/cobicistat/emtricitabine/TDF)	**Genvoya®** One tablet PO once daily **Stribild®** One tablet PO once daily	Hepatic and renal	<u>Concomitant administration with</u>: Rifampin — Contraindicated Rifabutin — Do not coadminister Rifapentine — Do not coadminister

Raltegravir **(Isentress®)**	Tablet: 400 mg Chewable tablets: 25 mg, 100 mg Powder for oral suspension: 100 mg single-use packet High dose tablet: 600 mh	<u>Regular tablet</u>: 400 mg PO BID <u>High dose tablet</u>: ARV-naïve or ARV-experienced with virologic suppression on a regimen containing RAL 400mg twice daily: 1200 mg PO once daily	Hepatic	No dosage adjustment necessary in renal insufficiency. No dosage adjustment with mild to moderate hepatic insufficiency No recommendation with severe hepatic insufficiency <u>Concomitant administration with</u>: Rifampin *Raltegravir 800mg BID Rifabutin No dosage adjustment Rifapentine Do not coadminister with once daily Rifapentine *standard tablet only

Fixed-dose Combinations Containing NRTI Pair Plus INSTIs

Drug	Dosage Forms	Dose	Excretory Route	Dosage Adjustment Renal or Hepatic Impairment
Bictegravir/ Emtricitabine/ Tenofovir AF (Biktarvy®)	Tablet: 50 mg bictegravir/ 200 mg emtricitabine/ 25 mg tenofovir AF	1 tablet once daily	Hepatic and renal	CrCl <30 mL/min – not recommended On chronic HD: 1 tablet PO once daily. On HD days, administer after dialysis Child-Pugh Class — Dose A or B — No dosage adjustment C — Not recommended Concomitant administration with: Rifampin — Contraindicated Rifabutin — Do not coadminister Rifapentine — Do not coadminister
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	CrCl <30 mL/min and not on chronic HD: not recommended On chronic HD: 1 tablet PO once daily. On HD days, administer after dialysis No dosage adjustment necessary in mild-moderate hepatic impairment Not recommended in severe 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
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 class A Contraindicated for Child-Pugh class B and C

Fixed-Dose Combinations Containing INSTIs and NNRTI

Drug	Dosage Forms	Dose	Excretory Route	Dosage Adjustment Renal or Hepatic Impairment
Dolutegravir/ Rilpivirine (Juluca®)	Tablet: 50 mg dolutegravir/ 25 mg rilpivirine	1 tablet once daily with food	Hepatic	No dosage adjustment with renal insufficiency Monitor for adverse effects when CrCl < 30 mL/min Child-Pugh Class — Dose A or B — No dosage adjustment C — No dose recommendation

Fixed-Dose Combinations Containing NRTI plus INSTI

Drug	Dosage Forms	Dose	Excretory Route	Dosage Adjustment Renal or Hepatic Impairment
Dolutegravir/ Lamivudine (Dovato®)	Tablet: 50 mg dolutegravir/ 300 mg lamivudine	1 tablet once daily	Hepatic and renal	Not recommended if CrCl <50 mL/min Child-Pugh Class — Dose A or B — No dosage adjustment C — No dose recommendation