ANTIMICROBIAL USE GUIDELINES

University of Wisconsin Hospital and Clinics Pharmacy and Therapeutics Committee Department of Pharmacy Drug Policy Program

> July 2011 to June 2012 Twenty-First Edition

PREFACE

The Antimicrobial Use Guidelines represent the expert opinion and advice of attending physicians of the University of Wisconsin Hospital and Clinics, particularly, the Infectious Diseases Section of the Department of Medicine and Department of Pediatrics. Originally conceived in 1988 as a selection guide to the more expensive antimicrobials intended to maximize optimal patient care, the document now has guidelines for use on all UWHC formulary antimicrobials. These guidelines serve not only the function of rational antimicrobial selection from a powerful array of choices, but also as guidelines for cost-effective use. The guidelines also function as the Drug Use Evaluation criteria for antimicrobial audits.

Although general guidelines can be written, not every patient will fit these guidelines. When faced with a therapeutic dilemma, the Infectious Diseases Section provides timely consults. If pharmacokinetic monitoring is desired, the unit pharmacist schedules levels and calculates a new regimen. The unit pharmacist also provides information on doses, routes of administration and other facts as they relate to drug use.

Care has been taken to make this publication error-free and as up-to-date as possible at the time of publication. However, no responsibility is assumed by UWHC, the Pharmacy and Therapeutics Committee or the UWHC Department of Pharmacy for any injury and/or damage to persons or property as a matter of product liability, negligence or otherwise, or from any use or operation of any methods, products, instructions, doses or ideas contained in this material. Because of the rapid advances in the medical sciences, the publisher recommends that drug doses and susceptibilities be independently verified.

Often empiric broad-spectrum coverage is appropriate before culture and susceptibilities are known. However, once culture and susceptibilities are known, therapy should be reviewed to change the patient's antimicrobials to the narrowest spectrum possible (de-escalation) or have doses adjusted based on pharmacokinetic and pharmacodynamic principles. This will decrease needless broad-spectrum antibiotic pressure, a factor in the emergence of resistant strains. This will also decrease unnecessary drug costs and potential adverse effects.

Costs reflect current prices as of April 2011

The Pharmacy and Therapeutics Committee wishes to specially thank the members of the Antimicrobial Use Subcommittee for their time and input into the writing of these guidelines: David Andes MD, James Conway MD, Barry Fox MD, Carol Spiegel PhD, and Andrew Urban MD. Also, special thanks to the following people who wrote or updated sections of the guidelines including Jennifer Schauer PharmD, MaryAnn Steiner PharmD, Michael Madalon RPh, Rick Kittell PharmD, Lucas Schultz, PharmD and Jeff Fish PharmD. The revision of this twenty-first edition was coordinated by Sara Shull, PharmD, MBA.

*Each drug entry includes: drug name, adult (70 kg) and pediatric doses, UWHC and managed care cost per day. **Pediatric dose should not exceed adult dose.

A version of this guideline is also available online on uconnect in the Drug Use Guidelines Section

Evidence based articles are available online on Workspaces at http://workspaces.uconnect.wisc.edu/display/AST/Home

Useful Web Sites and Resources

Information on HIV/AIDS Treatment, Prevention and Research http://aidsinfo.nih.gov/

Johns Hopkins AIDS Service http://www.hopkins-aids.edu/

UCSF Center for HIV Information http://hivinsite.ucsf.edu/

Johns Hopkins Antibiotic Guide http://hopkins-abxguide.org

Centers for Disease Control and Prevention http://www.cdc.gov/

University of California-San Francisco National HIV/AIDS Clinical Consultation Center http://www.nccc.ucsf.edu/

International AIDS Society – USA http://www.iasusa.org/

National HIV Telephone Consultation Service "Warmline" 1-800-933-3413 (Open Monday through Friday)

National Clinicians' Post-Exposure Prophylaxis Hotline ("PEPline") 1-888-448-4911 (Open 24 hours/7 days a week)

Guidelines at the CDC website: http://cdc.gov/DiseasesConditions/

- Guidelines for Preventing Opportunistic Infections among Hematopoietic Stem Cell Transplant Recipients
- Sexually Transmitted Diseases Treatment Guidelines
- Prevention and Control of Influenza
- U.S. Public Health Service Guidelines for the Management of Occupational Exposures to HBV, HCV, and HIV and Recommendations for Postexposure Prophylaxis
- Antiretroviral Postexposure Prophylaxis After Sexual, Injection-Drug Use, or Other Nonoccupational Exposure to HIV in the United States

Surbhi L, Terrell CL, Edson RS. General principles of antimicrobial therapy. Mayo Clin Proc. 2011;86(2):156-167.

Freifeld AG, Bow EJ, Sepkowitz KA, et al. Clinical practice guidelines for the use of antimicrobial agents in neutropenic patients with cancer: 2010 update by the Infectious Diseases Society of America. *Clin Infect Dis.* 2011;52(4):427-431.

UWHC Medication Shortages List: http://rx.uwhealth.wisc.edu/OrdeRx/Docs/DrugShortages.xls

Drug Form Dose Daily Cost Dose Daily Cost Sole Daily Cost Cefuroxime 15.g inj 1.5 g pre-op 2.80 1.5 g Q8 3.49 Cefuroxime 750 mg tab 750 mg Q8 4.02 1.5 g Q8 3.40 Ceftraxone 1 g inj 1 g Q24 2.89 2 g Q 24 5.76 Ceftraxone 1 g inj 1 g Q12 6.75 1 g Q 8 10.13 Ceftraxone 1 g inj 1 g Q 12 1.850 2 g Q 24 5.76 Ceftrofloxacin 400 mg tab 500 mg Q 12 0.28 500 mg Q 24 0.14 Ciprofloxacin 400 mg tab 400 mg Q 24 1.160 1.16 1.16 Moxfloxacin 400 mg tab 400 mg Q 24 2.51 1.16 1.33 1.1 3.376 g Q 6 3.83 3 g Q 4 6.03 Piperacilintazobactam 3.57 g inj 3.376 g Q 6 2.86 1.334 AmpLinitusbactam 1.5 g 1.1 1.5 g Q 6 6.86 3 g Q 6 1.334 AmpLinitusbactam 1	,			ernation out		2011)
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Oxacillin Inj 2 g Q4 91.48 2 g Q6 64.99 Vancomycin 1g inj 1 g Q12 8.12	Telithromycin 400 mg	tab	800 mg Q24	9.26		
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Antimicrobial Cost Table (Cost information current as of March 2011)



MEMORANDUM

Date: February 10, 2003

To: All UW Medical Faculty and UWHC House Staff

From:	Carl J. Getto, MD	Dennis G. Maki, MD
	UWHC Medical Director	Head, Section of Infectious Diseases
		Hospital Epidemiologist

Thomas S. Thielke, MS, FASHP UWHC Pharmacy Director

Re: Revised Antibiotic Order Form

In March 2002, an antimicrobial order form was initiated at UWHC, to improve the use of antimicrobial therapy at UWHC. This form has for the first time provided the capacity of obtaining real-time information on antimicrobial usage patterns, and has formed the basis for intensified efforts to improve antimicrobial use at UWHC.

Based on the positive experience with this initial effort, we have redesigned the antimicrobial order form to provide more specific information that can be used to target programs to improve use. More specific information is now being requested on the suspected site of infection, suspected microorganisms and whether this is a first-time order or modification of previous orders. During the next several months, this new form, which has replaced the original form, will be implemented on individual units. We further want to emphasize that, with the approval of the Surgical QI Committee, *all* antibiotics orders, including in cases where there may be a standing order form, will require completion of an antibiotic order form. This is necessary to provide comprehensive and detailed data on *all* antimicrobial use at UWHC.

We want to express our appreciation for your cooperation with this program to date, which is facilitating efforts at multiple levels to improve the use of antibiotic therapy at UWHC. Your comments and suggestions regarding the new form and the program in general are welcomed and can be conveyed to Dr. Barry Fox (Pager 3499) or Sarah Bland, RPh (Pager 2610), who are coordinating specific aspects of our Antibiotic Improvement Program.

This requirement includes pre- and post-operative antibiotic order requests and HealthLink ordering.

Summary of Antibiotic Order Form: Suggestions for Improvement

Barry Fox, MD

General Observations/Comments

There are several general types of patients that can be considered for making decisions on initial antimicrobial RX.

First, there are patients admitted from the community who are unlikely to have resistant bacteria, who can be treated for community-based pathogens.

Secondly, there are patients admitted from the community who have recently been hospitalized, or come from extendedcare facilities who have risk factors for resistant bacteria.

Thirdly, there are patients hospitalized for more than 72 hours with risk of acquiring resistant micro-organisms, where initial therapy may be targeted against potential resistant nosocomial pathogens.

Finally, there are hospitalized patients with the same risk factors as in the third group, but who are ill with SIRS (Systemic Inflammatory Response Syndrome), likely in the intensive care unit.

Antimicrobial therapy is a dynamic process. Results of cultures, then sensitivities of organisms (unless mixed infections) are usually available within 72 hours. *Hence, critical re-evaluation of initial therapy ("de-escalation") is essential to providing a balance between therapeutic efficacy, side effects, and the creation of antimicrobial resistant organisms. (Chest 2002;122: 2183-96)*

BY SITE of Documented or Suspected Infection

ABDOMINAL/PELVIC

Issue: There was an over-reliance on extended-spectrum antibiotics such as piperacillin/tazobactam or quinolone plus metronidazole. Furthermore, only 30% of orders indicated the need for anaerobic coverage.

Suggestions:

For community-based operative and perioperative prophylaxis, cefazolin, cefotetan and cefoxitin should be used. For community-acquired primary peritonitis, there are a number of efficacious antimicrobial regimens (Position paper of the Surgical Infection Society and of the Infectious Diseases Society of America; Clinical Infectious Diseases 2010;50:133-165). Anti-pseudomonal and anti-enterococcal coverage are rarely needed for initial RX (secondary peritonitis).

Extended-spectrum regimens (including piperacillin/tazobactam or anti-anaerobe/ceftriaxone, anti-anaerobe/quinolone) should be reserved for tertiary peritonitis or complicated abscesses where pretreatment with antibiotics (including recent hospitalizations) has led to the potential for documented or suspected resistant organisms.

Anaerobic coverage should always be considered for abdominal/pelvic infections or operative contamination of a hollow viscus. *However, double coverage with two anaerobic agents is usually unnecessary*. In poorly-drained abdominal abscesses, metronidazole may be the preferred anti-anaerobic agent due to enhanced penetration into abscess cavities. Antibiotic therapy for abdominal "contamination" less than 12 hours old and in the peri-operative setting is rarely needed for more than 24 hours.

New guidelines are also abstracted in Appendix M and have been approved by the Surgical QA committee in March 2010.

Reference: Solomkin JS et al. Diagnosis and management of complicated intra-abdominal infections in adults and children: Guidelines by the Surgical infection Society and the Infectious Diseases Society of America. *Clin Infect Dis* 2010;50:133-164.

BLOODSTREAM

Issue: Extended-spectrum antibiotics were used when more targeted antibiotics could be used, especially *after* culture results were known. For susceptible staphylococci and streptococci, there was an over-reliance on cefepime. For suspected gram-negative organisms, quinolones and cefepime were frequently used, even when *Pseudomonas aeruginosa* was not suspected or documented.

Suggestions:

Vancomycin should be used for known or suspected MRSA/MRSE, which are especially common in the ICU and in patients with extended hospital stays, and then reassessed at 72 hours. With the increased prevalence of CA-MRSA, vancomycin should generally be used until susceptibilities are known. Some patients in the critical care unit with known Staph aureus may receive daptomycin for up to 48 hours until the vancomycin MIC of the Staph is known.

For suspected gram-negative infections in patients with stable renal function, consider more frequent initial use of an aminoglycoside, especially tobramycin, for 48 hours of empiric therapy, and possibly longer. The pharmacist will assist with pharmacokinetic dosing.

For community-based infections **not** requiring intensive care, and in patients not recently hospitalized (and thus at risk for *Pseudomonas*), ceftriaxone should provide sufficient gram-negative coverage (and reasonable gram-positive coverage).

Empiric therapy in the ICU should target *Pseudomonas aeruginosa,* initially with more than one anti-pseudomonal drug, but then usually narrowing therapy after 72 hours.

Issue: For confirmed infections, the antimicrobial choices matched the sensitivity of the microorganisms. 85% of gramnegative bacteremias were treated with a single antimicrobial agent. **The lowest MIC is not necessarily the "best antibiotic" as there are different pharmacokinetic parameters guiding treatment.**

Suggestion: Continue to match micro-organisms causing infections with appropriate antimicrobial results at 48-72 hours. For selected gram-negative infections involving *Pseudomonas*, *Enterobacter*, *Serratia* and *Citrobacter* spp., a beta-lactam and aminoglycoside combination regimen may be appropriate. Discussion with Infectious Diseases should be considered. Guidelines for use of combination antimicrobial therapy are forthcoming.

URINARY TRACT INFECTIONS (UTIs)

Issue: Susceptible streptococci, staphylococci and anaerobes are rarely causes of UTIs. *Pseudomonas aeruginosa* UTIs in the absence of bacteremia usually do not require two antibiotics for extended treatment.

Suggestion: Target pathogens that cause UTIs. When *Pseudomonas aeruginosa* is isolated, under most circumstances, narrow empiric antibiotic therapy to a single agent, unless the infection is systemic.

Issue: Quinolones should not be relied upon for the treatment of enterococcal infections, and moxifloxacin has only 40% urinary excretion and is not indicated for the treatment of UTI.

Suggestion: Treat enterococcal infections with penicillin or ampicillin derivatives. Piperacillin/tazobactam has coverage for enterococci, but should only be used for mixed infections. If a quinolone is indicated for gram-negative infections of the urine, use ciprofloxacin NOT moxifloxacin.

Issue: Over-reliance on the use of quinolones to treat nosocomial UTI

Suggestion: Ceftriaxone has reasonable activity against most gram-negative hospital urinary pathogens, and should be used when *Pseudomonas aeruginosa* is not isolated, and especially **outside** the intensive care units.

Colonization of the indwelling catheters should not usually be treated. See updated guidelines by the Infectious Disease Society of America. Clinical Infectious Diseases 2010;50:625-663

LUNGS/PULMONARY

Community-Acquired Pneumonia (CAP)

Issue: Over-reliance on the use of moxifloxacin. Clinical experience using moxifloxacin for the treatment of anaerobic infections and sensitive staphylococci is limited. The American Thoracic Society and Infectious Diseases Society offer a choice of a respiratory quinolone or a combination of cephalosporin and macrolide for the treatment of community-acquired pneumonia. Moxifloxacin was chosen 70% of the time for CAP, and macrolide regimens only 25% of the time. Accumulating evidence suggests combination regimens containing a macrolide for CAP may be clinically superior. (Clin ID 2003; 36: 389-95, 396-99) The recent Infectious Diseases Society of America Guidelines suggest de-emphasizing the use of quinolones for CAP (Clinical Infectious Diseases 2003; 37:1405-33.) With the lowering of MICs for pneumococcal infections to penicillins and cephalosporins, virtually all respiratory infections can be treated with beta-lactams.

Suggestion: Restrict the use of quinolones for respiratory infections to community patients at risk for resistant pneumococci, beta-lactam failures, or patients with significant beta-lactam allergies. Consider using the combination cephalosporin/macrolide choice for CAP more frequently. See UWHC hospital guidelines for the treatment of CAP located on uconnect.

Hospital-Acquired Pneumonia

Issues: Although *Pseudomonas aeruginosa* is an important cause of 30-35% of nosocomial pneumonias, empiric antipseudomonal regimens are often continued too long when the antimicrobial spectrum can be narrowed. Antimicrobial therapy in general for nosocomial pneumonia is generally "too long." MRSA serious pneumonias may require alternative antimicrobial agents to vancomycin (Am Rev Resp Crit Care Med 2005:171:388-416 IDSA and ATS Guidelines for the treatment of Healthcare Associated Pneumonia).

Suggestion: Every effort should be made to obtain an adequate sputum specimen to guide antimicrobial therapy. When *Pseudomonas aeruginosa* is NOT isolated from an adequate specimen, antimicrobial therapy should be adjusted accordingly. The predictive value of a negative sputum gram stain for organisms is high, and this should prompt a search for alternative etiologies of pulmonary infiltrates and usually a discontinuation of antimicrobial therapy. **Due to the potential for bias by prior antibiotic use, the microbiology lab can be notified when a sputum sample is rejected for no bacteria seen and asked to implement the "exclude** *Pseudomonas* **and Staph protocol." Also see comments on double coverage of gram-negative pathogens in the bloodstream section.**

8 days of antimicrobial therapy **is usually** as good as 14 days (JAMA 2003:290:2588-98) under most clinical circumstances.

Treatment of MRSA pneumonia with vancomycin may be suboptimal, and in consultation with the Infectious Disease Service, therapy with linezolid may be considered (Chest 2003;124,1789-97 and 1632-34).

CELLULITIS

Issue: Overuse of vancomycin and quinolones to treat susceptible staphylococci and streptococci.

Suggestion: Unless there is a significant beta-lactam allergy, restrict the use of vancomycin and quinolones to other indications. Use first-generation cephalosporins, nafcillin, or clindamycin in allergic patients. However, with the rise of CA-MRSA, vancomycin may be needed as empiric therapy until more information is available.

Issue: Continued use of antipseudomonal antimicrobials (and combination antimicrobial therapy) without culturedocumented *Pseudomonas aeruginosa.*

Suggestion: Cellulitis is often a difficult condition for which to obtain microbiologic confirmation. Please weigh carefully whether the patient is at risk for a *Pseudomonas* infection. Similarly, after the patient improves in the first 72 hours, continued double gram-negative coverage is rarely necessary.

Also see Clinical Infectious Diseases 2005: 41: 1373-1406 IDSA guidelines for the treatment of skin and soft tissue infections.

NEUTROPENIC FEVER

Issue: Only 38% of orders indicated a gram-negative pathogen was suspected, and 34% of orders were written for susceptible Staphylococci.

Suggestion: Empiric therapy should usually include coverage against gram-negative pathogens, which most likely lead to sepsis/SIRS if untreated. Selected use of vancomycin for suspected gram- positive pathogens in the setting of catheterassociated cellulitis or line infection, and documented staphylococcal bacteremia is warranted. Most staphylococci will be methicillin-resistant in this patient population. Since the combination of a beta-lactam and an aminoglycoside is synergistic (while this is true only 25% of the time with a quinolone), empiric therapy in patients with SIRS with this combination should be considered empirically and even for established gram-negative sepsis. If staphylococci are not isolated from the blood at 72 hours, consideration for discontinuation of vancomycin should be addressed, especially with a rising incidence of VRE on the hematology/oncology wards.

SURGICAL WOUND

Issue: Appropriate coverage of susceptible staphylococci and streptococci for prophylaxis and empiric treatment. Prophylaxis in the ICU may require individual considerations. Choice of coverage for documented infections usually based on culture results.

Suggestion: The antimicrobial order form will be used for surgical prophylaxis. *Maximum duration of prophylaxis, except under unusual circumstances, should not exceed 24 hours*. Patients in the ICU should have their antimicrobial prophylactic regimens individualized based on the intended surgical procedure, patient colonization with known organisms, and patterns of antimicrobial susceptibility in the ICU.

SUGGESTIONS FOR IMPROVEMENT FOR SPECIFIC ORGANISMS

Enterococcus species

Issue: The perceived need for empiric coverage of enterococcal organisms, and the over-reliance on non-penicillin based antibiotics for coverage. Cephalosporins have no activity against these organisms. Empiric therapy requests for coverage of VRE will usually not be honored unless under special individual circumstances.

Suggestion: As noted above, for primary peritonitis, enterococcal coverage is rarely necessary. Use penicillin/ampicillin (or piperacillin/tazobactam in more complicated cases) for enterococcal cases, unless VRE is documented or beta-lactam allergy requires the use of vancomycin. Unless extended anaerobic coverage is needed, use ampicillin instead of ampicillin/sulbactam. Two synergistic drugs including a beta-lactam and aminoglycoside may be required for serious enterococcal infections (usually not for an isolated UTI), and ID consultation should be considered.

Staphylococci - susceptible and Staphylococci - methicillin-resistant

Issue: 24% of orders for abdominal/pelvic infections noted Staphylococci-susceptible and methicillin-resistant as potential pathogens.

Suggestion: Except in cases of secondary and, more likely, tertiary (healthcare-related) peritonitis, Staphylococcisusceptible and methicillin-resistant are rarely pathogens and **empiric** coverage is not necessary for these organisms.

Issue: In the TLC or other ICU settings, the overwhelming majority of staphylococcal bacteria are methicillin-resistant

Suggestion: Empiric coverage of suspected staphylococcal infections in the ICU setting should usually be with vancomycin, with modification of therapy after 72 hours if MRSA/MRSE is not documented. Positive blood cultures identified as presumptive Staph aureus may be considered for Daptomycin use for 24 hours until the vancomycin MIC of the Staph aureus is known. Clinical response to antimicrobials, without documented resistant organisms, is not usually sufficient justification for the continuation of vancomycin.

Pseudomonas aeruginosa and other gram-negative pathogens including Enterobacter spp., Serratia spp. and Citrobacter spp. (PESC organisms)

Issue: Antimicrobial orders targeted against *Pseudomonas aeruginosa* account for 10% of all hospital orders, and 25% of all empiric and confirmed bloodstream infections. Double coverage of these and other gram-negative organisms is often continued indiscriminately.

Suggestion: See discussion of pulmonary infections. The use of first-, second- and third-generation cephalosporins for extended periods of time with these PESC organisms in circumstances with high bacterial inoculum may result in the development of resistance to the cephalosporins. Caution is advised for high inoculum and long duration of therapy. Cefepime is usually active and stable for these organisms under these circumstances.

WHealth

University of Wisconsin Hospital and Clinics 600 N. Highland Ave. Madison, WI 53792

Date: December 27, 2004

To: All Staff Physicians, House Officers and other Antibiotic Prescribers

From: Layton F. Rikkers, MD, Department Chair

Re: UWHC Antibiotic Order Form

Approximately two years ago, after considerable discussion at all levels in the hospital, it was agreed that UWHC will institute an antibiotic order form, with the aim of further improving antibiotic utilization throughout the hospital. The form provides the only means to track antibiotic utilization throughout the institution, targeting settings where efforts are needed to improve use. University and community hospitals across the country have been using similar antibiotic order forms for many years.

Unfortunately, many UWHC physicians and other prescribers continue to write antibiotic orders without completing the form, expecting the pharmacist to complete it. Moreover, many physicians refuse to complete the form. As a consequence, the data obtained are incomplete or may then be unreliable. Moreover, these practices pose an unacceptable burden upon the pharmacists who have been charged with enforcing compliance with its' use and defeats the purpose of the form, a major portion of which is education. The pharmacist may not be aware of every clinical issue surrounding the case and all of the details surrounding the rationale for the use of the drugs prescribed.

I want to emphasize that I, with the other clinical chairs, strongly support this program to improve antibiotic utilization and stem the rising tide of antibiotic resistance at UWHC. Every staff physician, house officer and other prescriber is expected to complete the antibiotic form at the time antibiotic orders are written for current inpatients on the floor, whether for surgical prophylaxis or for treatment of suspected or proven infection.

Thank you.

Layton &

PART I: BY DRUG

ABACAVIR

For up-to-date information on the use of antiretrovirals, consult an HIV expert or www.aidsinfo.nih.gov/

ABACAVIR/LAMIVUDINE (Epzicom®) – non-formulary at UWHC

For up-to-date information on the use of antiretrovirals, consult an HIV expert or www.aidsinfo.nih.gov/

ABACAVIR/LAMIVUDINE/ZIDOVUDINE (Trizivir®) - non-formulary at UWHC

For up-to-date information on the use of antiretrovirals, consult an HIV expert or www.aidsinfo.nih.gov/

ACYCLOVIR

Usual Dose

Adult: 200 mg Q4H PO five doses per day, 400 mg PO TID or 800 mg five times daily PO (UWHC cost/day \$0.46-1.15) OR 5-12 mg/kg Q8H IV (UWHC cost/day \$7.31-17.54)

Pediatric: 20 mg/kg/day (maximum 800 mg/dose) PO/IV in divided doses four times daily or 25-50 mg/kg/day IV in divided doses Q8H

Indications

1. Herpes simplex encephalitis (10-12 mg/kg Q8H IV x 21 days). In children 3 months to 12 years old, the dose is 20 mg/kg every 8 hours for 10 days.

- 2. Herpes simplex (severe mucosal or cutaneous)
 - a. Immunocompromised or burn patients (5 mg/kg Q8H IV x 7-14 days).

b. In select immunocompetent patients, such as for eczema herpeticum, proctitis, severe primary oral or periorbital herpes or other severe mucosal or cutaneous disease (20 mg/kg/dose, up to 800 mg, four times daily PO x 5 days OR 5 mg/kg/dose Q8H IV).

- 3. Herpes simplex (genital herpes)
 - a. Immunocompetent

i. Initial acute, mild/moderate (200 mg 5 times daily PO x 10 days OR 400 mg TID PO x 10 days). Initial acute, severe (5 mg/kg Q8H IV x 5 days).

ii. Chronic recurrent, prophylaxis (400 mg BID PO for up to 6 months, then reassess need).

iii. Episodic (200 mg Q4H PO 5 times daily x 5 days OR 400 mg TID PO x 5 days).

- b. Immunocompromised
 - i. Acute, severe (5 mg/kg Q8H IV x 7 days).
- 4. Varicella (chicken pox)
 - a. Immunocompromised children (500 mg/m² Q8H IV over 1 hour x 7-10 days).

b. In selected immunocompetent pediatric or adult patients (20 mg/kg/dose, up to 800 mg, five times daily PO x 7 days – begin within the first 24 hours of onset of rash).

- c. Varicella (chicken pox) pneumonia, immunocompetent (10 mg/kg Q8H IV x 7 days).
- 5. Herpes zoster (shingles)
 - a. Immunocompetent (800 mg 5 times daily PO x 7-10 days); must be started within 72 hours of onset.
 - b. Immunocompromised (10-12 mg/kg Q8H IV x 7 days).
 - c. Immunocompromised disseminated, severe localized (but >1 dermatome), or involving ophthalmic division of the trigeminal nerve (10 mg/kg Q8H IV x 7 days).
- 6. Cytomegalovirus prophylaxis in transplant patients (800 mg four times daily PO x 3 months).
- 7. Herpes simplex prophylaxis for bone marrow transplant recipients (400 mg four times daily PO).
- 8. Neonatal herpes (20 mg/kg/dose Q8H IV x 14-21 days).

Comments

Dose adjustment required for renal impairment. See renal dosing guideline on uconnect.

With high dose (>10 mg/kg) IV therapy, administer over 60 minutes and maintain hydration to prevent urine crystallization. For obese patients the 10 mg/kg IV dose is based on ideal body weight. Maximum dose is 500 mg/m². Concomitant use of ganciclovir and acyclovir is unnecessary, and increases costs and toxicity. In general, it is not considered necessary to treat uncomplicated, single dermatome (unless trigeminal) herpes zoster in immunocompetent children or adolescents or pregnant women.

ADEFOVIR – nonformulary at UWHC

Usual Dose

Adult: 10 mg PO once daily (UWHC cost/day \$28.25)

Indications:

1. Chronic hepatitis B infection

Comments:

Adefovir may be taken without regard to food. Dosing interval should be increased in patients with renal insufficiency. No dose adjustment necessary in hepatic failure. Discontinuation of therapy may be followed by a severe exacerbation of hepatitis.

AMIKACIN

Usual Dose

Adult, Pediatric: 7.5 mg/kg IV Q12H or 15 mg/kg daily IV (UWHC cost/day \$8.48)

Note: Dose using IBW. For obese patients (BMI>30 kg/m²) use a dosing weight (DW) = 0.4 (ABW-IBW) + IBW.

(IBW=Ideal Body Weight ABW=Actual Body Weight)

Indications

1. Serious infections with aerobic Gram-negative bacilli with documented resistance to gentamicin and tobramycin, or where resistance is suspected based on history.

- 2. Resistant tuberculosis, adjunctive therapy (750 mg/day for patients <a>100 kg; for patients > 100 kg, 7.5 mg/kg/day).
- 3. Mycobacterium avium complex, adjunctive therapy (7.5 mg/kg/day).

Comments

Dose adjustment required for renal impairment. See renal dosing guideline on uconnect. Amikacin is comparable in toxicity to gentamicin. Contact the unit pharmacist for assistance in pharmacokinetic dosing. For extended-interval (Q24H) dosing draw midpoint level 8-12 H after the start of infusion. Peak: 30 minutes after the end of a 30- to 60-minute infusion. Trough: 15-30 minutes prior to next dose (peak and trough used with Q12H dosing only)

AMOXICILLIN

Usual Dose

Adult: 250-500 mg Q8H or 500-1000 mg Q12H PO (UWHC cost/day: \$0.15-0.21) Note: Q12H dose is for outpatient setting only.

Pediatric:** 40 mg/kg/day PO in divided doses Q8H; 80-90 mg/kg/day, divided, for suspected resistant *S. pneumoniae* infections

Indications

- 1. Acute otitis media First-line therapy.
- 2. Acute sinusitis First-line therapy.
- 3. Streptococcal pharyngitis in children First-line therapy.
- 4. Enterococcal cystitis Drug of choice for oral therapy.
- 5. Early Lyme disease in children < 8 years (40 mg/kg/day x 30 days) and pregnant women (500 mg Q8H x 2-4 weeks).
- 6. Bacterial endocarditis prophylaxis (see Appendix A).
- 7. *H pylori* infection as part of combination regimen.
- 8. Group A streptococcal pharyngitis in adults (500 mg PO BID).

Comments

Dose adjustment required for renal impairment. See renal dosing guideline on uconnect.

Moraxella catarrhalis is almost always (85-100%) resistant due to beta-lactamases. *Haemophilus influenzae* is also frequently (30%) resistant due to beta-lactamases and *Streptococcus pneumoniae* is increasingly showing penicillin resistance by altered penicillin-binding proteins. Ampicillin IV plus gentamicin or vancomycin plus gentamicin may be preferred for prophylaxis in patients with prosthetic heart valves, a previous history of endocarditis or surgically

constructed systemic-pulmonary shunts or conduits. Avoid use of ampicillin-class antibiotics in patients with mononucleosis due to high risk of development of erythematous rash and erroneous allergy attribution.

AMOXICILLIN/CLAVULANATE (Augmentin®)

Usual Dose

Adult. 500 mg amoxicillin component Q8-12H PO or 875 mg Q12H PO (UWHC cost/day \$1.06 -1.45) Also available in XL tablet formulation. Adult dose is 2000 mg Q12 PO (Non-formulary at UWHC; cost/day \$11.48). This formulation is preferred for stepdown of hospitalized patients on ampicillin/sulbactam.

Pediatric:** 45 mg amoxicillin component/kg/day in divided doses Q12H PO; 80-90 mg amoxicillin component/kg/day in resistant *S. pneumoniae* infections.

Indications

1. Cat, dog or human bites treatment or prophylaxis - drug of choice.

2. Acute sinusitis - second-line therapy.

3. Acute otitis media - second-line therapy. In high-risk or treatment failures with standard dose amoxicillin, amoxicillin/clavulanate 80-90 mg amoxicillin component/kg/day may be used.

4. Diabetic ulcers and other selected skin or skin structure infections.

5. For severe infections or lower respiratory tract infections (500 mg Q8H or 875 mg Q12H PO) as stepdown therapy.

Comments

Dose adjustment required for renal impairment. See renal dosing guideline on uconnect.

The amount of clavulanate (125 mg) is the same in the 500 mg and the 875 mg tablets. Do not cut tablets to make halfdoses, as this results in subtherapeutic amounts of clavulanate. When *Staphylococcus aureus* or streptococci are suspected, use dicloxacillin or cephalexin. Avoid use of ampicillin-class antibiotics in patients with mononucleosis due to high risk of development of erythematous rash and erroneous allergy attribution.

AMPHOTERICIN B

Usual Dose

Adult and Pediatric: 0.5 - 1 mg/kg daily IV (UWHC cost/day \$6.76-13.54)

Indications

1. Candida (including glabrata) and other nosocomial yeasts – deep infections.

- 2. Serious infections with Histoplasma capsulatum, Blastomyces dermatitidis, Coccidioides immitis.
- 3. Invasive infections with Aspergillus or Mucorales

4. Cryptococcus neoformans meningitis or other life-threatening infections. Use low dose (0.5 mg/kg daily), if combined with fluor topics or high dose (0.6 mg, 1 mg/kg daily) if used as menotherapy

with flucytosine, or high dose (0.6 mg - 1 mg/kg daily) if used as monotherapy.

5. Systemic sporotrichosis.

6. Persistent fever in the granulocytopenic patient, despite 4-5 days of empiric antibacterial therapy.

Comments

To avoid fever and rigors with amphotericin B, an antihistamine (e.g., diphenhydramine 25-50 mg PO/IV) and an antipyretic (e.g., acetaminophen 650 mg PO) should be given 30 minutes before the infusion. If the patient receives the pretreatment outlined above and the first dose is given slowly, a test dose is NOT needed. Acute infusion reactions usually occur 1-3 hours after starting the infusion. These reactions are generally more severe with initial doses and usually diminish with subsequent doses. Amphotericin B causes hypokalemia, hypomagnesemia, renal tubular acidosis and azotemia. A high-salt diet and saline loading with 500-1000 mL 0.9% sodium chloride pre- and post-infusion and replacement of potassium and magnesium losses along with treatment of metabolic acidosis are necessary to minimize azotemia. For *Candida* cystitis, amphotericin bladder irrigations containing 20 mg/L have been used, but their efficacy is questionable (dosing: 250 mL per Foley Q6H or by continuous irrigation).

AMPHOTERICIN B LIPID COMPLEX (ABLC, Abelcet[®]) – non-formulary at UWHC Infectious Disease approval required for all use of ABLC (see Appendix I)

AMPHOTERICIN B LIPOSOMAL (AmBisome®)

Infectious Disease approval required for all use of AmBisome[®] (see Appendix I) Usual Dose

Adult and pediatric: 3-5 mg/kg once daily IV (UWHC cost/day \$253.64-\$423.15)

1. Fungal infections in adult patients who satisfy at least one of the following criteria:

a. Baseline serum creatinine 1.5 to 2.0 mg/dL.

b. Intolerance to current treatment with conventional amphotericin B as indicated by a rise in serum creatinine to 2.0-2.5 mg/dL (in adults).

c. Failure of treatment with conventional amphotericin B as indicated by persistent positive cultures and/or clinical judgment after receiving at least 1 g of therapy.

d. Use in very fragile or hemodynamically unstable patients with known or suspected fungal infections, who are at greater risk for nephrotoxicity with conventional amphotericin B.

2. Aspergillus or other fungal infections of the CNS.

3 Immunocompromised patients with systemic fungal infections.

Comments

Acute infusion reactions occasionally occur with liposomal amphotericin . Acute infusion reactions usually occur 1-3 hours after starting the infusion. These reactions are generally more severe with initial doses and usually diminish with subsequent doses. To avoid fever and rigors with liposomal amphotericin, an antihistamine (e.g., diphenhydramine 25-50 mg PO/IV) and an antipyretic (e.g., acetaminophen 650 mg PO) should be given 30 minutes before the infusion. Serum creatinine should be monitored closely with liposomal amphotericin therapy. Infusion of 500 mL normal saline before and after liposomal amphotericin infusion may prevent or slow renal toxicity. Treatment of serious *Aspergillus* or other invasive mold infections may require doses up to 10 mg/kg. Idiosyncratic lung-related liposome agglutination reactions are also possible under rare circumstances.

See guidelines for use on uconnect

See Guidelines for Use of Antifungal Therapy (Appendix E) or on uconnect

AMPICILLIN

Usual Dose

Adult: Mild infections 250-500 mg Q6H IV/IM (UWHC cost/day \$2.36-4.71) Moderate/severe infections 1-2 g Q4-6H IV/IM (UWHC cost/day \$9.42-28.28) Meningitis, septicemia 8-14 g/day in divided doses Q3-4H IV *Pediatric*** 100 mg/kg/day IV (meningitis 200-400 mg/kg/day IV) in divided doses Q4-6H

Indications

1. Urosepsis, cholangitis or bacteremia due to *Escherichia coli*, *Proteus mirabilis* or *Enterococcus* spp. (If Enterococcus, combine with low-dose gentamicin outside the urinary tract).

2. Neonatal meningitis given with gentamicin.

3. Listeria meningitis/sepsis, usually combined with gentamicin.

- 4. Ampicillin-susceptible Haemophilus influenzae meningitis.
- 5. Shigellosis, salmonellosis or typhoid fever due to susceptible strains.

6. Endocarditis due to slow-growing, fastidious Gram-negative organisms (HACEK group), in combination with gentamicin.

7. Use for the same indications as amoxicillin when a parenteral drug is needed.

8. Bacterial endocarditis prophylaxis (see Appendix A).

Comments

Dose adjustment required for renal impairment. See renal dosing guideline on uconnect.

Oral ampicillin is non-formulary, but is preferred over oral amoxicillin for ampicillin-susceptible shigellosis. Resistance among *Salmonella* and *Shigella* (especially in patients who have been traveling) has made ampicillin a second-line agent for these infections unless the infecting strain is documented susceptible. Avoid use of ampicillin-class antibiotics in patients with mononucleosis due to high risk of development of erythematous rash and erroneous allergy attribution.

AMPICILLIN/SULBACTAM (Unasyn®)

Usual Dose

Adult: 1.5-3 g Q4-6H IV (UWHC cost/day \$6.88-20.01) Pediatric:** 100-200 mg ampicillin component/kg/day IV in divided doses Q4-6H

Indications

- 1. Community-acquired (aspiration) pneumonia with high suspicion of anaerobic component.
- 2. Polymicrobial soft tissue infections such as diabetic foot ulcers and postsurgical wound infections.

3. Polymicrobial community-based intra-abdominal or genitourinary infections with microbiologically documented sensitivities.

- 4. Serious infected animal or human bite wounds first-line intravenous therapy.
- 5. Haemophilus influenzae infections, except meningitis.
- 6. Susceptible Acinetobacter infections

Comments

Dose adjustment required for renal impairment. See renal dosing guideline on uconnect. Avoid use of ampicillin-class antibiotics in patients with mononucleosis due to high risk of development of erythematous rash and erroneous allergy attribution. Sulbactam enhances ampicillin's spectrum to include penicillinase-producing *Staphylococcus aureus*, *Haemophilus influenzae*, and anaerobic bacteria and improves its aerobic Gram-negative spectrum, but not for *Pseudomonas aeruginosa*. **For Gl anaerobes**, **Unasyn**[®] **has activity comparable to metronidazole**, Zosyn[®] (piperacillin/tazobactam) and meropenem but greater activity when compared to clindamycin, cefoxitin, and the third-generation cephalosporins. Safety and effectiveness have not been established for children for intra-abdominal infections. CAUTION: Increasing numbers of *Escherichia coli, Enterobacter, Klebsiella* and *Citrobacter* produce high amounts of beta-lactamase and are resistant to Unasyn[®]. NOTE: Other combination antibiotics base their dose either on one component (e.g. Primaxin[®]) or both components (e.g. trimethoprim/sulfamethoxazole). Unasyn[®] labeling states the dose by adding the two components of ampicillin (2 g) plus sulbactam (1 g), i.e., 3 g. For ampicillin-susceptible Enterococcus there is no evidence that Unasyn[®] is superior to ampicillin alone. Ampicillin is always the drug of first choice for patients who are not penicillin-allergic and have an ampicillin-susceptible strain of *Enterococcus*. Sodium content = 2.9-3.1 mEq/G.

ANIDULAFUNGIN – nonformulary at UWHC

Infectious Disease approval required for all use of anidulafungin (see Appendix I)

Anidulafungin, caspofungin and micafungin are therapeutically interchangeable at UWHC. Micafungin is the current formulary choice.

Usual Dose

Adult: 200 mg loading dose, then 100 mg IV daily (UWHC cost/day \$173.93)

Indications

- 1. Candidemia, Candida intra-abdominal abscesses and Candida peritonitis
- 2. Esophageal candidiasis

ARTEMETHER/LUMEFANTRINE (Coartem®)

Usual Dose

Adult: 4 tablets initially, 4 tabs again after 8 hours and then 4 tabs twice daily for the following two days (24 total tablets) (UWHC cost/day \$67.25)

Pediatric (dose by body weight):

5 to <15kg: 1 tablet initially, 1 tab again after 8 hours, then 1 tab twice daily for the following two days (6 total tablets) 15 to <25kg: 2 tablets initially, 2 tabs again after 8 hours, then 2 tabs twice daily for the following two days (12 total tabs) 25 to <35kg: 3 tablets initially, 3 tabs again after 8 hours, then 3 tabs twice daily for the following two days (18 total tabs)

Indications

1. Treatment of acute, uncomplicated malaria infection due to *Plasmodium falciparum* in patients of 5kg bodyweight and above

2. Shown to be effective in geographical regions where resistance to chloroquine has been reported

Comments

Please contact the ID service when considering use of this medication.

Artemether/Lumefantrine tablets are not approved for the prevention of malaria. Tablets should be taken with food and may be crushed and mixed with a small amount of water immediately prior to use. In the event of vomiting within 1 to 2 hours of administration, a repeat dose should be taken. If the repeat dose is vomited, the patient should be given an alternative antimalarial for treatment. May cause QT prolongation and should be used cautiously with other agents that may cause QT prolongation.

ATAZANAVIR – nonformulary at UWHC

For up-to-date information on the use of antiretrovirals, consult an HIV expert or www.aidsinfo.nih.gov/

ATOVAQUONE

Usual Dose

Adult. 750 mg BID PO for active therapy, once or twice daily for prophylaxis (UWHC cost/day \$21.72-43.44).

Indications

1. Mild to moderate *Pneumocystis jiroveci* pneumonia treatment in patients unable to tolerate trimethoprim/ sulfamethoxazole, dapsone, trimethoprim or pentamidine.

2. *P jiroveci* infection prophylaxis in patients unable to tolerate trimethoprim/sulfamethoxazole.

Comments

Atovaquone should be taken with food to improve bioavailability.

ATOVAQUONE/PROGUANIL (Malarone[®]) - nonformulary at UWHC

Usual Dose

Adult, prophylaxis: 250/100 mg daily (UWHC cost/day \$6.50). *Adult, treatment:* 1000/400 mg daily (UWHC cost/day \$26.00).

Indications

Prevention and treatment of malaria

ATRIPLA[®] -- tenofovir + emtricitabine + efavirenz

For up-to-date information on the use of antiretrovirals, consult an HIV expert or www.aidsinfo.nih.gov/

AZITHROMYCIN

Usual Dose

Adult: 500 mg daily PO on day 1, then 250 mg daily PO days 2-5 (UWHC cost/day \$1.03) OR 500 mg daily IV (UWHC cost/day \$4.46).

Pediatric: 10 mg/kg PO on day 1, then 5 mg/kg/day daily PO days 2-5.

Indications

1. Community-acquired pneumonia.

2. Non-gonococcal urethritis and cervicitis due to *Chlamydia trachomatis* or *Ureaplasma urealyticum* (1 g PO single dose).

3. Mild to moderate bacterial exacerbations of chronic obstructive pulmonary disease; community-acquired pneumonia of mild severity, including suspected mycoplasma or chlamydial pneumonia, in patients unable to tolerate erythromycin.

4. Pharyngitis/tonsillitis - Second-line therapy.

- 5. Uncomplicated skin and skin structure infections Second-line therapy.
- 6. Toxoplasmosis, Campylobacter and Helicobacter infections.
- 7. Mycobacterium avium complex prophylaxis and therapy (1.2 g/week).
- 8. Bacterial endocarditis prophylaxis (see Appendix A).
- 9. Second-line therapy for acute sinusitis and acute otitis media.
- 10. Pertussis
- 11. Legionnaire's disease (1 g daily).

12 Use as an anti-inflammatory in lung transplant recipients and patients with cystic fibrosis. The standard dose is 500 mg every other day OR 250 mg daily, not 500 mg daily.

Comments

The contents of a one gram packet should be mixed with two ounces (60 mL) of water and swallowed immediately. The packet should be rinsed with an additional two ounces of water and the contents mixed and swallowed.

Drug Interactions

Azithromycin may result in QTc prolongation when administered with Class I or Class III anti-arrhythmics, and concurrent use should be avoided. Azithromycin may disrupt gut microbes partially responsible for digoxin metabolism, resulting in increased digoxin levels and potential digoxin toxicity with concurrent use. Digoxin level monitoring is warranted if a prolonged course of azithromycin therapy is indicated. Azithromycin may decrease warfarin metabolism in patients on established warfarin regimens, increasing the risk of bleeding with concurrent use. Increased monitoring is recommended.

AZTREONAM- Infectious Disease approval is required for all use (see Appendix I)

Limit use to patients with severe penicillin allergy for suspected Gram-negative infections in patients with renal insufficiency. If patients can tolerate cephalosporins, they should receive cephalosporins or carbapenems before aztreonam. See Appendix J: Guidelines for the Use of Beta-Lactam Antibiotics in Patients with Reported Allergies to Penicillin or on uconnect

Usual Dose

Adult. 1-2 g Q8H IV (UWHC cost/day \$82.89-169.78). Pediatrics** 90-120 mg/kg/day IV/IM in divided doses Q6-8H.

Indications

Serious infections with aerobic Gram-negative bacilli in patients allergic to beta-lactams. Has activity against *Pseudomonas aeruginosa*, but does not provide synergy in combination with other beta-lactams.
 Aminoglycoside alternative in patients at increased risk for oto- or nephrotoxicity (not for double coverage with other beta-lactams).

Comments

Dose adjustment required for renal impairment. See renal dosing guideline on uconnect.

Aztreonam has no anaerobic or Gram-positive coverage. Many nosocomial Gram-negative organisms that are resistant to cephalosporins are also resistant to aztreonam, and the drug should not be used alone for nosocomial Gram-negative infection until it is known that the organisms are susceptible. Safety and effectiveness of aztreonam have not been established in infants and children. Since aztreonam and ceftazidime have the same side chain, animal models suggest that aztreonam may be cross-allergenic with ceftazidime but not other beta-lactams, which have different side chains.

An aztreonam product specifically created for nebulization (Cayston[®]) was approved in 2010. The dose is 75 mg Q8H using an Altera[®] Nebulizer System. Cayston® is approved for the improvement of respiratory symptoms in cystic fibrosis patients with *Pseudomonas aeruginosa*. Safety and efficacy are not established in patients under 7, in patients with FEV₁ <25% or >75% predicted or in patients colonized with *Burkholderia*. The product has a Black Box Warning indicating that severe allergic reactions have occurred in patients without a history of exposure to aztreonam, and warns against using in patients with a history of beta-lactam allergy, bronchospasm, decline in FEV_z after a 28-day cycle and about the risk of the development of drug-resistant bacteria.

CASPOFUNGIN – non-formulary at UWHC

Infectious Disease approval is required for all use of caspofungin (See Appendix I)

Anidulafungin, caspofungin and micafungin are therapeutically interchangeable at UWHC. Micafungin is the current formulary choice.

Usual Dose

Adult. 70 mg IV on day 1, then 50 mg Q24H IV (UWHC cost/day 338.72). Pediatric: 70 mg/m² on day 1, then 50 mg/m²

Indications

Invasive aspergillosis in patients intolerant or unresponsive to treatment with other therapies including: amphotericin B, lipid formulations of amphotericin B, and/or itraconazole. Occasionally used in combination with voriconazole.
 Systemic candidemia in patients at risk for infection by yeasts that may be resistant to azole antifungal agents.

See Guidelines for Use of Antifungal Agents (Appendix E) or on uconnect.

Comments

Reduce maintenance dose to 35 mg/day in patients with moderate hepatic impairment (Child-Pugh score 7-9); clinical experience in patients with severe hepatic impairment (Child-Pugh score>9) is limited; further dose adjustments or withholding caspofungin may be warranted. For established filamentous fungal infections, the usual dose is 70mg IV daily.

The most common side effects are infusion-related reactions, nausea, fever and frequent headaches. Transient elevations of liver function tests up to four times the upper limit of normal have been reported. Cyclosporine exacerbates this effect and concomitant administration should be weighed carefully. Caspofungin is not compatible with dextrose-containing solutions.

Drug Interactions

The clearance of caspofungin is increased by carbamazepine, dexamethasone, efavirenz, nelfinavir, nevirapine, phenytoin and rifampin, resulting in decreased serum levels of caspofungin. Cyclosporine increases the AUC of caspofungin. Caspofungin causes a decrease in the AUC of tacrolimus; dose adjustments of tacrolimus may be necessary in order to maintain therapeutic levels.

CEFAZOLIN

Usual Dose

Adult. Moderate/severe infections 1-2 g Q8H IV (UWHC cost/day \$1.74-3.49).

Surgical prophylaxis 1-2 g preop single dose (UWHC cost/day \$0.58-1.16). If patient weighs >80 kg, use 2 g dose. *Pediatrics*:** 50-100 mg/kg/day IV in divided doses Q8H.

Indications

1. Perioperative surgical prophylaxis; agent of choice for most elective operations with the exceptions of colorectal and cardiovascular surgery (see Appendix B). Duration of pre/post-op prophylaxis should not exceed a total of 24 hours. 2. Open fracture repair prophylaxis (see Appendix B).

- 3. Klebsiella or Escherichia coli infections caused by susceptible organisms.
- 4. Peritonitis in chronic ambulatory peritoneal dialysis patients intraperitoneal administration.
- 5. Bacterial endocarditis prophylaxis (see Appendix A).

Comments

Dose adjustment required for renal impairment. See renal dosing guideline on uconnect. The pharmacokinetics of cefazolin do not require dosing more frequently than Q8H.

CEFDINIR

Cefdinir suspension and cefpodoxime proxetil suspension are therapeutically interchangeable at UWHC. Cefdinir is the current formulary choice.

Usual Dose

Pediatrics: 7 mg/kg orally every 12 hours, up to 600 mg/day

Indications

- 1. Otitis media caused by H. influenzae, S. pneumoniae, or M, catarrhalis
- 2. Community-acquired pneumonia caused by H. influenzae, H. parainfluenzae, S. pneumoniae and M. catarrhalis
- 3. Skin or subcutaneous tissue infection caused by S. aureus and S. pyogenes
- 4. Acute maxillary sinusitis caused by H. influenzae, S. pneumoniae, and M. catarrhalis
- 5. Pharyngitis caused by S. pyogenes

Comments

Dose adjustment required for renal impairment. See renal dosing guideline on uconnect.

Drug Interactions

Iron, magnesium and aluminum decrease C_{max} and AUC by 40-60%. Separate from iron supplements and antacids by at least two hours.

CEFEPIME

Cefepime and ceftazidime are therapeutically interchangeable at the UWHC except for use in *Burkholderia cepacia* and *Stenotrophomonas maltophilia* infections. Cefepime is the current formulary choice.

Usual Dose

Adult: 0.5-2 g Q8-12H IM/IV (UWHC cost/day \$3.38-20.25). Neutropenic fever or *Pseudomonas:* 2 g Q8H IV (UWHC cost/day 20.25). *Pediatric*s** 150 mg/kg/day IV in divided doses Q8H.

Indications

1. Moderate to severe pneumonias and associated bacteremias caused by *K pneumoniae*, *P aeruginosa or Enterobacter* spp

2 .Complicated urinary tract infections including pyelonephritis caused by *E coli, K pneumoniae, P aeruginosa or P mirabilis.*

3. Bacteremias caused by *E coli, K pneumoniae, P aeruginosa or P mirabilis.*

4. Complicated skin infections caused by methicillin-sensitive strains of *S aureus* or *S pyogenes* where a broader spectrum of antimicrobial activity is initially needed. Maintains good spectrum of gram-positive activity for non-MRSA organisms.

5. Neutropenic fever, empiric therapy.

6 Complicated healthcare-associated intraabdominal infections in combination with metronidazole.

Comments

Dose adjustment required for renal impairment. See renal dosing guideline on uconnect.

Cefepime is a fourth-generation cephalosporin with activity against *P aeruginosa* similar to ceftazidime but with more activity against staphylococci, group G streptococci, *Enterobacter* sp., *C freundii*, and *M morganii* than ceftazidime. Cefepime is ineffective against *Burkholderia cepacia* and less effective than ceftazidime against *Stenotrophomonas maltophilia*. In these situations, ceftazidime is the preferred product. Cefepime can often be used to treat infections caused by Gram-negative bacteria possessing ESBL and AmpC resistance mechanisms.

CEFOTAXIME – non-formulary at UWHC except for neonates and for infants with hyperbilirubinemia Usual Dose

Adult: 1-2 g Q6-12H IV (up to 12 g daily) (UWHC cost/day \$2.30-9.20) Pediatric: 50-200 mg/kg/day in divided doses Q6-8 hours (up to 12 g daily)

CEFOXITIN

For adults, cefotetan and cefoxitin are therapeutically interchangeable at the UWHC. Cefoxitin is the current formulary choice

Usual Dose

Adult: 1-2 g Q6-8H IV (UWHC cost/day \$9.95-26.54).

Surgical prophylaxis 1-2 g IV as a single dose (UWHC cost/day \$3.32-6.64).

Pediatric: 80-160 mg/kg/day in divided doses Q4-6H.

Indications

1. Surgical prophylaxis where anaerobic coverage is needed, e.g., colorectal or gynecological surgery (see Appendix B). 2. Mixed community-acquired aerobic/anaerobic intraabdominal or pelvic infections. Drug of choice from 2010 IDSA and Surgical Infection Society Guidelines. Alternative to clindamycin, metronidazole or ampicillin/sulbactam. *It is usually NOT necessary to combine with metronidazole.*

3. Soft tissue and bone infection.

4. Penetrating abdominal trauma.

Comments

Dose adjustment required for renal impairment. See renal dosing guideline on uconnect.

CEFPODOXIME PROXETIL

For adults, cefpodoxime proxetil and cefuroxime axetil are therapeutically interchangeable at the UWHC. Cefpodoxime proxetil is the current formulary choice for **adults**. For children, cefpodoxime proxetil and cefdinir are therapeutically interchangeable at the UWHC. Cefdinir is the current formulary **pediatric** choice.

Usual Dose

Adult. 100-400 mg BID PO (UWHC cost/day \$5.25-12.23) depending of severity of disease.. *Pediatrics*** 10 mg/kg/day PO divided into 2 doses.

Indications

1. Sinusitis (200 mg BID PO) – third-line agent.

2. Community-acquired pneumonia in patients who have comorbidity and/or are 60 years of age or older (200 mg BID

PO). May be used for step-down therapy from ceftriaxone.

- 3. Cat or dog bites alternative to ampicillin/sulbactam or doxycycline.
- 4. Urinary tract, skin/soft tissue infections an alternative to less expensive agents.

Comments

Dose adjustment required for renal impairment. See renal dosing guideline on uconnect.

Cefpodoxime proxetil 100 mg BID PO is equivalent to cefuroxime axetil 250 mg BID PO (for upper respiratory tract infections and bronchitis).

CEFTAZIDIME

Use of ceftazidime is limited to endophtalmitis per order sets and in antibiotic lock solutions

Usual Dose

Adult: 2.25 mg in 0.1 mg for intravitreous administration for treating endophthalmitis; systemic dosing is 0.5-2 g Q8H depending on indication (UWHC cost/day \$5.41-21.66 for systemic dosing)

CEFTRIAXONE

Cefotaxime, ceftriaxone and ceftizoxime are therapeutically interchangeable at the UWHC. Ceftriaxone is the current formulary choice. Cefotaxime may be used in children 1 month of age or younger or in infants with hyperbilirubinemia. **Usual Dose**

Adult: Moderate infections 1 g Q24H IV/ IM (UWHC cost/day \$1.21). The 1 gram dose should be used for community acquired pneumonia, and should be efficacious in most infections.

Severe infections: 2 g Q24H IV/IM (UWHC cost/day \$2.89).

Pediatrics:** 50 - 100 mg/kg/day IV/IM in divided doses Q12 - 24H.

Meningitis 100 mg/kg/day IM/IV in divided doses Q12H, to a maximum dose of 2 g IV Q12H in adults.

Indications

1. Community-acquired pneumonia in patients >60 years old or with comorbidity, given with a macrolide or doxycycline. The usual dose in the CAP UW pathway is 1 gram/24 hours.

2. Bacterial meningitis, including infection with enteric Gram-negative bacilli, *S pneumoniae* or *Haemophilus influenzae*, pending susceptibility or test results.

3. H influenzae or pneumococcal life-threatening infections (e.g., bacteremias, epiglottitis).

4. Uncomplicated gonorrhea (125 mg IM as a single dose).

5. Serious Gram-negative bacillus infections, other than *Pseudomonas*, especially if the patient is at high risk for aminoglycoside toxicity (CAUTION: Many nosocomial Gram-negative bacillus infections, especially those due to *Enterobacter* spp. and *Pseudomonas aeruginosa*, are resistant to ceftriaxone).

6. Pneumonia caused by Gram-negative bacilli, other than P aeruginosa.

7. Acute otitis media

- a. One-time dose in patients unable to take oral medications.
- b. Single daily dose times 3 days in patients with clinical treatment failure with oral antibiotics.
- 8. Community-acquired pneumonia, urosepsis, skin and soft tissue infection or sepsis of unknown etiology.

9. Endocarditis due to slow-growing fastidious Gram-negative organisms, usually in combination with an aminoglycoside.

10. Alternative to ampicillin plus gentamicin. Also alternative therapy in endocarditis caused by Streptococcus viridans.

11. Lyme Disease, especially with rheumatologic, neurologic or cardiac involvement (2 g IV daily).

12. Presumptive bacteremia/sepsis in febrile children > 2 months old.

13. Meningococcal prophylaxis, in ambulatory clinics. (Pregnant women 250 mg IM single dose, children 125 mg IM single dose).

Comments

Do not use as empiric therapy for nosocomial infections where resistant Gram-negative rods such as *Pseudomonas* may be present. Ceftriaxone is not active against *Listeria monocytogenes*, an organism of increasing importance in immunosuppressed or transplant patients. Ceftriaxone can cause biliary sludging, especially in high doses in adults (2 g Q12H) and children. Ceftriaxone displaces bilirubin from plasma protein binding sites, which may be important if a neonate is already hyperbilirubinemic. For IM use, 1% lidocaine (without epinephrine) can be used as the diluent to decrease local pain. NOTE: Ceftriaxone 1 g/day is equal to cefotaxime 1 g Q8H and ceftriaxone 2 g/day is equal to cefotaxime 2 g Q8H. Monotherapy is usually possible for community-acquired Gram-negative bacillus septicemia, pneumonia, osteomyelitis and sepsis of unknown cause (unless in ICU, where double coverage is recommended for CAP). Ceftriaxone in combination with vancomycin is now considered the initial regimen of choice for suspected penicillin-resistant pneumococcal meningitis given the increase and spread of pneumococcal strains highly resistant to penicillin, including southern Wisconsin and northern Illinois (up to 5%). Most pulmonary infections

can still be successfully treated with ceftriaxone even if the breakpoint MIC is intermediate or resistant to penicillin. Breakthrough infections with coagulase-negative staphylococci, enterococci and Candida are occurring with increasing frequency with cephalosporin use.

Do not administer ceftriaxone with calcium-containing IV solutions in the same IV line, including continuous calcium-containing infusions such as parenteral nutrition via a Y-site concurrently. In patients other than neonates, ceftriaxone may be administered sequentially with calcium-containing solutions with thorough flushing of lines with compatible fluid between administrations.

CEFUROXIME

Usual Dose

Adult. 750 mg-1.5 g Q8H IV (UWHC cost/day \$4.20-8.40). Surgical prophylaxis 1.5 g IV (UWHC cost/day \$2.80), then 750 mg – 1.5 g Q8H or q 12 h. if subsequent doses are given. There are no comparative prophylaxis efficacy studies comparing q12h vs. q8h prophylaxis. *Pediatric*s:** 100-150 mg/kg/day IV/IM in divided doses Q8H. *Pediatric surgical prophylaxis:* 30 mg/kg/dose IV Q8H

Indications

1. Cardiovascular surgery prophylaxis (see Appendix B).

2. Orthopedic surgery prophylaxis (see Appendix B).

3. Community-acquired pneumonia, with age >60 or comorbidity, given with a macrolide or doxycycline. (But not severe infection requiring ICU care).

4. Periorbital cellulitis, buccal cellulitis in children.

Comments

Dose adjustment required for renal impairment. See renal dosing guideline on uconnect.

Cefuroxime may have similar oral anaerobic activity to penicillin G (*Acta Clin Belg* 1989;44:228-36) with greatest activity against Gram-positive strict anaerobes (*Pathol Biol (Paris)* 1990;38:343-6). Safety and effectiveness have not been established in children below the age of 3 months. Should not be used to treat meningitis in children as treatment failures have been reported. Oral cefuroxime and cefpodoxime are therapeutically interchangeable at UWHC. The current formulary choice is cefpodoxime.

CEPHALEXIN

Cephalexin and cephradine are therapeutically interchangeable at the UWHC. Cephalexin is the current formulary choice. Step-down therapy from cefazolin.

Usual Dose

Adult: 250-500 mg PO Q6H (UWHC cost/day \$0.25-0.50). *Pediatric*s:** 25-50 mg/kg/day PO in divided doses Q6H.

Indications

1. Skin and skin structure infections caused by susceptible staphylococci or streptococci in patients unable to tolerate dicloxacillin (the drug of choice).

2. Bacterial endocarditis prophylaxis (see Appendix A).

Comments

Dose adjustment required for renal impairment. See renal dosing guideline on uconnect.

CHLORAMPHENICOL

Usual Dose

Adult. 12.5-18.75 mg/kg Q6H IV (up to 4 g daily) (UWHC cost/day \$61.62-70.42). *Pediatric*:** 50-100 mg/kg/day IV in divided doses Q6H.

Indications

1. Typhoid fever. (NOTE: Third-generation cephalosporins and quinolones have supplanted chloramphenicol in Western medical practice.)

2. Rickettsial infections. Alternative to tetracyclines in adults and the drug of choice in children less than 8 years of age. (Rocky Mountain Spotted Fever – 500 mg four times daily PO).

3. Invasive meningococcal disease in patients with anaphylactoid-type allergies to penicillins or cephalosporins.

Comments

Dose adjustment may be required for severe renal impairment. See renal dosing guideline on uconnect.

Chloramphenicol should be used only for serious infections where other antibiotics are ineffective or contraindicated. Chloramphenicol should not be used for prophylaxis. Chloramphenicol can cause life-threatening bone marrow depression, gray-baby syndrome in premature newborn infants and optic neuritis. Doses up to 25 mg/kg Q6H should be reserved for CNS infections or for severe infections where the organisms are moderately susceptible. In general, Infectious Disease consultation should be sought prior to chloramphenicol use. Kinetics: IV peak 2 hours after last dose; trough: before next dose.

CHLOROQUINE PHOSPHATE

Usual Dose

Adult: 500 mg weekly - 1 g daily PO (UWHC cost/day \$1.55-3.10).

Indications

Prophylaxis and treatment of malaria due to *P vivax, P malariae, P ovale* and susceptible strains of *P falciparum.* 300 mg (base) OR 500 mg (salt), weekly beginning 1-2 weeks prior to exposure until 4 weeks after leaving endemic area.
 Second-line agent for treatment of extraintestinal amebiasis. The dose is 1 g PO daily for 2 days followed by 500 mg PO daily for 2-3 weeks (with iodoquinol and dehydroemetine).

Comments

Most countries have shown increasing malarial resistance to chloroquine. Chloroquine is an antipyretic and may mask fever due to bacterial infection. Chloroquine-resistant falciparum malaria should be treated with an alternate antimalarial.

CIDOFOVIR

Usual Dose

Induction: 5 mg/kg IV Q week x 2 weeks; Maintenance: 5 mg/kg Q 2 weeks (UWHC cost \$667.38 per dose).

Indications

- 1. Ganciclovir-resistant cytomegalovirus infection.
- 2. Under investigation for BK virus infection

Comments

The dose-limiting toxicity of cidofovir is nephrotoxicity. The initial dose of cidofovir should be adjusted in renal impairment. Serum creatinine and urine protein should be monitored prior to each dose. If the serum creatinine increases by 0.3 to 0.4 mg/dL from baseline during treatment, the dose should be adjusted to 3 mg/kg. If the serum creatinine increases greater than 0.5 above baseline or 3+ proteinuria occurs, cidofovir should be discontinued. Concomitant probenecid (2 g PO 3 hours prior to infusion, then 1 g PO 1 hour after infusion and 8 hours after infusion, for a total of 4 g) and aggressive saline diuresis (a minimum of 500 mL before and 500 mL after treatment) have been shown to reduce the incidence of nephrotoxicity (Polis MA et al. *Antimicrob Agents Chemother.* 1995;39:882-6).

Cidofovir has been used in the treatment of BK polyomavirus infection after transplant; the dose ranges from 0.25-1 mg/kg given at two-week intervals for at least four doses (Blanckaert K et al. *Nephrol Dial Transplant* 2006;21:3364-7.

The safety and efficacy of cidofovir in children have not been established.

CIPROFLOXACIN

Usual Dose

Adult: 500-750 mg BID PO (UWHC cost/day \$0.28-0.44) OR 400 mg Q8-12H IV (UWHC cost/day \$3.08 -4.62). Urinary tract infections: 250 mg BID PO (UWHC cost/day \$0.20).

Pediatrics:** (not approved for children < 18 years) 20 - 30 mg/kg/day PO/IV in divided doses Q12H; PO dose not to exceed 1500 mg/day and IV dose not to exceed 800 mg/day.

Indications

1. Pyelonephritis or prostatitis, especially if the Gram-negative organisms are known or likely to be resistant to ampicillin and/or trimethoprim/sulfamethoxazole.

2. Pseudomonas aeruginosa or other Gram-negative infections with presumed or documented susceptibility to

ciprofloxacin. In sites other than the urinary tract, higher doses are employed and usually used in combination with a betalactam antibiotic.

3. Severe enteric infections with Salmonella, Shigella, Campylobacter or toxigenic Escherichia coli.

- 4. Gram-negative osteomyelitis.
- 5. Open, massively contaminated fractures, where Gram-negative contamination is likely.
- 6. *Mycobacterium avium* complex infections as part of a multi-drug regimen.
- 7. Legionella/atypical pneumonia organisms.
- 8. Meningococcal prophylaxis (500 mg PO single dose). Drug of choice.
- 9. Neutropenic fever empiric therapy in the outpatient setting.
- 10. Traveler's diarrhea treatment.

Comments

Dose adjustment required for renal impairment. See renal dosing guideline on uconnect.

Oral ciprofloxacin has excellent bioavailability and is much less expensive than the IV form. **The intravenous formulation should be reserved for treating known or strongly suspected pseudomonal or severe Gram-negative infections.** An IV-to-oral conversion policy exists at UW, and physicians and pharmacists are encouraged to step patients down from IV to oral therapy when the infection seems contained and the patient is taking other medication and food orally.

IV Dose	PO Dose
200 mg Q 12 hours	250 mg Q 12 hours
400 mg Q 12 hours	500 mg Q 12 hours
400 mg Q 8 hours	750 mg Q 12 hours

Use of quinolones is generally contraindicated in children <18 years of age or pregnant women because of cartilage damage seen in animal models In special circumstances, such as life-threatening infections for which no alternative exists or cystic fibrosis, use in children may be justified. Pediatric Infectious Disease consultation should be obtained before prescribing in children. All fluoroquinolones carry a Black Box Warning regarding the risk of tendon rupture in patients of all ages. Risk increases with age >60, steroid use, and kidney, heart or lung transplantation. Doses of 750 mg PO BID or 400 mg IV Q8H are needed only for Gram-negative bacillus osteomyelitis, serious *Pseudomonas aeruginosa* or other Gram-negative infections, or *Mycobacterium avium* complex. Not indicated for anaerobic or known streptococcal infections. Ciprofloxacin should not be used for treatment of methicillin-resistant staphylococcus infections regardless of species; reports of therapeutic failures and rapid development of *Staphylococcus aureus* resistance have been published. Ciprofloxacin may **not** be effective for *S pneumoniae* infections. Ciprofloxacin should not be used for uncomplicated UTIs unless due to *Pseudomonas* or organisms resistant to TMP/sulfa or ampicillin. Use of ciprofloxacin should be limited to the listed indications because of concerns regarding emergence of resistant strains. See IV-to-PO conversion policy (Appendix F) or on uconnect. Dose adjustment required for renal impairment. See renal dosing guideline on uconnect.

Drug Interactions

The following drugs have serum levels that are increased by ciprofloxacin's inhibition of CYP1A2 or 3A4-mediated metabolism:

-Alosetron	-Erlotinib
-Bendamustine	-Olanzapine
-Caffeine	-Rasagiline
-Clozapine	-Ropinirole
-Cyclosporine	-Ropivacaine
-Duloxetine	-Simvastatin

-Dutasteride -Eltrombopag -Theophylline -Tizanidine (contraindicated)

Ciprofloxacin may result in QTc prolongation when administered with the following drugs, and concurrent use should be avoided:

Class I anti-arrhythmics

- Disopyramide
- Flecainide
- Lidocaine
- Mexiletene
- Moricizine
- Phenytoin
- Procainamide
- Propafenone
- Tocainide

Miscellaneous drug interactions with ciprofloxacin

- The efficacy of BCG is decreased
- Chloroquine increases the rate of excretion of ciprofloxacin
- With corticosteroids, there is an increased risk of tendon rupture
- Oral ciprofloxacin is chelated by divalent cations, such as Ca⁺⁺, Mg⁺⁺, Fe⁺⁺ and Al⁺⁺, and should be scheduled two hours before or six hours after an antacid or medications such as sucralfate or a dairy product
- With indomethacin, there are complexes that form that deposit in the eye
- With insulin and oral antidiabetic agents, there is an increased risk of hyper- or hypoglycemia
- Methotrexate levels may be increased
- Metoprolol and propranolol levels may be increased
- With phenytoin and fosphenytoin, blood levels of phenytoin may increase or decrease
- Rifapentine decreases the efficacy of ciprofloxacin
- The efficacy of live typhoid vaccine is decreased
- Ciprofloxacin prolongs prothrombin times in patients on warfarin

CLARITHROMYCIN

Usual Dose

Adult: 250-500 mg Q12H PO (UWHC cost/day \$1.04-\$1.26) *Pediatrics:* 7.5 mg/kg Q12H PO

Indications

- 1. Acute bacterial exacerbation of chronic bronchitis
- 2. Acute otitis media
- 3. Prevention of disseminated infection with Mycobacterium avium intracellulare in HIV patients
- 4. Helicobacter pylori gastrointestinal tract infection
- 5. Uncomplicated skin and soft tissue infection
- 6. Acute maxillary sinusitis
- 7. Mycobacterium avium complex lung infection
- 8. Pharyngitis
- 9. Tonsillitis

Comments

Dose adjustment required in renal impairment. See renal dosing guideline on uconnect.

Class III anti-arrhythmics

- Amiodarone
- Bretylium
- Sotalol

Drug Interactions

Clarithromycin is an inhibitor of CYP3A4 and may increase serum levels of the following drugs that are CYP3A4 substrates or may be metabolized by CYP3A4 in some individuals with CYP2D6 deficiency; dose reductions may be necessary if the drugs are administered concomitantly with clarithromycin (* = contraindication): Alfentanil Darunavir/ritonavir Ixabepilone Solefenacin

Alfentanil Alfuzosin Alosetron Ambrisentan Aprepitant Atorvastatin Benzodiazepines Bortezomib Bosentan Bromocriptine Carbamazepine Cilostazol Cinacalcet Colchicine Conivaptan Corticosteroids Cvclosporine Darifenacin

Darunavir/ritonavir Dasatanib Dronaderone Ergot alkaloids* Eletriptan Eplerenone Erlotinib Estrogens Eszopiclone Etravitine Everolimus Fentanyl Fesoterodine Fluoxetine Fluticasone Fluoxetine Fosaprepitant Imatinib

Lapatanib Lovastatin Maraviroc Nifedipine Nilotinib Oxybutynin Paracalcitol Phenytoin Repaglinide Rifabutin Salmeterol Saguinavir Saxagliptin Sildenafil Silodosin Simvastatin Sirolimus

Solefenacin Sunitinib Tacrolimus Tadalafil Tedisamil Temsirolimus Theophylline Tolterodine Tolvaptan Trazodone Valproic acid Vardenafil Venlafaxine Verapamil Vinorelbine Warfarin

Clarithromycin may result in QTc prolongation when administered with the following drugs, and concurrent use should be avoided (* = contraindication):

Amiodarone Amoxapine Arsenic trioxide Atazanavir Artemether Azimilide Bepridil Bretylium Chloral hydrate Chloroquine Chloropromazine Cisapride* Disopyramide Dofetilide Dolasetron Droperidol Enflurane Erythromycin Flecainide Fluconazole Foscarnet Gemifloxacin Halofantrine Haloperidol Halothane Ibutilide Hydroxyquinidone Iloperidone Isoflurane Isradipine Levomethadyl Locainide Mefloquine Mesoridazne Octreotide Pentamidine Pimozidel Probucol Procainamide Prochlorperazine Propafenone Quetiapine Quinidine Ranolazine Risperidone Sertindole Spiramycin Sulfamethoxazole Telithromycin Terfenadine* Thioridazine Tricyclic antidepressants Trifluoperazine Trimethoprim Vasoressin Voriconazole Ziprasidone Zolmitriptan

The following miscellaneous drug interactions occur with clarithromycin: **Delavirdine**, **Iopinavir** and **ritonavir** increase serum levels of clarithromycin and may increase its side effects. **Rifabutin** and **nevirapine** decrease serum levels of clarithromycin and may decrease its efficacy. With **indinavir**, **tipranivir** and **itraconazole**, serum levels of both drugs are increased. Clarithromycin decreases serum levels of **zidovudine**.

There is an increased risk of hypoglycemia when clarithromycin is administered with **glipizide**, **glimepride** or **glyburide**. There is an increased risk of drug rash when clarithromycin is administered with **efavirenz**. Clarithromycin decreases metabolism of digoxin by intestinal bacteria and can increase serum **digoxin** levels. Clarithromycin decreases the efficacy of **BCG**.

Concurrent administration with **lansoprazole** has been reported to cause glossitis and blackening of the tongue. Concurrent administration with **paroxetine** has been reported to result in serotonin syndrome. Concurrent administration with **prednisone** increases the risk of psychotic symptoms due to prednisone.

CLINDAMYCIN

Usual Dose

Adult: 600-900 mg Q8H IV OR 150-450 mg Q6H PO (UWHC cost/day IV \$4.03-6.05; PO \$0.25-0.75). The usual tolerable adult dose orally is 300 mg 4 times a day. *Pediatric*s:** 25-40 mg/kg/day IM/IV/PO in divided doses Q6-8H.

Indications

1. Anaerobic infections above the diaphragm such as lung abscesses, peritonsillar abscess, cervical adenoiditis.

2. Community-acquired aspiration pneumonia. For hospital-acquired aspiration pneumonia, clindamycin is usually given with an aminoglycoside, third-generation cephalosporin, or fluoroquinolone.

3. Recurrent Group A beta streptococcal pharyngitis.

4. Clostridial sepsis, particularly gas gangrene. Clindamycin plus penicillin may be superior to penicillin alone. NOTE: the rate of clostridial resistance to clindamycin is 10 to 20%. Also, clindamycin may be effective in reducing microbial toxigenicity in toxic shock syndrome caused by *S aureus* or Group A beta-hemolytic streptococci.

5. Toxoplasmosis in patients allergic to sulfonamides, combined with pyrimethamine.

6. Chloroquine-resistant malaria – as part of a multi-drug regimen.

7. Osteomyelitis caused by S aureus or other susceptible organisms.

8. Perioperative prophylaxis as an alternative to cefazolin for clean-contaminated head and neck surgery (see Appendix B).

9. Diabetic foot ulcer treatment in combination with ciprofloxacin.

10. Bacterial endocarditis prophylaxis in patients allergic to beta-lactam antibiotics (see Appendix A).

11. Penicillin-resistant pneumococcal otitis media or sinusitis when clindamycin susceptibility is established.

12. Bacterial vaginosis (2% cream 5 g intravaginally at bedtime x 7 days or 300 mg BID PO x 7 days).

13. PJP treatment in combination with primaquine as second/third-line therapy.

14. Community-based MRSA with confirmed clindamycin sensitivity.

Comments

Metronidazole is less expensive for intra-abdominal anaerobic coverage. Clindamycin oral suspension is poorly accepted due to unpleasant taste. Conversion to oral therapy usually occurs when the infection is under control. High doses of oral clindamycin (>450 mg Q6H) may cause esophagitis. Due to increased incidence of Bacteroides spp resistant to clindamycin, no longer recommended for community based intraabdominal infections by the 2010 IDSA and Surgical Infection Society guidelines.

CLOFAZIMINE – nonformulary at UWHC

Usual Dose

Adult. 100 mg Q24H PO (UWHC cost/day \$0.32) Pediatrics:** 1 mg/kg/day PO

Indications

1. Mycobacterium leprae (lepromatous leprosy).

2. Second-line therapy for MAI.

Comments

The drug has a high incidence of side effects: hyperpigmentation (75-100%), GI intolerance (40-50%), ichthyosis and dryness (8- 28%) and rash/pruritus (1-5%).

This drug is not available through usual commercial sources. For the treatment of leprosy, it is available through an IND application. The contact person for the IND is Renee Painter at (225)756-3773. For other indications, contact the FDA's CDER Division of Anti-Infective and Ophthalmology Products at (301)796-1400. Use must be approved by the UWHC IRB and the Pharmaceutical Research Center should be contacted (263-8902).

CLOTRIMAZOLE

Usual Dose

10 mg troches five times a day PO for treatment (UWHC cost/day \$1.74); two to three times daily for prophylaxis (UWHC cost/day \$0..69-1.04).

Indications

1. Oropharyngeal candidiasis.

COARTEM[®] (see Artemether/Lumetantrine)

COLISTIMETHATE SODIUM (Coly-Mycin[®])

Usual Dose Adult: 2.5-5 mg/kg/day divided Q6-12H IV (UWHC cost/day \$12.06 - \$24.12) Pediatric:** 2.5-5 mg/kg/day divide Q6-12H IV

Indications

1. Susceptible Gram-negative infections caused by multi-drug-resistant organisms, including *E. coli, P. aeruginosa, K. pneumoniae, E. cloacae* and *Acinetobacter baumanii.*

2. Inhalation therapy of respiratory infections due to *P. aeruginosa*.

3. Maintenance inhalation for suppression of resistant Gram-negative bacteria in cystic fibrosis patients

Comments

Dose adjustment required for IV dosing renal impairment. See renal dosing guideline on uconnect. Dose for inhalation therapy of *P. aeruginosa* respiratory infection is 150 mg Q8H. Dose for maintenance inhalation in cystic fibrosis patients is 75-150 mg twice daily. Colistimethate sodium (CMS) is not FDA-approved for nebulization. Solutions for nebulization should be used promptly because CMS in solution undergoes spontaneous hydrolysis to form colistin, which is toxic to lung tissue. See the FDA's Information for Healthcare Professionals:

http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm124896.htm

COMBIVIR[®]

For up-to-date information on the use of antiretrovirals, consult an HIV expert or www.aidsinfo.nih.gov/

DAPSONE

Usual Dose

Adult: 50-100 mg daily PO (UWHC cost/day \$1.04-1.70). *Pediatric*s:** 1 mg/kg/day PO.

Indications

1. Leprosy.

2. Pneumocystis jiroveci pneumonia.

a. Prophylaxis, second-line agent, with or without pyrimethamine.

b. Treatment, third-line agent, in combination with trimethoprim.

3. Alternate for *Pneumocystis jiroveci* prophylaxis in patients with a sulfa allergy. Dose is 50 mg Q12H or 100 mg once daily.

4. Toxoplasma gondii treatment.

Comments

The most frequent adverse effects of dapsone are methemoglobinemia and dose-related hemolytic anemia (check glucose-6-phosphate dehydrogenase prior to prescribing dapsone).

Drug Interactions

Amprenavir and **Saquinavir** inhibit the metabolism of dapsone by CYP3A4, potentially increasing its toxicity. **Probenecid** and **trimethoprim** reduce the clearance of dapsone, thereby potentially increasing serum levels. **Rifabutin** and **rifampin** decrease the efficacy of dapsone, possibly by inducing CYP 3A4. **Zidovudine** increases the hematologic toxicity of dapsone.

DAPTOMYCIN Infectious Disease approval is required for all use of daptomycin (See Appendix I). Usual Dose

Adult: 4 or 6 mg/kg once daily IV based on IBW (UWHC cost/day \$136.04-203.28).

Indications

- 1. Complicated skin and skin-structure infections caused by resistant Gram-positive pathogens, including penicillinresistant *Streptococcus pneumoniae*, methicillin-resistant *Staphylococcus aureus with vancomycin MIC greater than 1.5*, and vancomycin-resistant enterococci.
- 2. Gram-positive right-sided Endocarditis and complicated Staphylococcal bacteremias. Dose is 6 mg/kg/day.
- 3. Empiric therapy for known Staph aureus bacteremia for 24-48 hours until the vancomycin MIC for MRSA is known to be less than 1.5.

Comments

Increased dosing interval to every 48 hours recommended in renal insufficiency with creatinine clearance less than 30 mL/min. Not indicated in pneumonia. Dosing in HD patients should occur after the dialysis session for inpatients. The recommended dosing strategy for outpatient dialysis is the 2 minute infusion immediately following the HD session. This method does not require a supplemental dosage increase.

DARUNAVIR

For up-to-date information on the use of antiretrovirals, consult an HIV expert or www.aidsinfo.nih.gov/

DELAVIRIDINE non-formulary at UWHC

For up-to-date information on the use of antiretrovirals, consult an HIV expert or www.aidsinfo.nih.gov/

DICLOXACILLIN

Usual Dose

Adult: 250-500 mg four times daily PO (UWHC cost/day \$0.82-1.45). *Pediatric*s:** 12 – 25 mg/kg/day PO in divided doses Q6H (no suspension available – use nearest capsule size).

Indications

Infections caused by or suspected of being caused by methicillin-susceptible staphylococci. Dicloxacillin is the drug of choice for outpatient therapy of susceptible *S aureus* infections.
 Skin and soft tissue infections.

Comments

Dicloxacillin should not be used for initial treatment of severe, life-threatening infections but can be used as follow-up to parenteral therapy in osteomyelitis or septic arthritis. GI intolerance may require switch to alternate antimicrobial.

Drug Interaction

Dicloxacillin decreases the anticoagulant effect of warfarin.

DIDANOSINE

For up-to-date information on the use of antiretrovirals, consult an HIV expert or www.aidsinfo.nih.gov/

DORIPENEM – non-formulary at UWHC. Therapeutically interchangeable with meropenem and imipenem at UW. Usual Dose

Adult: 500 mg Q8H IV (UWHC cost/day \$111.09) *Pediatric:* safety and efficacy not established in children

Comments

For use in patients with reported penicillin allergies, see Appendix J: UWHC Guidelines For the Use of Beta-Lactam Antibiotics in Patients with Reported Allergies to Penicillin.

DOXYCYCLINE

Usual Dose

Adult: Load 200 mg, then 100 mg Q12H IV/PO; Maintenance 100-200 mg daily or 100 mg BID IV/PO (PO UWHC cost/day \$0.14-0.28; IV UWHC cost/day \$14.79-29.58).

Pediatrics:** 2-4 mg/kg/day PO Q12H on day 1, then half dose Q24H (not for children < 8 years).

Indications

- 1. Pneumonia caused by Mycoplasma pneumoniae, Chlamydia or Legionella -- alternative treatment to macrolides.
- 2. Uncomplicated *Chlamydia trachomatis* and non-gonococcal urethritis infections in adults.
- 3. Brucellosis and bartonellosis in combination with rifampin.
- 4. Rickettsial infections (e.g. Rocky Mountain Spotted Fever, Q fever).
- 5. Acute exacerbations of chronic bronchitis.
- 6. Lyme disease in adults and children 8 years or older.

7. Malaria chemoprophylaxis in areas where chloroquine-resistant *Plasmodium falciparum* is prevalent (100 mg daily PO, start 1-2 days before travel and continue for 4 weeks after leaving malarious area). Alternative to mefloquine.

8. Treatment of chloroquine-resistant *Plasmodium falciparum* in combination with quinine.

9. Traveler's diarrhea – third-line agent (after quinolones and trimethoprim/sulfamethoxazole) for treatment or prophylaxis in persons traveling to high risk areas.

10. Plague and tularemia - alternative to streptomycin for treatment. May be used for prophylaxis in selected patients.

- 11. Inflammatory acne alternative to oral erythromycin or tetracycline.
- 12. Ehrlichiosis.
- 13. Primary or secondary syphilis in patients with an anaphylactoid-type reaction to penicillin.
- 14. CAP treatment: alternative for outpatient treatment and for non-ICU inpatient
- 15. Susceptible community-acquired MRSA infections.
- 16. Susceptible VRE in the urine.

Comments

Doxycycline can cause discoloration of permanent teeth and should not be used during the last half of pregnancy nor in children < 8 years old. Doxycycline may cause photosensitivity reactions. Patients should be counseled to avoid direct sunlight and to apply sunscreens. The IV load may be given as one or two infusions. Close follow-up is mandatory in patients with syphilis who receive tetracyclines due to reduced cure rates compared to penicillin. Tetracyclines appear to be superior to penicillin for treatment of early Lyme disease.

Drug Interactions

Doxycycline is **contraindicated** with acitretin because the combination may increase ICP.

Concurrent administration with isotretinoin may cause pseudotumor cerebri.

Divalent cations such as **calcium, iron, aluminum** or **zinc** will chelate doxycycline, preventing its absorption.

Medications containing these ions should be given 2 hours before or 6 hours after doxycycline.

Concurrent administration with **methotrexate** increases methotrexate toxicity due to displacement from plasma proteins. Concurrent administration with many **neuromuscular blockers** increases the activity of the NMB.

Concurrent administration with warfarin increases the risk of bleeding.

Concurrent administration with **porfimer** increases intracellular damage due to increased photosensitivity.

Concurrent administration with **oral contraceptives** may cause a failure of the contraceptive.

Rifampin decreases the efficacy of doxycycline via increased clearance.

Phenytoin and fosphenytoin decrease the efficacy of doxycycline due to induction of metabolism.

Phenobarbital decreases the efficacy of doxycycline due to the induction of metabolism.

Concurrent administration with chronic **carbamazepine** administration reduces the efficacy of doxycycline due to increased metabolism.

Concurrent administration with **penicillins** results in antagonism of the antibiotic effect of the penicillin because doxycycline is a bacteriostatic drug and penicillins act on bacteria in an active growth phase.

EFAVIRENZ

Also a component of Atripla[®] For up-to-date information on the use of antiretrovirals, consult an HIV expert or <u>www.aidsinfo.nih.gov/</u>

EMTRICITABINE – nonformulary at UWHC

Also a component of the combination products Truvada[®] and Atripla[®] For up-to-date information on the use of antiretrovirals, consult an HIV expert or <u>www.aidsinfo.nih.gov/</u>

ENFUVIRTIDE – nonformulary at UWHC

For up-to-date information on the use of antiretrovirals, consult an HIV expert or www.aidsinfo.nih.gov/

EPZICOM[®] -- see abacavir/lamivudine

For up-to-date information on the use of antiretrovirals, consult an HIV expert or www.aidsinfo.nih.gov/

ERTAPENEM – requires ID approval.

Usual Dose

Adult: 1 g daily IV (UWHC cost/day \$57.72). *Pediatric:* 3 mo-12 yr: 15 mg/kg Q12H, not to exceed 1 g/day; ≥13 years: 1 g Q24H **Indications**

- 1. Complicated skin and skin-structure infections
- 2. Complicated urinary tract infections
- 3. Pelvic infections
- 4. Community-acquired pneumonia
- 5. Diabetic foot infections
- 6. Intraabdominal infections
- 7. Bloodstream infections due to susceptible organisms
- 8. Infections caused by ESBL-producing Enterobacteriaceae

9. Although approved for prophylaxis by the FDA for colorectal surgery, routine use for this indication at UWHC is strongly discouraged.

Comments

Infuse over 30 minutes. Dose adjustment recommended in severe renal impairment. Patients with CrCl<30 mL/min should receive 500 mg Q24H. Not effective against *Pseudomonas* species, *Acinetobacter* species and the enterococci. **May be prescribed in anticipation of discharge where outpatient therapy will be continued. If patient is being treated with frequent interval imipenem or meropenem, consolidation to ertapenem may be appropriate.** For use in patients with reported penicillin allergies, see Appendix J: UWHC Guidelines For the Use of Beta-Lactam Antibiotics in Patients with Reported Allergies to Penicillin.

Drug Interaction

Ertapenem decreases the serum concentrations and efficacy of valproic acid.

ERYTHROMYCIN

Usual Dose

Adult: 250-1000 mg Q6H IV (UWHC cost/day \$14.49-57.97) OR 250-500 mg base Q6-8H PO (UWHC cost/day \$1.94-3.88).

Pediatrics:** 40 mg/kg/day PO in divided doses Q6H OR 15-20 mg/kg/day IV in divided doses Q6H.

Indications

1. Mycoplasma pneumonia, Chlamydia pneumoniae, Campylobacter jejuni, Bordetella pertussis or Haemophilus ducreyi (chancroid) infections.

2. Community-acquired pneumonia. (Given with additional medications in patients over the age of 60 with comorbidity or severe pneumonia).

3. Alternative for susceptible Gram-positive bacterial infections, such as streptococcal pharyngitis, in patients allergic to penicillin or cephalosporins.

4. Legionnaire's disease.

5. Acne vulgaris - topical.

6. Surgical prophylaxis orally, as the base, with neomycin, in therapeutic doses prior to colorectal surgery (see Appendix B).

7. Prevention of further toxin production and eradication of the carrier state in Corynebacterium diphtheriae infections.

8. Bordetella pertussis prophylaxis and treatment (40-50 mg/kg/day PO in 4 divided doses or 500 mg Q6H PO x 10 days). 9. Chlamydial conjunctivitis or pneumonia in infants.

10. Gonococcal ophthalmia neonatorum prophylaxis - topical.

Comments

IV dose adjustment required for renal impairment. See renal dosing guideline on uconnect.

Orally, use the minimally effective dose because as many as 30% of patients experience severe gastrointestinal intolerance which can limit erythromycin's use. Patients with severe infections should receive the drug intravenously. The IV dose for Legionnaire's pneumonia is 2 to 4 g daily in divided doses, dependent upon the severity of the infection. Case reports have documented that ototoxicity can occur with high dose (1 g Q6H) therapy. For IV administration, lidocaine 10 mg may be added to the erythromycin to decrease pain in adults.

Drug Interactions

Erythromycin inhibits the hepatic metabolism of many drugs, resulting in increased serum levels and reduced clearance. Some of the drugs affected in this way are:

- Azole antifungals
- Felodipine
- Benzodiazepines
- Bosentan .
- Budesonide
- Buspirone •
- Carbamazepine •
- Cilostazol
- Cinacalcet
- Colchicine
- Cyclosporine •
- Docetaxel

•

- Ergot derivatives (contraindicated) Warfarin
- Eplerenone
- Erythromycin prolongs the QT interval and has additive effects with other drugs that prolong the QT interval, such as:
 - Anti-arrhythmics •
 - Anti-emetics •
 - Anti-psychotic drugs •
 - Arsenic trioxide •
 - Astemizole (contraindicated)
 - Chloral hydrate •
 - Chloroquine •
 - Clindamycin

- Fluconazole
- Fluoroquinolones
- Isradipine
- Pentamidine
- Terfenadine (contraindicated)
- TMP/Sulfa
- Vasopressin
- Verapamil

- Fentanyl
- HMG-CoA reductase inhibitors
- Sirolimus
- Tacrolimus
- Tadalafil
- Theophylline
- Tolterodine
- Tramadol
- Triptans
- Valproic acid

- Cisapride (contraindicated)
- Voriconazole

- Diltiazem
- Dolasetron

Erythromycin disrupts the gut flora, biliary excretion and/or inhibits P-glycoprotein, which may alter the absorption or metabolism of:

- Carbidopa/levodopa
- Digoxin
- Estrogens
- Oral contraceptives

ETRAVIRINE (Intelence[®]) – non-formulary at UWHC

For up-to-date information on the use of antiretrovirals, consult an HIV expert or www.aidsinfo.nih.gov/

FLUCONAZOLE

Usual Dose

Adult: Treatment 400-800 mg on day 1, then 200-400 mg daily IV/PO (UWHC cost/day IV \$2.68-5.37; PO \$0.14-0.28) Prophylaxis 50-100 mg daily PO (UWHC cost/day \$0.07-0.08).

Pediatrics:** 3-12 mg/kg/day PO/ IV.

Pediatric Prophylaxis 5 mg/kg/day (not to exceed 400 mg/day)

Recommended Fluconazole Doses For Prevention and Treatment of *Candida albicans* Infections

Infection Site	Route	Adult Dose	Pediatric Dose*
Bloodstream	IV/PO	400 mg/day	6 mg/kg/day
Lung	IV/PO	400 mg/day	6 mg/kg/day
Abdomen	IV/PO	400 mg/day	6 mg/kg/day
Oropharynx	PO	100 mg/day	3 mg/kg/day
Urinary tract** (cystitis)	PO	200 mg/day	3 mg/kg/day
Urinary tract (pyelonephritis)	IV/PO	400 mg/day	6 mg/kg/day
Neutropenic prophylaxis	IV/PO	400 mg/day	6 mg/kg/day

*Use loading dose of twice this amount for initial dose; pediatric dose should not exceed adult dose **Asymptomatic candiduria should not be treated

Indications

1. Oropharyngeal candidiasis when topical antifungal therapy is ineffective and esophageal candidiasis (200-400 mg daily).

2. Deep candidal infections, non-CNS cryptococcal infections, with demonstrated susceptibility to fluconazole or documented response to therapy. CAUTION: Fluconazole failures have been reported in fungal infections caused by *C krusei* and some *C glabrata;* thus, fluconazole is NOT recommended as first-line therapy for these organisms when there is a serious infection. Isolates of these organisms from sterile body sites are sent automatically

by the microbiology lab for susceptibility testing for fluconazole. Verify testing is being performed with the microbiology lab in critical isolates.

3. Cryptococcal meningitis, in patients with AIDS, as a step-down from IV amphotericin B or as an alternative in patients intolerant of or unresponsive to amphotericin B.

4. For indefinite suppression of *Cryptococcus neoformans* infections in AIDS or other immunocompromised patients (200 mg once daily).

5. Non-life-threatening infections with *Histoplasma capsulatum*, *Blastomyces dermatitidis* and *Coccidioides immitis*. Itraconazole appears to be more effective *in vitro* and clinically. *Chemotherapy* 1992;38 Suppl 1:3-11.

6. Prophylaxis of fungal infections in adult and pediatric patients undergoing chemotherapy or allogenic bone marrow transplantation (400 mg daily), and sometimes high risk liver transplant patients.

7. Vaginal yeast infection due to Candida, in immunocompetent patients, (150 mg PO as a single dose).

8. Candiduria. Treatment is only indicated in symptomatic patients or in asymptomatic patients who are

immunocompromised or have a urinary tract obstruction. Lower doses may be used (100 mg PO day 1, then 50 mg PO daily). Urinary catheter should be removed to prevent relapses.

Comments

Dose adjustment required for renal impairment. See renal dosing guideline on uconnect.

Chronic therapy is often required for AIDS patients and may be required for recurrent oropharyngeal candidiasis.

Resistance has been reported in patients treated with prolonged or multiple courses of fluconazole.

Oral therapy is bioequivalent to IV therapy, and IV should be reserved for those patients who cannot tolerate oral medications.

See IV-to-PO conversion policy (Appendix F) or on uconnect. See Guidelines for Use of Antifungal Agents (Appendix E) or on uconnect.

NOTE: Prompt removal of intravenous catheters is essential to improve outcomes in patients with systemic catheterrelated fungal infections, especially in patients who are neutropenic or are receiving combination antimicrobials.

Drug Interactions

Fluconazole inhibits drug metabolism because of inhibition of the cytochrome P450 isoenzymes 2C9 and 3A4; patients should be monitored for drug interactions. Some drugs that may have increased levels when administered concomitantly with fluconazole due to 2C9 inhibition are:

- Bosentan
- Celecoxib
- Ramelteon
- Warfarin

Some drugs that may have increased levels when administered concomitantly with fluconazole due to 3A4 inhibition are:

- Benzodiazepines
- Carbamazepine
- Cyclosporine
- Dihydropyridine calcium channel blockers
- Eplerenone
- Ergot derivatives
- Everolimus
- Fentanyl
- Ixabepilone

- HMG-CoA reductase inhibitors
- MethadonePrednisone
- Prednisor
 Rifabutin
- Rilabulin
 Sirolimus
- SirolimusTacrolimus
- Tipranivir
- Tipranivi
 Trintene
- Triptans
- Zidovudine

Fluconazole may prolong the QT interval, an effect that may be additive with the QT-prolonging effects of many drugs including the following:

- Anti-emetics
- Antipsychotic drugs
- Arsenic trioxide
- Astemizole (contraindicated)
- Chloral hydrate
- Chloroquine
- Cisapride
- Class la anti-arrhythmic drugs

Other drugs that interact with fluconazole include the following:

- Cimetidine reduced oral absorption of fluconazole
- Nevirapine levels increased
- Nitrofurantoin levels increased

- Class III anti-arrhythmic drugsFluoxetine
- Fluoroquinolones
- Telithromycin
- Terfenadine (contraindicated)
- Tricyclic antidepressants

- Oral contraceptives/hormones levels may increase or decrease
- Phenytoin levels increased
- Tretinoin levels increased

FLUCYTOSINE

Usual Dose

Adult: 50-100 mg/kg per day PO in 4 divided doses (UWHC cost/day \$278.18-556.36). *Pediatric*s:** 50-100 mg/kg/day PO in divided doses Q6H.

Indications

1. Uncomplicated cystitis due to *Candida* (including *C glabrata*) (NOTE: Fluconazole is safer and may be more effective for *Candida*.)

- 2. Cryptococcal infections in combination with amphotericin B.
- 3. Selected life-threatening *Candida* infections in combination with amphotericin B.

Comments

Dose adjustment required for renal impairment. See renal dosing guideline on uconnect.

Some *Candida* species are resistant to flucytosine and repeat culture or susceptibility testing should be done if treatment with this agent is considered outside the urinary tract. Other than for the treatment of urinary tract infections, flucytosine should not be used alone for the treatment of *Candida* infections. To avoid toxicity in patients with impaired renal function, the peak level should be monitored and maintained at <100 mg/L. Nausea and vomiting can occur especially with doses greater than 500 mg. To reduce the incidence, instruct the patient to take one to two capsules at a time, spaced at 15 minute intervals. Flucytosine is sometimes used in combination with amphotericin B for possible synergy, which has been demonstrated *in vitro*.

Peak: draw 2 hours after dose; trough: before next dose

FOSAMPRENAVIR (non-formulary at UWHC)

For up-to-date information on the use of antiretrovirals, consult an HIV expert or www.aidsinfo.nih.gov/

FOSCARNET

Usual Dose

Adult. Induction 60 mg/kg Q8H IV (UWHC cost/day \$146.95); Maintenance 90-120 mg/kg Q24H IV (UWHC cost/day \$73.47-97.96)

Pediatrics:** Induction 180 mg/kg IV Q8H; Maintenance 90 mg/kg/day IV Q24H.

Indications

1. Cytomegaloviral retinitis in patients resistant to ganciclovir, often given with ganciclovir.

2. Other ganciclovir-resistant cytomegalovirus infections or serious infections caused by acyclovir-resistant herpes simplex virus or varicella-zoster virus infections.

Comments

Dose adjustment is required in renal impairment See renal dosing guideline on uconnect. Patients with creatinine clearance <70 mL/min are at higher risk for renal toxicity. Many patients receiving foscarnet will develop some degree of renal impairment. Patients must be well hydrated prior to therapy. Serum creatinine, serum electrolytes, magnesium and calcium should be measured at baseline and at least 2-3 times per week. Foscarnet deposits in the teeth and bones of experimental animals. Safety and efficacy have not been established in children.

Drug Interactions

Foscarnet may prolong the QT interval, an effect that may be additive with the QT-prolonging effects of many drugs including the following:

- Anti-arrhythmics
- Anti-emetics
- Anti-psychotic drugs

- Fluoxetine
- Inhalation anesthetics
- Macrolide antibiotics
- Astemizole (contraindicated)
- Chloral hydrate
- Cisapride (contraindicated)
- Fluconazole

- Terfenadine (contraindicated)
- TMP/SMZ
- Tricyclic antidepressants

Concurrent administration of foscarnet with other **nephrotoxic drugs** increases the risk of development of renal impairment.

FOSFOMYCIN (Monurol[®])

Usual Dose

Adult women: Single 3 g dose mixed in 3 to 4 ounces of water (UWHC cost/day \$37.90)

Indications

- 1. Uncomplicated urinary tract infections in women due to E. coli and E. faecalis
- 2. Fosfomycin may have utility in UTIs caused by ESBL-producing organisms and VRE.

Comments

Lab is capable of providing susceptibilities for E. coli and Enterococcus faecialis organisms only.

GANCICLOVIR (Also see valganciclovir)

Usual Dose *Adult*: Treatment 5 mg/kg Q12H IV (UWHC cost/day \$87.93). Maintenance 5 mg/kg Q24H IV (UWHC cost/day \$43.97) *Pediatric*s:** Induction 5 mg/kg Q12H IV. Maintenance 5 mg/kg Q24H IV.

Indications

- 1. Cytomegalovirus (CMV) retinitis, pneumonitis or enterocolitis, esophagitis or bloodstream infections.
- 2. CMV prophylaxis oral formulation is now valganciclovir
- 3. Congenital CMV infections

Comments

Dose adjustment required for renal impairment. See renal dosing guideline on uconnect. Dosing in excess of that recommended by the renal dosing guideline may occasionally be necessary depending on the clinical scenario.

Ganciclovir has a high incidence of complicating neutropenia (30-40%) and thrombocytopenia (20%). Dosage reductions should be considered if patients develop neutropenia, anemia or thrombocytopenia. Do not administer to patients with severe neutropenia. Patients have received longer courses of ganciclovir when the neutropenia has been controlled with colony-stimulating factors. If colony-stimulating factors are given to maintain ANC >1000, the cost is less than foscarnet therapy. The alkaline pH of ganciclovir causes pain and phlebitis at the injection site. The manufacturer recommends that ganciclovir be handled similarly to chemotherapeutic drugs during preparation and administration – discard waste in black medication bins. Ganciclovir has activity against herpes simplex virus and varicella-zoster virus. Concomitant use of ganciclovir and acyclovir is unnecessary, and increases costs and toxicity.

Drug Interactions

Ganciclovir increases the hematotoxicity of **zidovudine**.

Ganciclovir increases the bioavailablity of didanosine, thus increasing the toxicity of didanosine.

Ganciclovir increases drug exposure to **tenofovir** (and vice-versa) due to competition for drug secretion, potentially increasing toxicity.

Concurrent administration with tacrolimus increases the risk of nephrotoxicity.

GENTAMICIN

Usual Dose

Adult. Systemic infections 5 mg/kg daily or 2.5 mg/kg Q12H or 1.5 mg/kg Q8H IV (UWHC cost/day \$2.48-4.31). Urinary tract infections 1-3 mg/kg daily IV/IM (UWHC cost/day \$0.83-2.48).

Synergy in infective endocarditis and enterococcal/staphylococcal infections 1 mg/kg Q8H IV/IM or 1.5 mg/kg Q12H IV/IM (UWHC cost/day \$2.48). Recent literature suggests the increased risk of renal insufficiency for use in staphylococcal infections, even at low doses, may outweigh any potential benefit.

Healthcare-associated pneumonia 7 mg/kg daily IV (UWHC cost/day \$6.03)

Pediatrics:** 3-7.5 mg/kg/day IV/IM in divided doses Q8H.

(Cystic fibrosis 7-10 mg/kg/day).

Note: Dose using IBW. For obese patients (BMI>30kg/m²) use a dosing weight (DW) = 0.4 (ABW-IBW) + IBW. (IBW=Ideal Body Weight ABW=Actual Body Weight)

Indications

1. Serious infections with aerobic Gram-negative bacilli (if *Pseudomonas aeruginosa*, consider tobramycin in combination with a beta-lactam) especially until identification and sensitivities of organisms are known.

Enterococcal endocarditis, in combination with penicillin (Microbiology Laboratory will confirm *in vitro* synergy.)
 Contaminated fractures, where Gram-negative contamination is likely.

4. Serious urinary tract infections. When using urinary tract infection doses, monitoring plasma levels is generally unnecessary except in patients with moderate-to-severe renal dysfunction.

5. Bacterial endocarditis prophylaxis (see Appendix A).

6. Neonatal bacteremia/sepsis - in combination with ampicillin as presumptive therapy.

Comments

For extended-interval (Q24H) dosing draw midpoint level 8 - 12 H after the start of infusion (infuse over 60 minutes). For Q12H dosing draw peak and trough (peak: 30 minutes after the end of either a 30-minute or 60-minute infusion; trough: 15-30 minutes prior to next dose). All patients receiving aminoglycosides require determination of a pretreatment serum creatinine. **Aminoglycosides must be used with caution in patients with renal insufficiency, cirrhosis with ascites, or patients who have been on cisplatin within the last 21 days, all because of the increased risk of nephrotoxicity.** Gentamicin has greater activity than tobramycin, except for *P aeruginosa* where tobramycin is more active. Note: The dose listed for urinary tract infections assumes the patient does not have systemic inflammatory response syndrome. For most open fractures, gentamicin is not needed for prophylaxis. (Cefazolin or cefuroxime should be adequate.) Many patients are candidates for once-daily dosing. (*Antimicrob Ag Chem* 1995;39:650.) The unit pharmacist will assist in pharmacokinetic dosing. With Q 12 to 24 hour dosing blood level monitoring is needed only for patients with compromised renal function or patients with rapid clearances. Once-daily dosing is contraindicated in burn patients or patients treated for endocarditis. Experience is limited in pediatrics but not in neonates.

Dose interval adjustment recommended for renal impairment. See Appendix A of renal dosing guideline on uconnect.

GRISEOFULVIN, ULTRAMICRO

Usual Dose

Adult: 375-750 mg daily in single or divided doses PO with fatty food for 2 weeks to 18 months depending on site of involvement (UWHC cost/day \$5.48-10.96).

Pediatrics:** (7.3 mg/kg/day PO in one or two divided doses).

Indications

1. Tinea capitis – drug of choice. Usual duration of treatment is 6 weeks.

2. Dermatophyte infections (ringworm) of the skin, hair or nails, namely: tinea corporis, tinea barbae, tinea capitis or tinea unguium (onychomycosis).

3. Tinea pedis and tinea cruris only when unresponsive to topical therapy

Comments

The use of griseofulvin is not justified in minor or trivial infections, which will respond to topical antifungal agents. Additionally, azoles, such as ketoconazole or itraconazole, are superior to griseofulvin and are associated with fewer side effects.

Drug Interactions

Griseofulvin in combination with warfarin causes decreased anticoagulation.

IMIPENEM/CILASTIN (Primaxin®) - non-formulary at UWHC

Primaxin[®], meropenem and doripenem are therapeutically interchangeable at the UWHC. Merrem[®] is the preferred formulary product.

Usual Dose

Adult: 500 mg-1 gram Q6-8H IV (UWHC cost/day \$94.56-252.16). *Pediatric*s:** 40-60 mg/kg/day IV, IM in divided doses Q6H.

INDINAVIR

For up-to-date information on the use of antiretrovirals, consult an HIV expert or www.aidsinfo.nih.gov/

ITRACONAZOLE

Usual Dose

Adult. 200 mg Q24H PO (UWHC cost/day \$11.08) or oral solution 200 mg Q24H (UWHC cost/day \$24.44) For lifethreatening infections, give a loading dose of 200 mg TID PO x 3 days, then 200-400 mg PO Q24H. *Pediatric*s:** 100 mg PO Q24H (for children 3 - 16 years).

Indications

- 1. Blastomycosis, pulmonary and extrapulmonary.
- 2. Histoplasmosis, including chronic cavitary pulmonary disease and disseminated, non-meningeal histoplasmosis.
- 3. Aspergillus infections (replaced by voriconazole as first-line therapy).
- 4. Chromomycosis.

5. Onychomycosis (200 mg Q24H x 12 weeks; "Pulse therapy" for onychomycosis of the fingernail consists of two 1-week periods of itraconazole 200 mg twice daily, each separated by a 3-week period without any drug. Therapy should continue for three 1-week periods for treatment of onychomycosis of the toenail. (*J Amer Acad Dermatol* 1997;36:231-5 and *Arch Dermatol* 1996;132:34-41).

Comments

Itraconazole attains low CSF levels but high brain tissue levels.

NOTE: Itraconazole solution provides higher blood levels than the tablet formulation. For appropriate use, see Guidelines for the Use of Antifungal Agents (Appendix E) or on uconnect.

Drug Interactions

Food enhances the absorption of itraconazole from capsules, but decreases absorption from the solution. Antacids, including the buffering agent in didanosine, proton pump inhibitors and histamine H₂ blockers decrease oral absorption from capsules. Patients should be advised to take capsules with orange juice or cola. The oral solution should be taken on an empty stomach. Although not routinely used, itraconazole serum levels are useful in serious infections if poor absorption or treatment failure is suspected. Serum levels should be measured 2-4 hours following a dose, or as a trough level, during the second week of therapy.

Itraconazole is an inhibitor of the cytochrome P450 enzymes 2C9 and 3A4 as well as p-glycoprotein. Drugs that are metabolized by these enzymes and may have increased drug levels when used concomitantly with itraconazole include:

- Alosetron
- Alprazolam (contraindicated)
- Amprenavir/fosamprenavir
- Antipsychotic drugs
- Aprepitant/fosaprepitant
- Benzodiazepines
- Bexarotene
- Bortezomib
- Bosentan
- Buspirone
- Busulfan
- Cilostazol
- Cinacalcet

- Erlotinib
- Ergot alkaloids
- Estrogens
- Eszopiclone
- Etravirine
- Everolimus
- Fentanyl
- Fesoterodine
- Gefitinib
- Halofantrine
- HMG-CoA reductase inhibitors
- Iloperidone
- Imatinib

- Oxycodone
- Pazopanib
- Praziquantel
- Ranolazine
- Repaglinide
- Romidepsin
- Salmeterol
- Saquinavir
- Saxagliptin
- Silodosin
- Sirolimus
- Solifenacin
- Sunitinib

- Colchicine •
- Conivaptan
- Corticosteroids
- Cyclosporine •
- Darifenacin
- Dasatanib
- Darunavir
- Dihydropyridine calcium channel blockers •
- Docetaxel •
- Dronaderone •
- Eplerenone •

- Indinavir
- Ixabepilone
- Lapatinib •
- Loperamide •
- Maraviroc •
- Methadone •
- Midazolam (contraindicated) •
- Mifepristone ٠
- Modafanil •
- Nilotinib
- Oxybutynin •

- Tacrolimus
- Tamsulosin
- Telithromycin •
- Tolterodine
- Tolvaptan •
- Trazodone •
- Triazolam •

(contraindicated)

- Venlafaxine ٠
- Vinca alkaloids •

Other drugs that have increased levels and/or increased toxicity when used concomitantly with itraconazole include:

- Diaoxin •
- Warfarin •

Drugs that increase itraconazole levels when used concomitantly include:

- Amprenavir
- Clarithromycin •
- Erythromycin •
- Indinavir •
- Lopinavir
- Ritonavir •
- Saguinavir •
- Tipranavir •

Drugs that decrease itraconazole levels when used concomitantly include:

- Antacids
- Carbamazepine • Calcium salts
- Micafungin • Nevirapine
- Phenobarbital
- Cimetidine
- Efavirenz •

•

- Etravirine
- H₂-blockers •
- Isoniazid

Itraconazole may prolong the QT interval, an effect that may be additive with the QT-prolonging effects of many drugs including the following:

- Amiodarone •
- Artemether/lumefantrine •
- Astemizole (contraindicated)
- Bretylium •
- Cisapride (contraindicated) •
- Disopyramide •
- Dofetilide •
- Halofantrine •

- Ibutilide
- lloperidone •
- Levomethadyl
- Methadone
- Quinidine •
- Ranolazine •
- Sotalol •
- Terfenadine (contraindicated) •

KALETRA[®] – see lopinavir/ritonavir

KETOCONAZOLE

Usual Dose

Adult: 200-400 mg daily PO (UWHC cost/day \$0.16-0.32). Pediatric:** 5 - 10 mg/kg/day PO Q24H or in divided doses Q12H.

- Rifapentine
- Rifabutin •
- Rifampin •
- •
- Proton pump inhibitors
- Phenytoin/fosphenytoin •

Indications

1. *Blastomyces dermatitidis, Coccidioides immitis* and *Histoplasma capsulatum,* non-life-threatening infections (second-line therapy to itraconazole)

2. Candida vaginitis, recurrent (fluconazole preferred).

3. *Candida* esophagitis or chronic mucocutaneous candidiasis, non-life-threatening (second-line therapy after fluconazole).

- 4. Paracoccidioides brasiliensis infections.
- 5. Tinea versicolor.
- 6. Dermatophyte infections refractory to topical antifungals or griseofulvin.
- 7. Dandruff, severe shampoo once a month.

Comments

Ketoconazole should NOT be used when fungal meningitis is suspected or documented, because the drug does not penetrate the CNS. Because ketoconazole can cause hepatotoxicity, patients receiving other potentially hepatotoxic drugs, or with a history of liver disease, should be carefully monitored. Ketoconazole has not been studied in children. The potential benefit must outweigh the risk. NOTE: Fluconazole should replace ketoconazole therapy if any of the following are true - the patient (1) has an absorption problem (ileus, achlorhydria); (2) has had a documented failure to ketoconazole; (3) is taking histamine H₂ blockers which cannot be discontinued; (4) has a candidal urinary tract infection; (5) has AIDS and requires indefinite suppressive therapy for *Cryptococcus neoformans*.

Drug Interactions

Antacids, calcium salts, histamine H₂ receptor antagonists and proton pump inhibitors all may decrease ketoconazole absorption by increasing gastric pH. Absorption may improve by taking with orange juice or colas.

Ketoconazole inhibits the cytochrome P450 enzymes 3A4 and 2C9 as well as p-glycoprotein. Drugs that are metabolized by these enzymes and may have increased levels when administered concomitantly with ketoconazole include:

- Alfuzosin
- Aliskiren
- Alosetron
- Alprazolam*
- Amprenavir/fosamprenavir
- Antipsychotic drugs
- Aprepitant/fosaprepitant
- Astemizole*
- Benzodiazepines
- Bortezomib
- Bosentan
- Buprenorphine
- Carbamazepine
- Cilostazol
- Cinacalcet
- Cisapride*
- Colchicine
- Conivaptan
- Corticosteroids
- Cyclosporine
- Darifenacin
- Darunavir
- Dasatanib
- Delavirdine
- Dihydropyridine Ca⁺⁺ channel blockers
- Docetaxel
- Dofetilide

- ErythromycinEstrogens
- Estrogens
- Eszopiclone
- Etravirine
- Everolimus
- Fentanyl
- Fesoterodine
- Galantamine
- Gefitinib
- HMG-CoA reductase inhibitors
- Imatinib
- Indinavir
- Irinotecan
- Ixabepilone
- Lapatinib
- Levomethadyl
- Maraviroc
- Methadone
- Mifepristone
- Modafanil/armodafanil
- Nilotinib
- Oxybutynin
- Oxycodone
- Paracalcitol
- Pazopanib
- Paracalcitol
- Phosphodiesterase-5 inhibitors

- Ritonavir
- Romidepsin
- Salmeterol
- Saguinavir
- Saxagliptin
- Sibutramine
- Silodosin
- Sirolimus
- Solifenacin
- Sunitinib
- Tacrolimus
- Tamsulosin
- Telithromycin
- Temsirolimus
- Terfenadine*
- Tinidazole
- Tolbutamide
- Tolterodine
- Tolvaptan
- Topotecan
- Tramadol
- Triazolam*
- Trimetrexate
- Valdecoxib
- Venlafaxine

- Donepezil
- Dronaderone
- Dutasteride
- Efavirenz
- Eplerenone
- Ergot derivatives

- Pioglitazone
- Praziquantel
- Ramelteon
- Ranolazine
- Reboxetine
- Repaglinide
- * Drug is **contraindicated** to administer concurrently with ketoconazole

Other drugs that interact with ketoconazole include:

- Amprenavir increases ketoconazole levels
- Clopidogrel has decreased efficacy due to reduced metabolism to active moiety
- Digoxin has its levels increased by ketoconazole
- Efavirenz increases ketoconazole levels
- Erythromycin increases ketoconazole levels
- Escitalopram decreases ketoconazole levels
- Etravirine decreases ketoconazole levels
- Isoniazid decreases ketoconazole levels
- Lopinavir increases ketoconazole levels
- Nevirapine decreases ketoconazole levels
- Phenytoin/fosphenytoin decreases ketoconazole levels; variable effects on phenytoin levels
- Rifampin decreases ketoconazole levels
- Rifapentane decreases ketoconazole levels
- Ritonavir increases ketoconazole levels
- Tipranivir increases ketoconazole levels

Ketonazole may prolong the QT interval, an effect that may be additive with the QT-prolonging effects of many drugs including the following:

- Amiodarone
- Artemether/lumefantrine
- Astemizole (contraindicated)
- Bretylium
- Cisapride (contraindicated)
- Dofetilide
- Halofantrine
- Ibutilide

- Iloperidone
- Levomethadyl
- Mefloquine
- Methadone
- Quinidine
- Ranolazine
- Sotalol
- Terfenadine (contraindicated)

LAMIVUDINE

Also a component of the combination products Combivir[®], Epzicom[®], and Trizivir[®]

- 1. For up-to-date information on the use of antiretrovirals, consult an HIV expert or www.aidsinfo.nih.gov/
- Also used in chronic hepatitis B at a daily dose of 100 mg, with adjustments for renal insufficiency. (UWHC cost/day \$11.01)

LEVOFLOXACIN

Infectious Disease approval required for use of levofloxacin except for concurrent pneumonia and UTI or for susceptible *Stenotrophomonas maltophilia*

Usual Dose

Adult 250-750 mg IV/PO Q24H (UWHC cost/day PO \$15.06-29.40; IV \$17.64-46.84) Safety and efficacy in children have not been established.

Safety and efficacy in children have not bee

- 1. Community-acquired pneumonia in patients with penicillin-resistant pneumococcal infections or penicillin allergy.
- 2. Complicated and uncomplicated urinary tract infections with susceptible organisms.

- 3. Pyelonephritis.
- 4. Susceptible Stenotrophomonas maltophilia infections.
- 5. Mycobacterial infections.
- 6. Bacterial sinusitis.
- 7. Acute bacterial exacerbations of chronic bronchitis.
- 8. Skin and skin structure infections.
- 9. Bacterial proctatitis.
- 10. Chlamydial infections.
- 11. Epidydimitis
- 12. Non-gonococcal urethritis.
- 13. Nosocomial pneumonia.
- 14. Inhalational anthrax post-exposure prophylaxis.

Comments

Dose adjustment required in renal failure. See guideline on uconnect.

Drug Interactions

Levofloxacin may prolong the QT interval, an effect that may be additive with the QT-prolonging effects of many drugs including the following:

- Anti-arrhythmic agents
- Antipsychotic drugs
- Dronaderone
- Droperidol
- Fluconazole

SunitinibTelavancin

Nilotinib

HaloperidolLapatinib

Tetrabenazine

Lumefantrine

Methadone

Pazopanib

Levofloxacin has other miscellaneous drug interactions:

- Insulin and oral antidiabetic agents increased risk of hyper- or hypoglycemia
- Nonsteroidal anti-inflammatory drugs increased risk of seizures, especially in patients with seizure disorders
- Antacids and divalent cations chelate levofloxacin; must be administered 2H before or 6H after levofloxacin dose
- · Corticosteroids increased risk of quinolone-related tendon rupture
- · Quercetin reduced efficacy of levofloxacin via competition for DNA gyrase binding sites

LINEZOLID

Infectious Disease approval is required for all use of linezolid (See Appendix I). Usual Dose

Adult: 600 mg BID PO/IV (UWHC cost/day PO \$148.12; IV \$193.43).

Pediatric: 10 mg/kg dose PO/IV Q8H

Indications

1. Vancomycin-resistant Enterococcus faecium infections, including those with concurrent bacteremia.

2. Methicillin-resistant *S. aureus* infections in patients unable to tolerate vancomycin therapy, or in transition to outpatient therapy where IV therapy would be necessary. Combination therapy may be warranted if Gram-negative organisms are present.

3. Serious MRSA infections, including documented MRSA hospital-acquired pneumonia.

4. In the rare case of a patient with a Gram-positive infection who is unable to tolerate other conventional antibiotics.

Comments

Myelosuppression (including anemia, leukopenia, pancytopenia, and thrombocytopenia) has been reported with prolonged use, especially greater than 14 days. Complete blood counts should be monitored weekly in patients who receive linezolid, particularly in those who receive linezolid for longer than 2 weeks, and especially transplant patients, those with pre-existing myelosuppression, those receiving concomitant drugs that produce bone marrow suppression or those 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. Peripheral neuropathies have been reported with prolonged use. See IV-to-PO conversion policy (Appendix F) or on uconnect

See guidelines for use on uconnect.

Drug Interactions

Serotonin syndrome has been reported with concurrent use of linezolid and other serotonergic dugs, including:

- Bupropion
- Buspirone
- Dextromethorphan
- Flesinoxan
- Hydroxytryptophan
- Levodopa
- Lithium
- Maprotiline
- Meperidine

Tramadol

Methadone

Risperidone

Tapentadol

Metoclopramide

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The following medications are metabolized by monoamine oxidases and may have their serum levels increased by linezolid, potentially resulting in toxicity:

Tricyclic antidepressants

- Albuterol/levalbuterol
- Amphetamines*
- Clenbuterol
- Cyclobenzaprine
- Cvproheptadine
- Diethylpropion*
- Diphenhydramine
- Dobutamine
- Dopamine
- Entacapone
- Epinephrine
- Formoterol/arformoterol
- Other MAOIs*

* -- Medication is contraindicated to give with linezolid

The following miscellaneous drug interactions are associated with linezolid:

- Carbamazepine decreases linezolid serum levels
- Phenobarbital decreases linezolid serum levels
- Phenvtoin decreases linezolid serum levels
- Rifampin decreases linezolid serum levels
- Altretamine linezolid increases the risk of severe orthostatic hypotension
- Morphine linezolid increases hypotension and exaggerates CNS and respiratory depression
- Oxycodone linezolid increases CNS depression
- Droperidol prolongs QTc interval; additive effects with linezolid (MAOI effect can generate arrhythmias)
- Levomethadyl prolongs QTc interval; additive effects with linezolid (MAOI effect can generate arrhythmias)

The following drugs are **contraindicated** to administer with linezolid:

- Apraclonidine potentiates the MAOI activity of linezolid (and other MAOIs)
- Brimonidine concurrent administration may result in hypertensive urgency/emergency
- Guanadrel concurrent administration may result in decreased antihypertensive effect of guanadrel or hypertensive emergency
- · Guanethedine concurrent administration may result in decreased antihypertensive effect of guanethidine or hypertensive emergency

- Mazindol*
- Methylphenidate*/dexmethylphenidate*

Norepinephrine reuptake inhibitors

Norepinephrine-serotonin reuptake inhibitors

- Norepinephrine
- Phendimetrizine*
- Phentermine*
- Phenylpropanolamine*
- Phenmetrazine*
- Pirbuterol
- Salmeterol
- Tetrabenazine*
- Triptans
- Terbutaline

- Methyldopa concurrent administration may result in hypertensive emergency
- Reserpine increased catecholamine toxicity

LOPINAVIR/RITONAVIR (Kaletra®)

For up-to-date information on the use of antiretrovirals, consult an HIV expert or www.aidsinfo.nih.gov/

MALARONE[®] --see atovaquone/proguanil

MARAVIROC (Selzentry®) – nonformulary at UWHC

For up-to-date information on the use of antiretrovirals, consult an HIV expert or www.aidsinfo.nih.gov/

MEFLOQUINE

Usual Dose

Adult: Prophylaxis 250 mg weekly PO (UWHC cost/day \$4.19). Treatment 1.25 g PO one dose only (UWHC cost/day \$20.959). *Pediatric:*** Prophylaxis in children >6 years 4.6 mg/kg weekly PO. Treatment 20 – 30 mg/kg PO one dose only.

Indications

1. Malaria prophylaxis in regions with chloroquine and multiple-drug-resistant malaria. Prophylaxis should begin 1 week prior to traveling, then continue weekly during travel in malarious area followed by at least 4 weeks of prophylaxis after leaving the malarious area. If mefloquine is used, it is **NOT** necessary to give chloroquine for prophylaxis of nonfalciparum malaria.

2. Malaria treatment (utility may be limited by central nervous system toxicity): Alternative to quinine in chloroquineresistant malaria.

Comments

Increasing mefloquine resistance of *P falciparum* in many parts of Southeast Asia may contraindicate its use for treatment of falciparum malaria in these areas. Safety and effectiveness in children have not been established; however, most experts believe that benefits outweigh risk in prophylaxing traveling children.

FDA warning: Lariam[®] is contraindicated for prophylaxis in patients with active depression, a recent history of depression, generalized anxiety disorder, psychosis, schizophrenia or other major psychiatric disorders, or with a history of convulsions. During prophylactic use, if psychiatric symptoms such as acute anxiety, depression, restlessness or confusion occur, these may be considered prodromal to a more serious event. In these cases, the drug must be discontinued and an alternative medication should be substituted.

MEROPENEM (Merrem[®]) - requires ID approval with some exceptions

Primaxin[®], meropenem and doripenem are therapeutically interchangeable at the UWHC. Merrem[®] is the preferred formulary product.

Usual Dose

Adult: 500 mg Q6H IV; Serious infections with high MIC (>2 mcg/mL) organisms (outside TLC or Neuro ICU) 2 g Q8H IV (UWHC cost/day \$58.04-\$174.16).

Usual dose is 500 mg IV Q6H. Higher doses may be used depending on clinical circumstances. Febrile neutropenia dose is 500 mg IV Q6H. Dose in cystic fibrosis is 1 or 2 g IV Q8H. Meningitis dose is 2 g IV Q8H. *Pediatric*s:** 10-40 mg/kg Q8H IV, IM; maximum dose 2 g/dose

Indications

1. Multiply-resistant Pseudomonas aeruginosa or other Gram-negative bacilli (usually with an aminoglycoside).

2. Nosocomial Gram-negative bacillary pneumonia (usually given with an aminoglycoside until susceptibility is confirmed),

especially when ESBL-producing Gram-negative bacteria are suspected.

3. Intra-abdominal sepsis

4. Life-threatening Gram-negative infections due to organisms such as *Acinetobacter* species known or likely to be resistant to third-generation cephalosporins (e.g., *P aeruginosa, Enterobacter, Serratia* or *Citrobacter*) or in patients vulnerable to nephrotoxicity with aminoglycosides.

5. Neutropenic fever (dose as 500 mg IV Q6H).

Comments

All doses *except* the first dose are given as prolonged infusion. The first dose is given over 30 minutes to rapidly achieve therapeutic concentrations. Excusion criteria: patients receiving CVVH and patients treated for meningitis. Cystic fibrosis patients may receive prolonged infusion, but are not limited to lower doses specified in the prolonged infusion guideline. Dose adjustment required for renal impairment. See renal dosing guideline on uconnect.

For use in patients with reported penicillin allergies, see Appendix J: UWHC Guidelines For the Use of Beta-Lactam Antibiotics in Patients with Reported Allergies to Penicillin.

METRONIDAZOLE

Usual Dose

Adult. 500 mg Q8H IV OR 1 g Q12H IV (UWHC cost/day \$3.31-4.41) OR 250-750 mg TID PO OR 250 mg four times daily PO (colitis) (UWHC cost/day \$0.36-1.08).

Pediatrics:** 15-35 mg/kg/day PO in divided doses Q8H OR 30 mg/kg/day IV in divided doses Q6H.

Indications

1.Intra-abdominal abscesses where anaerobes are likely to be pathogens. Usually given with an aminoglycoside or other antibiotic with Gram-negative activity.

- 2. Bacterial vaginosis.
- 3. Trichomonal vaginitis.
- 4. Giardiasis (250 mg TID PO x 5 days).

5. *Clostridium difficile* colitis (usually oral only; IV is less effective for *C difficile* colitis, although IV is used with PO vancomycin in initial, severe, complicated cases).

- 6. Prophylaxis for colorectal surgery (see Appendix B).
- 7. Brain abscess or anaerobic meningitis (usually given with beta-lactam antibiotics).
- 8. Amebic dysentery and other Entamoeba histolytica infections (especially liver abscesses).
- 9. Treatment of *H pylori* infection as part of combination regimens.

Comments

The manufacturer recommends a loading dose of 15 mg/kg IV, although this is rarely, if ever, used. Disulfiram-like reactions have been reported. Patients should be counseled regarding alcohol use while taking metronidazole. (NOTE: Many agents contain alcohol as a vehicle.) Metronidazole has limited activity against Gram-positive anaerobic cocci; it has essentially no activity against aerobic bacteria and no activity against anaerobic Gram-positive rods other than *Clostridium* (e.g., *Actinomyces* and *Propionibacterium*). This usually limits its use to anaerobic infections below the diaphragm. It is not usually necessary to combine metronidazole with ampicillin/sulbactam or piperacillin/tazobactam as these drugs have adequate anaerobic coverage for most situations. An exception to this would be a case where *C. difficile* is suspected or an undrained intra-abdominal abscess. Avoid in first trimester of pregnancy. Safety and efficacy in children have not been established except for amebiasis. Metronidazole is used as a second-line drug for giardiasis in children. See IV-to-PO conversion policy (Appendix F) on uconnect. The oral formulation is preferred for treating *C. difficile*. The 2010 IDSA Guidelines for the treatment of *C. difficile* recommend a dose of 500 mg Q8H PO for the initial and first recurrence of mild-to-moderate *C. difficile*.

Drug Interactions

Metronidazole in combination with warfarin causes increased anticoagulation.

MICAFUNGIN

Infectious Disease approval required for all use of micafungin (see Appendix I)

Anidulafungin, caspofungin and micafungin are therapeutically interchangeable at UWHC. Micafungin is the current formulary choice.

Usual Dose

Adult: 50-100 mg/day IV (UWHC cost/day \$43. 37-86.74). Daily dose is 50 mg for prophylaxis, 100 mg for treatment of yeast (*Candida*), and 100 mg for treatment of molds (*Aspergillus*). *Pediatric:* 1-3 mg/kg/day IV

Indications

- 1. Systemic candidiasis in patients at risk for infection by yeasts that may be resistant to azole antifungals
- 2. Invasive aspergillosis in patients intolerant of or unresponsive to treatment with alternative agents
- 3. Empiric therapy for candidemia with yeast in blood until idenfication of yeast known.

MINOCYCLINE

Usual Dose

Adult: Load 100-200 mg PO x1 dose; then 100 mg Q12H PO (UWHC cost/day \$0.20). *Pediatric.*** (Not for children <8 years) Load 4 mg/kg PO x1; then 4 mg/kg/day PO in divided doses Q12H.

Indications

- 1. Inflammatory acne alternative to oral erythromycin or oral tetracycline.
- 2. Mycobacterium marinum skin granulomas alternative to tetracycline.
- 3. Methicillin-resistant S aureus (MRSA)
 - a. Decolonization (usually given with rifampin) second-line agent.
 - b. Treatment of CA-MRSA
- 4. Nocardiosis treatment second-line agent.

Comments

Vestibular reactions limit minocycline usefulness. The reported incidence ranges from 21-90%. Minocycline can cause discoloration of permanent teeth and should not be used during the last half of pregnancy nor in children < 8 years old. No IV formulation is currently available.

Drug Interactions

Minocycline is **contraindicated** with acitretin because the combination may increase ICP. Concurrent administration with **isotretinoin** or **vitamin A** may cause pseudotumor cerebri. Divalent cations such as **calcium, iron, aluminum** or **zinc** will chelate minocycline, preventing its absorption. Medications containing these ions should be given 2 hours before or 6 hours after minocycline.

Concurrent administration with **methotrexate** increases methotrexate toxicity due to displacement from plasma proteins. Concurrent administration with many **neuromuscular blockers** increases the activity of the NMB. Concurrent administration with **warfarin** increases the risk of bleeding.

Concurrent administration with **porfimer** increases intracellular damage due to increased photosensitivity.

Concurrent administration with oral contraceptives may cause a failure of the contraceptive.

Concurrent administration with **penicillins** results in antagonism of the antibiotic effect of the penicillin because minocycline is a bacteriostatic drug and penicillins act on bacteria in an active growth phase. Concurrent administration with **atazanavir** results in reduced serum levels of atazanavir. Concurrent administration with **digoxin** results in increased digoxin levels.

MOXIFLOXACIN

Levofloxacin and moxifloxacin are therapeutically interchangeable for respiratory tract infections at the UWHC where Pseudomonas is not suspected. Moxifloxacin is the current preferred choice.

Usual Dose

Adult. 400 mg Q24H IV/PO (UWHC cost/day IV \$11.60; PO \$2.51).

Indications

- 1. Community-acquired pneumonia caused by S pneumoniae, H influenza, H parainfluenzae, K pneumoniae, M catarrhalis, Chlamvdia pneumoniae, Legionella pneumophila, or Mycoplasma pneumoniae (7- to 10-day regimen).
- 2. Acute exacerbations of chronic bronchitis (5-day regimen).
- 3. Sinusitis.
- Skin and skin-structure infections, uncomplicated
- 5. As monotherapy, stepdown, for intra-abdominal infections.

Comments

Oral moxifloxacin has excellent bioavailability and is much less expensive than the IV form. The oral form should be used in any patient taking other oral medications or nutrition. Use of guinolones is generally contraindicated in children <18 years of age or pregnant women because of cartilage damage seen in animal models. In special circumstances, such as life-threatening infections for which no alternative exists or cystic fibrosis, use in children may be justified. Pediatric Infectious Disease consultation should be obtained before prescribing in children. Moxifloxacin attains lower concentrations in urine than other guinolones, so it is **NOT** approved for complicated or uncomplicated UTIs, although it may be effective for bacteria with low minimum inhibitory concentrations. See IV-to-PO Interchange Policy (Appendix F) or on uconnect.

Drug Interactions

Moxifloxacin may prolong the QT interval, an effect that may be additive with the QT-prolonging effects of many drugs including the following:

- Anti-arrhythmic agents
- Antipsychotic drugs
- Cisapride (contraindicated)
- Dronaderone
- Droperidol
- Erythromycin
- Fluconazole
- Haloperidol
- Lapatinib

Moxifloxacin has other miscellaneous drug interactions:

- Insulin and oral antidiabetic agents increased risk of hyper- or hypoglycemia
- Antacids and divalent cations chelate moxifloxacin; must be administered 2H before or 6H after levofloxacin dose
- Corticosteroids increased risk of guinolone-related tendon rupture
- · Quercetin decreases the efficacy of fluoroquinolones by competing for DNA gyrase binding sites
- Rifampin decreases moxifloxacin serum concentrations
- Warfarin concurrent administration may result in increased INR, risk of bleeding

MUPIROCIN

Usual Dose

Topical application of 2% ointment TID x 5-14 days (UWHC cost per tube \$5.91). Intranasal application 2% ointment BID x 5 days.

Indications

1. Impetigo, minor cases, due to S aureus, Group A beta-hemolytic strep.

2. S aureus (including methicillin-resistant) nasal carrier state eradication in MRSA outbreaks or in high-risk patients (dialysis).

- Lumefantrine
- Methadone
- Nilotinib
- Pazopanib
- Sunitinib
- Telavancin
- Tetrabenazine
- Tricyclic antidepressants

NAFCILLIN

Nafcillin and oxacillin are therapeutically interchangeable at the UWHC. Oxacillin is the current formulary choice. **Usual Dose**

Adult: 1 - 2 g Q4H IV (UWHC cost/day \$51.42-99.48).

Pediatric:** 150-200 mg/kg/day IV in divided doses Q4H.

Indications

1. Staphylococcus aureus infections sensitive to oxacillin.

- 2. Skin and soft tissue infections due to Staphylococcus or group A streptococcus.
- 3. Empiric therapy of community-acquired Gram-positive skin and soft-tissue infections.

Comments

CAUTION: None of the semi-synthetic penicillins are effective against enterococci, methicillin-resistant *S aureus*, methicillin-resistant coagulase-negative staphylococci, Gram-negative bacilli or *Bacteroides fragilis*. For endocarditis, the dose is 1.5 - 2 g Q4H IV or 9 -12 g/24H by continuous infusion. For IV administration, lidocaine 10 mg/1 mL may be added to nafcillin to decrease phlebitis.

Drug Interactions

- Warfarin concurrent administration with warfarin causes decreased anticoagulation.
- Cyclosporine nafcillin decreases cyclosporine concentrations or interferes with assay
- Aminoglycosides inactivated by penicillins in admixtures when penicillin:AG ratio is 50:1 or higher
- Nifedipine decreased AUC due to induced metabolism at CYP 3A isoenzymes by nafcillin
- Live typhoid vaccine decreased efficacy; wait 24 hours after end of therapy to give vaccine

NELFINAVIR

For up-to-date information on the use of antiretrovirals, consult an HIV expert or www.aidsinfo.nih.gov/

NEVIRAPINE

For up-to-date information on the use of antiretrovirals, consult an HIV expert or www.aidsinfo.nih.gov/

NITAZOXANIDE (Alinia[®])

Usual Dose

Adult: 500 mg Q12-24H PO (UWHC cost/day \$19.91-\$39.82).

Pediatric: Ages 12-47 months: 100 mg Q12H PO; Ages 4-11 years: 200 mg Q12H PO (UWHC cost/day \$12.85-25.70); Ages 12 and over: 500 mg Q12H PO.

Indications

- 1. Cryptosporidiosis in patients 1 year old and older.
- 2. Giardiasis in patients 1 year old and older.

Comments

Product is available as a 500 mg tablet or a 100 mg/5 mL suspension; suspension contains 1.48 g sucrose/5 mL. No data in hepatic or renal impairment. Safety and efficacy in immunocompromised patients have not been established.

NITROFURANTOIN

Usual Dose

Adult: Treatment generic nitrofurantoin 50-100 mg Q6H PO (UWHC cost/day \$1.46-1.90) OR Macrobid[®] 100 mg BID PO (UWHC cost/day \$6.89). Prophylaxis for UTI 50 mg HS PO. *Pediatric*:** Treatment 5-7 mg/kg/day PO in divided doses Prophylaxis 1 mg/kg/day

Indications

- 1. Uncomplicated cystitis treatment of initial and recurrent.
- 2. Recurrent cystitis prophylaxis.
- 3. Vesicoureteral reflux prophylaxis.
- 4. UTI due to susceptible enterococci including VRE.

Comments

Nitrofurantoin is not indicated for pyelonephritis or systemic infections. Nitrofurantoin is contraindicated in children less than one month of age. Nitrofurantoin is not useful in patients with creatinine clearance <30 mL/minute due to impaired concentration in urine. Prolonged use may produce pulmonary fibrosis or neuropathy. Duration of therapy for cystitis is usually 7-10 days.

NORFLOXACIN

Usual Dose

Adult: 200-400 mg BID PO (UWHC cost/day \$3.55-7.10).

Indications

- 1. Non-febrile traveler's diarrhea prophylaxis and treatment. Duration of treatment is usually 72 hours.
- 2. Neisseria gonorrhoeae infection (800 mg as a single dose). Oral alternative for penicillinase-producing organisms.
- 3. Uncomplicated urinary tract infections (200 mg Q12H PO).
- 4. Prophylaxis for SBP in patients with GI bleeding as alternative to ceftriaxone.

Comments

Dose adjustment required for renal impairment. See renal dosing guideline on uconnect.

Norfloxacin is **not** effective for systemic infections. Use for noninvasive urinary tract infections or enteric infections only. Also, norfloxacin does not elevate theophylline blood levels as ciprofloxacin does. Use of quinolones is generally contraindicated in children <18 years of age or pregnant women because of cartilage damage seen in animal models. In special circumstances, such as multiply resistant organisms, use in children may be justified. Pediatric Infectious Disease consultation should be obtained before prescribing in children.

Drug Interactions

Antacids, sucralfate (due to its aluminum content) and other cations, including zinc, iron and the buffering agent in didanosine significantly decrease the bioavailability of norfloxacin. Episodes of hypo- and hyperglycemia have been reported when fluoroquinolones are administered concomitantly with sulfonylureas.

NYSTATIN

Usual Dose

Adult. 500,000 units/5 mL two to four times daily swish and swallow (UWHC cost/day \$1.30-2.60). *Pediatric*:** 200,000 units/2 mL – 500,000 units/5 mL PO (not swallowed) Q6H.

Indications

1. Oropharyngeal candidiasis

Comments

Esophagitis requires treatment with fluconazole or alternative antifungal agent. Nystatin powder (1/8 tsp in water) may be used as an alternative to the suspension if a product without a sweetener is desired.

OXACILLIN

Oxacillin and nafcillin are therapeutically interchangeable at the UWHC. Oxacillin is the current formulary choice. **Usual Dose**

Adult: 1-2 g Q 4 hours IV (UWHC cost/day \$45.74-91.48)

Pediatric: 25-100 mg/kg/day in divided doses Q 4 hours IV;

Indications

1. Staphylococcus aureus infections sensitive to oxacillin.

- 2. Skin and soft tissue infections due to Staphylococcus or group A streptococcus.
- 3. Empiric therapy of community-acquired Gram-positive skin and soft-tissue infections.

CAUTION: None of the semi-synthetic penicillins are effective against enterococci, methicillin-resistant *S aureus*, methicillin-resistant coagulase-negative staphylococci, Gram-negative bacilli or *Bacteroides fragilis*. For endocarditis, the dose is 1.5 - 2 g Q4H IV or 9 -12 g/24H by continuous infusion.

Drug Interactions

- Aminoglycosides inactivated by penicillins in admixtures when penicillin: AG ratio is 50:1 or higher
- Oral contraceptives decreased efficacy due alteration of intestinal flora and resultant reduction of enterohepatic circulation of hormones
- · Live typhoid vaccine decreased efficacy; wait 24 hours after end of therapy to give vaccine

PAROMOMYCIN

Usual Dose

Adult. 500 mg four times daily PO (UWHC cost/day \$8.08). *Pediatric*:** 30 mg/kg/day PO in divided doses Q8H.

Indications

- 1. Intestinal amebiasis (with metronidazole).
- 2. Dientamoeba fragilis infections alternative treatment to iodoquinol (non-formulary).
- 3. Tapeworm alternative treatment to praziquantel for tapeworm (niclosamide is a second-line agent).
- 4. Cryptosporidial diarrhea (effectiveness unproven).
- 5. Intestinal Giardia infection during pregnancy.

Comments

A non-absorbable oral aminoglycoside. Paromomycin is only effective for intestinal disease and as a back-up antimicrobial for all the indications listed with the exception of cryptosporidial diarrhea. The most prominent side effect is diarrhea in doses >3 g daily.

PENICILLIN G (K⁺ or Na⁺ Salts)

Usual Dose

Adult. 1-4 million units Q4-6H IV (UWHC cost/day \$2.68-16.13). Meningitis 2-4 million units Q4H or continuous infusion IV (UWHC cost/day \$8.06-16.13). *Pediatric*:** 100,000 – 500,000 units/kg/day IV in divided doses Q4H.

Indications

1. Susceptible pneumococci, beta-hemolytic streptococci, viridans streptococci, meningococci, clostridia and *Pasteurella multocida* infections.

2. Severely contaminated open fractures, especially those occurring in the farm yard setting, to cover for potential clostridial contamination.

- 3. Actinomycosis.
- 4. Lyme Disease (ceftriaxone is recommended for therapy of late disease).
- 5. Congenital syphilis.
- 6. CNS syphilis.

Comments

Dose adjustment required for renal impairment. See renal dosing guideline on uconnect.

For systemic infantile group B streptococcal infections and viridans streptococcal infections in immunocompromised hosts, gentamicin should be added for synergy until the penicillin MIC is known. Low-level and occasional high-level penicillin-resistant *Streptococcus pneumoniae* have been reported from multiple geographic areas in the US, including Wisconsin. For serious *Streptococcus pneumoniae* infections (e.g., meningitis or life-threatening sepsis), ceftriaxone is recommended in combination with vancomycin and sometimes rifampin until penicillin susceptibility is documented. Penicillin G potassium contains 1.7 mEq potassium per million units. Penicillin G sodium contains 2 mEq sodium per million units. **One million units of penicillin G equal 625 mg**. Long-acting injectable penicillin is available on the UWHC formulary as penicillin G benzathine (Bicillin L-A[®]) and penicillin G benzathine/procaine (Bicillin C-R[®]). Usual adult doses are 1,200,000 units via deep IM injection every 7-28 days.

Drug Interactions

- Aminoglycosides inactivated by penicillins in admixtures when penicillin: AG ratio is 50:1 or higher
- Oral contraceptives decreased efficacy due alteration of intestinal flora and resultant reduction of enterohepatic circulation of hormones
- Live typhoid vaccine decreased efficacy; wait 24 hours after end of therapy to give vaccine
- Tetracyclines bacteriostatic drugs may antagonize antibiotics such as penicillins, which work on actively growing bacteria
- Methotrexate penicillin has been reported to increase methotrexate toxicity in some cases, possibly by competing for renal tubular secretion

PENICILLIN VK

Usual Dose

Adult. 125-500 mg Q6-12H PO (UWHC cost/day \$0.07-0.51). Note: Q12H dose is for outpatient setting only. *Pediatric*:** 25 - 50 mg/kg/day PO in divided doses Q6H.

Indications

1. Group A streptococcal pharyngitis – First-line therapy (Children: 250 mg BID-TID PO. Adolescents and adults: 500 mg BID-TID PO).

2. Oral/dental infections.

3. Rheumatic fever prophylaxis in children (250 mg BID PO).

4. Pneumococcal infection prophylaxis in children with sickle cell anemia (children < 5 years 125 mg BID PO, children > 5 years 250 mg BID PO).

Comments

Dose adjustment required for renal impairment. See renal dosing guideline on uconnect.

Oral penicillin VK should not be used preferentially over IV penicillin for severe pneumonia, empyema, bacteremia, pericarditis, meningitis or arthritis. Beta-streptococci are still very susceptible to penicillin. Some viridans streptococci and enterococci may be resistant. Caution is warranted due to emergence of penicillin-resistant pneumococci. Penicillin VK contains 2.6 mEq potassium per gram. One million units of penicillin G equal 625 mg.

Drug Interactions

- Aminoglycosides inactivated by penicillins in admixtures when penicillin: AG ratio is 50:1 or higher
- Oral contraceptives decreased efficacy due alteration of intestinal flora and resultant reduction of enterohepatic circulation of hormones
- Live typhoid vaccine decreased efficacy; wait 24 hours after end of therapy to give vaccine
- Tetracyclines bacteriostatic drugs may antagonize antibiotics such as penicillins, which work on actively growing bacteria
- Guar gum reduces oral penicillin's bioavailability when taken at the same time
- Methotrexate penicillin has been reported to increase methotrexate toxicity in some cases, possibly by competing for renal tubular secretion

PENTAMIDINE

Usual Dose

Adult: Treatment: 4 mg/kg daily IV (UWHC cost/day \$47.50). Prophylaxis: 300 mg Q 3-4 weeks by inhalation (UWHC cost/day \$50.90). Weekly IV prophylaxis is NOT effective. *Pediatric*:** 4 mg/kg/day IV Q24H. By inhalation: in children <5 years 8 mg/kg, in children >5 years 300 mg Q 3-4 weeks.

Indications

1. Pneumocystis jiroveci infections - treatment (IV) or prophylaxis (aerosol).

Comments

Aerosolized pentamidine is inferior to TMP/SMZ or other systemic regimens for prophylaxis of PJP. To increase patient tolerance and efficacy of the aerosolized treatment, consider administering two puffs of an inhaled bronchodilator (e.g., albuterol) prior to pentamidine doses. Pentamidine by inhalation should be administered in rooms with negative airflow. Patients receiving pentamidine IV should have glucose monitored frequently and creatinine levels monitored daily. Consider obtaining Infectious Disease assistance if intending to use IV pentamidine.

PIPERACILLIN

Usual Dose

Adult: Mild/moderate infections or empiric therapy 4 g Q6H IV (UWHC cost/day \$51.32). Documented *P aeruginosa* or life-threatening infections 3 g Q4H IV or 4 g Q6H IV (UWHC cost/day \$51.38-57.73). *Pediatric*:** 200-300 mg/kg/day IV in divided doses Q4-6H.

Indications

1. Treatment of Pseudomonas aeruginosa (in combination with an aminoglycoside or fluoroquinolone).

2. Empiric therapy of febrile neutropenic patients (always in combination with an aminoglycoside or anti-staphylococcal beta-lactam antibiotic).

3. For enterococcal coverage when additional broad-spectrum Gram-negative coverage is needed.

Comments

Dose adjustment required for renal impairment. See renal dosing guideline on uconnect.

Piperacillin is not effective against *S aureus*. Some clinicians have noted piperacillin has a higher incidence of neutropenia compared with other extended-spectrum penicillins but produces less platelet dysfunction than ticarcillin. Piperacillin has a higher incidence of hypersensitivity reactions in cystic fibrosis patients. Each gram of piperacillin contains 1.85 mEq sodium.

Drug Interactions

- Aminoglycosides inactivated by penicillins in admixtures when penicillin: AG ratio is 50:1 or higher
- · Vecuronium piperacillin has caused cases of enhanced neuromuscular blockade
- Live typhoid vaccine decreased efficacy; wait 24 hours after end of therapy to give vaccine

PIPERACILLIN/TAZOBACTAM (Zosyn[®]) Usual Dose

Adult. 2.25 to 3.375 Q4-6H or 4.5g Q6-8H IV (UWHC cost/day \$26.60-53.24). *Pediatric*:** 150-400 mg of piperacillin component/kg/day IV in divided doses Q4-8H

Indications

- 1. Multiply-resistant Gram-negative infections at various sites.
- 2. Multiply-resistant, mixed polymicrobial infections that include anaerobes.
- 3. Enterococcal infections when ampicillin will not suffice.
- 4. Polymicrobial infections with *P aeruginosa* and *S aureus*, (e.g., in cystic fibrosis patients).
- 5. Neutropenic fever.
- 6. Empiric therapy of patients with suspected drug-resistant bacterial infections, including hospital-acquired pneumonia.

Comments

All doses *except* the first dose are given as prolonged infusion. The first dose is given over 30 minutes to rapidly achieve therapeutic concentrations. Excusion criteria: patients receiving CVVH and patients treated for meningitis. Cystic fibrosis patients may receive prolonged infusion, but are not limited to lower doses specified in the prolonged infusion guideline. Dose adjustment required for renal impairment. See renal dosing guideline on uconnect.

NOTE: Other combination antibiotics base their dose either on one component (e.g. Primaxin[®]) or both components (e.g. trimethoprim/sulfamethoxazole). Zosyn[®] labeling states the dose (3.375 g) by adding the two components of piperacillin (3 g) plus tazobactam (375 mg). Zosyn[®] should be used with an aminoglycoside or ciprofloxacin for the treatment of *P aeruginosa* infections. For documented serious *Pseudomonas* infections, 3.375 g Q4H or 4.5 g Q6H IV is recommended. For intra-abdominal infections, 3.375 g IV Q6H is equivalent to 4.5 g Q8H. Zosyn[®] contains 2.35 mEq (54 mg) of sodium per gram of piperacillin. Given as extended-infusion therapy in some ICUs. Tazobactam is important for enhanced anaerobic activity, but **piperacillin/tazobactam should not be relied upon for serious oxacillin-sensitive** *S. aureus* **infections**.

Drug Interactions

- Aminoglycosides inactivated by penicillins in admixtures when penicillin: AG ratio is 50:1 or higher
- Vecuronium piperacillin has caused cases of enhanced neuromuscular blockade
- Live typhoid vaccine decreased efficacy; wait 24 hours after end of therapy to give vaccine

POSACONAZOLE

Infectious Disease approval required for all use of posaconazole outside HEM/BMT standard procedures (See Appendix I)

Usual Dose

Adult: 200 mg Q8H-Q6H PO (UWHC cost/day \$82.28-\$109.20) Prophylaxis 200 mg PO TID; Therapeutic 200mg PO Q6H *Pediatric:* Safety and efficacy not established in children under age 13

Indications

- 1. Candidiasis prophylaxis in prolonged neutropenia
- 2. Treatment of invasive fungal infections caused by resistant pathogens

Comments

Food and/or acid is required for the absorption of posaconazole; 15 grams of fat are necessary for maximal absorption of a dose. A meal, nutritional supplement shake or serving of ice cream should be provided with each dose. Ideally, PPI acid suppressants should be avoided, or another class, i.e., histamine H_2 -blockers, substituted to maximize absorption. Jacqueline Sullivan, RD, kindly provided the following list of fat content in Room Service foods and supplements:

- 2 cartons whole milk = 16 g
- 2 1 oz slices cheese = 15 g
- 2 packets (2 Tbsp.) peanut butter = 15 g
- 1 Tbsp. cooking oil or olive oil = 14 g
- 4 pats butter = 16 g
- 1 croissant = 19 g
- 1 serving brownie = 22 g
- 1 serving cherry pie = 14 g
- 1 serving apple cinnamon coffee cake = 23 g
- 1 package brown sugar Pop-Tart = 14 g
- 1 chocolate chip cookie = 10 g

- 1 serving French fries = 19 g
- 1 serving cheeseburger = >15 g
- 1 serving hot dog = > 15 g
- 1 serving fried chicken breast sandwich = > 15g
- 1 serving Ensure Plus (240 mL) = 11 g
- 1 serving Magic Cup = 11 g
- 1 serving Scandishake (240 mL) = 31 g
- 1 serving Ensure High Protein (240 mL) = 6 g
- 1 serving Enlive = 0 g

Drug Interactions

Posaconazole is an inhibitor of CYP3A4; concomitant administration of other CYP3A4 substrates may result in increased plasma levels of those drugs, leading to adverse reactions. The following list of drugs are CYP3A4 substrates that may cause QT interval prolongation and potentially torsades de pointes when serum levels are increased, thus concomitant administration with posaconazole is contraindicated:

- astemizole
- cisapride
- halofantrine
- pimozide
- quinidine
- terfenadine

The following drugs may have their levels increased by CYP3A4 inhibition with posaconazole; there is the potential for increased toxicity so caution and increased vigilance are indicated:

- Amlodipine
- Atazanavir
- Cyclosporine
- Diltiazem
- Ergot alkaloids
- Etravirine
- Everolimus

- Felodipine
- Lercanidipine
- Midazolam
- Nifedipine
- Nisoldipine
- Nitrendipine
- Phenytoin

- Rifabutin
- Ritonavir
- Sirolimus
- Tacrolimus
- Verapamil
- Vinca alkaloids

The following drugs decrease serum levels of posaconazole when administered concurrently:

- Efavirenz induces glucuronidation elimination pathway
- Metoclopramide due to decreased GI motility
- Phenytoin induces metabolism
- Rifabutin induces metabolism

Miscellaneous drug interactions with posaconazole are as follows:

- Digoxin increased digoxin serum levels with concurrent administration
- Topiramate increased topiramate serum levels with concurrent administration

PRIMAQUINE

Usual Dose

Adult: Malaria treatment: 15 mg base Q24H PO X 14 days (UWHC cost/day \$1.21) **or** 45 mg base once a week PO X 8 weeks (UWHC cost/dose \$3.63).

Malaria prophylaxis: 30 mg base PO Q24H beginning 1 day before departure and continuing for 7 days after leaving malarious area (UWHC cost/day \$2.42).

Pneumocystis jiroveci treatment: 30 mg base Q24H PO X 21 days.

Pediatric: Malaria treatment: 0.3 mg/kg/day PO X 14 days.

Malaria prophylaxis: 0.5 mg base Q24H PO beginning 1 day before departure and continuing for 7 days after leaving malarious area.

Indications

1. Malaria treatment.

2. Malaria prophylaxis.

3. *Pneumocystis jiroveci* treatment in combination with clindamycin in patients intolerant to conventional therapy.

Comments

Primaquine is contraindicated in pregnancy. Screen for G-6-PD status before initiating therapy. A 26.3 mg primaquine phosphate tablet equals 15 mg primaquine base.

Drug Interactions

- Aurothioglucose –increased risk of blood dyscrasias with concurrent administration
- Levomethadyl increased risk of QT prolongation, torsades de pointes or cardiac arrest with concurrent administration
- Grapefruit juice increases C_{max} and AUC of primaquine by approximately 20%

Primaxin[®] - see imipenem/cilastatin.

QUINUPRISTIN/DALFOPRISTIN (Synercid[®]) – nonformulary at UWHC. Infectious Disease approval is required for all use of Synercid[®] (See Appendix I) Usual Dose

Adult. 7.5 mg/kg IV Q 8-12 hours (UWHC cost/day \$348.65-523.03).

Indications

1. Symptomatic, laboratory-documented deep infections with vancomycin-resistant (MIC > 16 mcg/mL) *Enterococcus faecium* (not *faecalis*) in patients who are unable to tolerate or are treatment failures on linezolid or daptomycin. The presence of infection is indicated by positive blood cultures or deep cultures from an intra-abdominal or deep surgical wound specimen or bile, or a complicated urinary tract infection, associated with fever, leukocytosis, or other signs of deep infection (use Q8H dosing).

2. Laboratory-documented methicillin-resistant *Staphylococcus aureus* in a patient unable to tolerate vancomycin or refractory to parenteral therapy with vancomycin, with or without rifampin or other drugs or in a patient who is unable to tolerate or is a treatment failure on linezolid or daptomycin (use Q12H dosing).

Comments

Each dose should be infused over at least 60 minutes. Doses diluted in at least 250 mL D5W may be infused via peripheral or central line. If the patient is fluid-restricted, the volume may be decreased to 100 mL and infused via central line only. After completing infusion of the dose, flush the line with D5W. Heparin or saline flushes should not be used. Myalgia/arthralgia syndrome may be a dose-limiting side effect. Quinupristin/dalfopristin is usually a third-line agent behind linezolid and daptomycin.

Drug Interactions

Quinupristin/dalfopristin is a potent cytochrome P450 3A4 isoenzyme inhibitor and is likely to cause increases in serum level and AUC of most drugs that are metabolized through this pathway. The potential for increased toxicity exists. Caution and increased vigilance are indicated when concurrently administering such a drug if it has serious toxicities.

RALTEGRAVIR (Isentress®) – nonformulary at UWHC

For up-to-date information on the use of antiretrovirals, consult an HIV expert or www.aidsinfo.nih.gov/

RIBAVIRIN – capsules are nonformulary at UWHC

Usual Dose

Adult: (average of 1.1 g/day) 6 g in 300 mL sterile water aerosolized (UWHC cost/day \$4,196.64). Hepatitis C (200 mg capsules in combination with interferon alfa). If \leq 75 kg 800 mg PO per day in 2 divided doses. If > 75 kg 1200 mg PO per day in 2 divided doses. (UWHC cost/day \$1.36-2.04). Capsules may be effective for RSV in adults at a dose of 1800 mg/day.

Indications

1. Respiratory syncytial virus infections - may be considered for use in treating:

a. infants at high risk for severe or complicated RSV infection, i.e., infants with congenital heart disease, bronchopulmonary dysplasia, other chronic lung conditions, immunodeficiency, recent transplants, cancer chemotherapy and selected premature infants.

b infants with lower respiratory tract infections who are severely ill

c. infants who are not initially that ill, but who are at increased risk for progressively severe disease, e.g., the very young (<6 weeks), those with multiple congenital abnormalities, neurologic or metabolic diseases.

d. immunocompromised adults. Oral formulation may be as effective as aerosolized.

2. Hantavirus, Korean Hantaan virus, Lassa Fever virus and other susceptible viruses causing hemorrhagic fever syndrome. Use intravenous form (see Comments).

3. RSV life-threatening pneumonia.

4. Hepatitis C infection. Use oral form in combination with PEG-interferon. Duration of treatment is typically 6-12 months.

Comments

Duration of therapy for inhalation is 3 to 5 days. Because of concerns regarding environmental exposure to aerosolized ribavirin, refer to the Respiratory Therapy Ribavirin Policy and Procedure #2:29. The drug must be administered via a Small Particle Aerosol Generator (SPAG-2). Although the product information warns that ribavirin aerosol should not be used in infants requiring assisted ventilation because precipitation of the drug in the respiratory equipment may interfere with ventilation, Respiratory Therapy has solved the problem by using high efficiency hydrophobic filtration of the exhalation circuitry of the ventilator. Also, Respiratory Therapy scavenges into wall suction all excess ribavirin that is administered regardless of the mode of administration. For suspected or overwhelming cases of RSV or Hantavirus infection, consult the Infectious Disease Section for specific recommendations. Intravenous ribavirin is available only through compassionate use protocols. For assistance in obtaining a supply of the drug contact the Pharmaceutical Research Center (pager #2717). Dose adjust oral capsules in patients with renal dysfunction. Dose reductions are recommended in patients with decreasing hemoglobin levels; in patients with no cardiac history, decrease oral dose to 600 mg/day (200 mg AM/400 mg PM) when hemoglobin <10 g/dL and discontinue ribavirin when hemoglobin goes below 8.5 g/dL. In patients with a cardiac history, decrease dose to 600 mg/day when hemoglobin decreases by 2 g/dL during any 4-week treatment period; discontinue ribavirin when hemoglobin <12 g/dL.

Drug Interactions

Ribavirin has a number of serious interactions with non-nucleoside analogues, as follows:

- Abacavir lactic acidosis, fatal and nonfatal
- Didanosine lactic acidosis, fatal and nonfatal; increased mitochondrial toxicity; peripheral neuropathy; pancreatitis
- Lamivudine lactic acidosis, fatal and nonfatal; hepatic decompensation
- Stavudine lactic acidosis, fatal and nonfatal; decreased stavudine efficacy
- Zalcitabine lactic acidosis, fatal and nonfatal
- Zidovudine lactic acidosis, fatal and nonfatal; hepatic decompensation; decreased zidovudine efficacy; neutropenia

Other drug interactions with ribavirin:

- Azathioprine increased azathioprine-related myelotoxicity due to decreased clearance
- Interferon alfa-2B increased severity of neuropsychiatric symptoms (depression, anger and hostility)

RIFABUTIN

Usual Dose

Adult (150 mg capsules): Prophylaxis 300 mg Q24H PO (UWHC cost/day \$22.07). Treatment 150-450 mg Q24H PO (UWHC cost/day \$11.03-33.10).

Indications

1. Mycobacterium avium complex

a. prophylaxis in AIDS patients with CD4 cell counts <100 cells/mm³. Third-line after azithromycin and clarithromycin due to potential for multiple drug interactions.

b. treatment - as part of a multi-drug regimen

2. Mycobacterium tuberculosis in HIV infected individuals who require protease inhibitor or non-nucleoside reverse transcriptase inhibitor therapy.

Comments

Side effects similar in type and incidence to rifampin. Side effects are less with the doses used for prophylaxis. Uveitis has been reported in patients receiving rifabutin therapy (600 mg/day, NEJM 1994;330:438-9). Although prophylaxis reduces the incidence of MAC infections, its use has not been associated with prolonged survival. In HIV- positive patients requiring tuberculosis and antiretroviral therapy, consult Infectious Diseases for dose adjustments. Use as single agent may lead to rifabutin/rifampin resistance.

Drug Interactions

Rifabutin, like all rifamycins, induces cytochrome P450 enzymes in the liver and uridine 5-diphosphate transferases. However, its effects are not as potent as rifampin, and interacting drugs may be stronger inhibitors, resulting in increases in rifabutin blood levels and potentially increasing its toxicity. With some drugs, both effects may be seen. The following drugs have blood levels reduced by rifabutin as a result of induction of metabolic enzymes:

- Atovaguone
- Indinavir Irinotecan (& active metabolite) •
- Clarithromycin Cyclosporine
- Dapsone Dasatanib

Delavirdine

Efavirenz

• Erlotinib

• Etravirine

• Everolimus

- Itraconazole Ixabepilone
- Lapatinib
- Maraviroc
- Nelfinavir
- Nilotinib
- - Posaconazole
- Ranolazine*

- Romidepsin
- Saguinavir
- Sirolimus
- Sunitinib
- Tacrolimus
- Temsirolimus (\downarrow levels of active metabolite)
- Tolvaptan
- Trimetrexate
- Voriconazole*
- Warfarin
- Zidovudine

 Imatinib * - indicates drug is contraindicated to administer concurrently with rifabutin

The following drugs may increase blood levels of rifabutin and also increase the risk of rifabutin toxicity:

Fluconazole

• Indinavir

Lopinavir

• Fosamprenavir

- Amprenavir/Fosamprenavir
- Atazanavir
- Azithromycin
- Clarithromycin
- Darunavir
- Delavirdine
 - Nelfinavir - indicates drug is contraindicated to administer concurrently with rifabutin

Rifabutin also interacts with sulfamethoxazole to increase exposure to the toxic sulfamethoxazole hydroxylamine metabolite, increasing the risk of rash, thrombocytopenia, leukopenia and liver enzyme increases.

• Didanosine (buffered powder)

- Nevirapine
 - Posaconazole
 - Ritonavir
 - Tipranivir
 - Voriconazole*

- Oral Contraceptives

RIFAMPIN

Use of rifampin *for injection* requires Infectious Diseases approval (See Appendix I) Usual Dose

Adult: 600 mg Q12-24H PO/IV (UWHC cost/day PO \$1.94-3.88; IV \$36.72-73.44);

Endocarditis: 300 mg PO/IV TID (UWHV cost/day PO \$2.91; IV \$55.08)

IV formulation requires ID approval.

Pediatric:** Treatment 10-20 mg/kg/day PO/IV in divided doses Q12-24H.

Indications

1. Active tuberculosis, always as part of a multiple drug regimen.

2. Latent tuberculosis infection treatment, in combination with pyrazinamide (treat for 2 months). Not currently recommended by CDC.

3. Meningococcal prophylaxis, in persons with close exposure to *Neisseria meningitidis*. (600 mg BID PO x two days). Second-line therapy.

4. Methicillin-resistant coagulase-negative *Staphylococcus* valvular endocarditis or CNS shunt infections, in combination with vancomycin and gentamicin.

5. *Haemophilus influenzae* meningitis prophylaxis. Drug of choice in pediatrics, second-line agent in adults. Drug of choice in adults is ciprofloxacin.

Dosing in adults: 600 mg daily PO x four doses.

Dosing in children: (>1 month) 20 mg/kg/day PO x 4 doses (maximum 600 mg daily)

Dosing in patients <1 month: 10 mg/kg/day PO x four doses.

6. Leprosy as part of a multiple drug regimen.

7. Staphylococcal osteomyelitis and prosthetic valve endocarditis infection, in combination with a beta-lactam or quinolone.

8 Complicated methicillin-resistant staphylococcal infection, in combination with vancomycin.

9. MRSA decontamination given in combination with TMP/SMX or minocycline.

Comments

Rifampin discolors (orange) the urine, stools, saliva, sweat, sputum and tears. Soft contact lenses may be permanently discolored. Rifampin, especially for the therapy of TB, should be taken on an empty stomach unless stomach upset occurs. This is less critical for secondary indications. Hepatotoxicity has been associated with long-term rifampin therapy; liver function tests should be monitored. MRSA decolonization with rifampin should not be routinely attempted; the Infectious Disease service should be consulted. Rifampin should not be used as single agent for the treatment of infection; it may be used as a single agent for prophylaxis. Infectious Disease approval is required for the intravenous dosage form (See Appendix I). See IV-to-PO conversion policy (Appendix F) or on uconnect.

Drug Interactions

Rifampin is a potent inducer of cytochrome P450 isoenzymes, uridine 5-diphosphate transferases and p-glycoprotein, and as such has the potential for interacting with many drugs/drug classes, including, but not limited to those listed below. Concurrent administration of rifampin with these drugs results in reduced serum levels and AUC and potentially loss of efficacy. If concurrent use cannot be avoided, increase monitoring of efficacy and serum levels where appropriate; consider increasing the dose of the interacting drug. Remember to adjust the dose back down when rifampin is discontinued. An asterisk (*) next to the drug name indicates that it is **contraindicated** to administer rifampin concurrently with the drug.

- Ambrisentan
- Amiodarone
- Azole Antifungals
- BCG
- Bexarotene
- Bortezomib
- Buprenorphine
- Buspirone
- Carvedilol
- Caspofungin

- Fosamprenavir*/Amprenavir
- Gadoxetate
- Gefitinib
- Glimepiride
- Glyburide
- Haloperidol
- HMG-CoA reductase inhibitors
- Lamotrigine
- Lapatinib

- Praziquantel
- Propafenone
- Propranolol
- Quetiapine
- Quinidine
- Quinine
- Raltegravir
- Ramelteon
- Ranolazine*
- Repaglinide

- Chloramphenicol
- Chlorpropamide
- Citalopram
- Clofibrate
- Clozapine
- Corticosteroids
- Cyclosporine
- Dapsone
- Darunavir*
- Dasatinib
- Deferasirox
- Delavirdine
- Diazepam
- Digoxin
- Diltiazem
- Disopyramide
- Doxycycline
- Dronaderone
- Efavirenz
- Erlotinib
- Estazolam
- Eszopiclone
- Estrogens
- Etravirine
- Everolimus
- Fentanyl
- Fesoterodine

- Leflunomide
- Levothyroxine
- Linezolid
- Lopinavir*
- Lorcainide
- Losartan
- Maraviroc
- Medroxyprogesterone
- Mefloquine
- Methadone
- Metoprolol
- Mexiletine
- Midazolam
- Mifepristone
- Monteleukast
- Morphine
- Moxifloxacin
- Mycophenolate
- Nelfinavir
- Nevirapine
- Nifedipine
- Nilotinib
- Nisoldipine
- Oral Contraceptives
- Oxycodone
- Pazopanib
- Pioglitazone

- Saquinavir*
- Sertraline
- Sirolimus
- Sorafenib
- Sunitinib
- Tacrolimus
- Tadalafil
- Tamoxifen
- Telithromycin
- Temsirolimus
- Terbinafine
- Theophylline
- Tinidazole
- Tipranivir*
- Tocainide
- Tolbutamide
- Tolvaptan
- Tramadol
- Triazolam
- Trimetrexate
- Valproic acid
- Verapamil
- Voriconazole*
- Warfarin
- Zaleplon
- Zidovudine
- Zolpidem

Miscellaneous drug interactions with rifampin are as follows:

- Bosentan trough level is initially increased, then at steady state blood levels are decreased
- Carbamazepine rifampin may inhibit its metabolism, resulting in increased blood levels
- Eltrombopag is an OATP1B1 inhibitor that is in turn inhibited by rifampin; concurrent administration of an OATP1B1 substrate results (for example, rosuvastatin) results in increased blood levels of the substrate
- Enalapril decreased efficacy due to increased clearance of active metabolite
- Entacapone increased blood levels due to interference with biliary secretion
- Ethionamide increased risk of hepatotoxicity
- · Levomethadyl increased risk of QT prolongation, torsades de pointes
- Probenecid increases rifampin blood levels
- Valsartan increased blood levels due to OATP1B1 inhibition by rifampin

RIFAXIMIN (Xifaxan[®]) Usual dose Adult: 200-400 mg Q8H PO (UWHC cost/day \$24.06-48.12)

Indications

- 1. Travelers' diarrhea.
- 2. Reduction of the risk of recurrence of overt hepatic encephalopathy (NOT approved for treatment)

Comments

In the limited studies that have been done with Rifaximin in the reduction of the risk of recurrence of overt hepatic encephalopathy, the most effective dose was found to be 600 mg Q12H. However, it was not possible to manufacture a tablet this large; the largest tablet that could be manufactured was a 550 mg tablet. This was the tablet that was used in the pivotal trial for FDA approval for the hepatic encephalopathy indication, but this dose is not the optimal dose for this indication.

RITONAVIR

For up-to-date information on the use of antiretrovirals, consult an HIV expert or www.aidsinfo.nih.gov/

SAQUINAVIR

For up-to-date information on the use of antiretrovirals, consult an HIV expert or www.aidsinfo.nih.gov/

SPECTINOMYCIN

No longer available in the U.S.

STAVUDINE

For up-to-date information on the use of antiretrovirals, consult an HIV expert or www.aidsinfo.nih.gov/

STREPTOMYCIN

Usual Dose

Adult: 15 mg/kg/day (max 1 g) or 20-40 mg/kg (max 1.5 g) two or three times per week IM (UWHC cost/day \$10.15-15.22).

Indications

1. *Mycobacterium tuberculosis* – initial treatment in combination with isoniazid, rifampin and pyrazinamide in situations where ethambutol is contraindicated or ineffective (see Appendix E).

Streptococcal or enterococcal endocarditis caused by high-level gentamicin-resistant but streptomycin-sensitive strains.
 Plague, tularemia, or brucellosis.

Comments

Monitor serum drug levels (test must be sent out). Use extreme caution and reduce dose when prescribing for patients with renal insufficiency.

SULFADIAZINE

Usual Dose

Adult. Load 2-4 g PO; Maintenance 500 mg-2 g Q6H PO (UWHC cost/day \$7.40-29.62). Pediatric:** 120 - 150 mg/kg/day PO in divided doses Q4-6H.

Indications

1. Toxoplasmosis - treatment of choice. Use in combination with pyrimethamine (1-1.5 g Q6H PO for 3-6 weeks, then 1 g BID PO for maintenance dosing).

Comments

Sulfadiazine is not recommended for use in infants less than 2 months of age with the exception of congenital toxoplasmosis treatment (in combination with pyrimethamine) where the benefit might exceed the risk. Do not confuse with sulfasalazine.

SULFISOXAZOLE

No longer available as a single entity.

TELAVANCIN (Vibatif[®])- requires ID approval for all use **Usual Dose**

Adult: 10 mg/kg Q24H IV (UWHC cost/day 139.34) Pediatric: Not indicated for use in children

Indications

- Complicated skin and skin structure infections due to MSSA, MRSA, streptococcal species and vancomycin-1.
- susceptible enterococci.

Comments

Telavancin is a vancomycin derivative, and may produce similar infusion reactions (histamine-like reactions) as vancomycin. At least 10% of patients will experience nausea, vomiting, taste disturbances and/or foamy urine. Telavancin interferes with the laboratory tests used to evaluate clotting times; the actual clotting times are not affected. but the test results are affected. Blood samples for these tests should be drawn just prior to a dose for the least interference. Due to animal studies suggesting fetal harm, telavancin must not be given to pregnant women (Black box warning). A patient drug monograph (PDM) should be provided to each patient at the start of therapy. Dose adjustment required in renal insufficiency. See renal dosing guideline on uconnect.

Drug Interactions

Telavancin prolongs the QT interval. This effect is more pronounced when it is given with other drugs that also prolong the QT interval. The following is a list of drugs that interact with telavancin to prolong the QT interval; an asterisk (*) indicates that the drug is contraindicated to administer at the same time as telavancin.

- Amiodarone
- Arsenic Trioxide
- Asenapine
- Astemizole
- Bepridil
- Cisapride
- Dasatinib
- Dofetilide
- Dronaderone
- Droperidol
- Fluconazole
- Gatifloxacin
- Halofantrine

- Haloperidol • Ibutilide
- Iloperidone
- Lapatinib
- Levofloxacin
- Levomethadyl
- Lumefantrine
- Mesoridazine
- Methadone
- Nilotinib
- Paliperidone
- Pimozide
- Quinidine

- Ranolazine • Sodium Phosphate
- Sparfloxacin
- Sunitinib
- Telithromycin
- Tetrabenazine
- Thioridazine

TELBIVUDINE (Tyzeka[®]) – Non-formulary at UWHC

For up-to-date information on the use of antiretrovirals, consult an HIV expert or www.aidsinfo.nih.gov/

- - Vardenafil
 - Voriconazole
 - Ziprasidone

Sotalol

TELITHROMYCIN

Usual Dose

Adult: 800 mg Q24H PO (UWHC cost/day \$9.26)

Indications

1.Community-acquired pneumonia of mild-to-moderate severity caused by proven or highly suspected multidrug-resistant *S pneumoniae*

Comments

Telithromycin may only be used where penicillin or macrolide-resistant pneumococci are suspected as infectious agents.

Drug Interactions

Telithromycin inhibits the CYP450 3A4 enzyme, causing many drug-drug interactions with other drugs that are metabolized by that enzyme system. The use of telithromycin is contraindicated in patients taking pimozide or cisapride. Serum levels of statin drugs, digoxin, theophylline and alprazolam may become elevated with concomitant use of telithromycin. Itraconazole and ketoconazole increase serum levels of telithromycin. Concomitant administration of rifampin significantly decreases serum levels of telithromycin. Several cases of severe liver toxicity have been reported in patients taking telithromycin, which led the FDA to retract all but one indication for use in 2007.

TENOFOVIR

Also a component of the combination product Truvada[®]. For up-to-date information on the use of antiretrovirals, consult an HIV expert or <u>www.aidsinfo.nih.gov/</u>

TENOFOVIR/EMTRICITABINE (Truvada®) – non-formulary at UWHC

For up-to-date information on the use of antiretrovirals, consult an HIV expert or <u>www.aidsinfo.nih.gov/</u> Please verify the indication for use; continuation of pre-exposure prophylaxis for inpatients may not be appropriate.

TETRACYCLINE

Usual Dose

Adult: 250-500 mg Q6H PO OR 500 mg Q12H PO (UWHC cost/day \$0.10-0.21). Pediatric:** 25-50 mg/kg/day PO in divided doses Q6H (not for children <8 years).

Indications

1. Mycoplasma pneumoniae or Chlamydia pneumoniae atypical pneumonia - alternative to erythromycin and doxycycline

- 2. Chlamydia trachomatis infections, uncomplicated, in adults.
- 3. Brucellosis and bartonellosis drug of choice
- 4. Rickettsial infections (e.g. Rocky Mountain spotted fever, Q fever).
- 5. Prophylaxis and treatment of chronic bronchitis acute exacerbations as an alternative to doxycycline.
- 6. Lyme disease in adults and children 8 years or older.

7. Alternative to mefloquine for malaria chemoprophylaxis in areas where chloroquine-resistant *Plasmodium falciparum* is prevalent. Tetracycline and doxycycline are the only available drugs for drug-resistant malaria in Thailand because mefloquine resistance has been found.

8. Plague and tularemia. Alternative to streptomycin for treatment. May be used for prophylaxis in selected patients.

9. Balantidium coli infections - drug of choice.

- 10. Inflammatory acne alternative to oral erythromycin or oral doxycycline.
- 11. *H pylori* infection alternative to amoxicillin or doxycycline.
- 12. Ehrlichiosis alternative to doxycycline.

Comments

Tetracycline can cause discoloration of the permanent teeth and should not be used during the last half of pregnancy, nor in children < 8 years old.

Drug Interactions; Dairy products and antacids will impair the absorption of tetracycline if they are taken less than 2 hours apart. Tetracycline in combination with warfarin causes increased anticoagulation.

TICARCILLIN/CLAVULANATE (Timentin®)

Usual Dose

Adult: 3.1 g Q4-6H IV (UWHC cost/day \$40.70-61.05).

Pediatric:** 200-400 mg of ticarcillin component/kg/day IV in divided doses Q4-6H.

Indications

- 1. Stenotrophomonas maltophilia, second-line agent for sulfa-allergic patients or for TMP/SMZ-resistant strains.
- 2. Intraabdominal infections caused by healthcare associated organisms.

Comments

Dose adjustment required for renal impairment. See renal dosing guideline on uconnect.

NOTE: Other combination antibiotics base their dose either on one component (e.g. Primaxin[®]) or both components (e.g. trimethoprim/sulfamethoxazole). Timentin[®] labeling states the dose (3.1 g) by adding the two components of ticarcillin (3 g) plus clavulanate. Ticarcillin is not effective against most strains of *S aureus* and, unlike piperacillin, is ineffective against *Enterococcus*. Ticarcillin may have less toxicity (neutropenia, drug fever or rash) than piperacillin. Ticarcillin has higher MICs than, but equivalent efficacy to, piperacillin. Not recommended for use in pregnancy. Each gram of ticarcillin contains 5.2-6.5 mEq sodium.

TIGECYCLINE

Infectious Disease approval is required for use of tigecycline (see Appendix I). Usual Dose

Adult: Initial dose of 100 mg IV followed by 50 mg Q12H IV (UWHC cost/day \$120.31)

Indications

- 1. Complicated skin and skin structure infections caused by susceptible strains of *Escherichia coli*, *Enterococcus faecalis* (vancomycin susceptible isolates), methicillin-sensitive *Staphylococcus aureus*, methicillin-resistant *S. aureus*, *Streptococcus agalactiae*, the *Streptococcus anginosus* group, *Streptococcus pyogenes* and *Bacteroides fragilis*
- 2. Complicated intra-abdominal infections caused by susceptible strains of *Citrobacter freundii*, *Enterobacter cloacae*, *E. coli*, *Klebsiella oxytoca*, *Klebsiella pneumoniae*, *E. faecalis* (vancomycin susceptible isolates), methicillin-susceptible *S. aureus*, *S. anginosus* group, *B. fragilis*, *Bacteroides thetaiotamicron*, *Bacteroides uniformis*, *Bacteroides vulgatus*, *Clostridium perfringens* and *Peptostreptococcus micros*.
- 3. Alternative for community-acquired pneumonia in patients highly allergic to beta lactams and fluoroquinolones.

Comments

Nausea and vomiting occur frequently with the use of tigecycline. Tigecycline should not ordinarily be used to treat infections caused solely by gram-positive infections because there are other effective choices for most gram-positive organisms, but instead should be reserved for use against resistant gram-negative bacteria, especially in the ICU, or in mixed infections where there are resistant microorganisms.

Drug Interactions

Tigecycline causes a decrease in the clearance of R-warfarin and S-warfarin and increases the C_{max} of both isomers, although prolongation of INR was not observed. Nevertheless, increased monitoring of anticoagulation times is warranted when the drugs are administered concomitantly.

TIMENTIN® - see ticarcillin/clavulanate

TIPRANAVIR (Aptivus®) – Nonformulary at UWHC

For up-to-date information on the use of antiretrovirals, consult an HIV expert or <u>www.aidsinfo.nih.gov/</u> **Black Box Warning:** Hepatic decompensation and clinical hepatitis, occasionally with fatal outcomes, have been associated with the use of tipranavir. Fatal and nonfatal intracranial hemorrhages have been reported with tipranavir.

TOBRAMYCIN

Usual Dose

Adult: 2.5 mg/kg Q12H IV/IM OR 5 mg/kg Q24H IV/IM OR 1.5 mg/kg Q8H IV OR 7 mg/kg Q24H IV [in VAP] (UWHC cost/day \$3.75-5.84).

Urinary tract infections 1-3 mg/kg daily IV/IM.

TOBI nebulizer solution 300 mg Q12H

Pediatric:** 3-6 mg/kg/day in divided doses Q8H (cystic fibrosis 7-10 mg/kg/day).

Note: Dose using IBW. For obese patients (BMI>30 kg/m²) use a dosing weight (DW) = 0.4 (ABW-IBW) + IBW. (IBW=Ideal Body Weight; ABW=Actual Body Weight)

Indications

- 1. Pseudomonas aeruginosa infections (use with an anti-pseudomonal beta-lactam).
- 2. Pseudomonas aeruginosa bronchitis, bronchiectasis or pneumonia in cystic fibrosis patients.

3. Gram-negative organisms with documented or suspected gentamicin resistance where susceptibility to tobramycin is known or considered likely.

- 4. Serious urinary tract infections as monotherapy.
- 5. Febrile neutropenia in combination with a beta-lactam.

Comments

Tobramycin has superior activity to gentamicin against *P aeruginosa*, but is less active against other Gram-negative bacilli. Tobramycin may be marginally less nephrotoxic and ototoxic than gentamicin. In cystic fibrosis patients with normal renal function, the initial dose for tobramycin is 10 mg/kg given once daily or divided into two to three doses. Further dose adjustments may be based upon serum levels. For extended-interval (Q24H) dosing draw midpoint level 8 - 12 H after the start of infusion. For Q12H dosing draw peak and trough (peak: 30 minutes after the end of either a 30 minute or 60 minute infusion; trough: 15-30 minutes prior to next dose). Note: The dose listed for urinary tract infections assumes the patient does not have systemic inflammatory response syndrome. The unit pharmacist will assist in pharmacokinetic dosing. With Q12 to 24 hour dosing blood level monitoring is needed only for patients with compromised renal function or patients with rapid clearances, e.g., burn patients. Clearance into urine is poor with creatinine clearance < 15 mL/min. **Aminoglycosides must be used with caution in patients with renal insufficiency, cirrhosis with ascites or patients who have been on cisplatin within the last 21 days, all because of the increased risk of nephrotoxicity.**

If susceptibility testing indicates susceptibility to gentamicin, except for *Pseudomonas* infections, changing from tobramycin to gentamicin may result in a significant cost savings.

TRIMETHOPRIM

Usual Dose

Adult: PJP treatment 20 mg/kg/day PO (UWHC cost/day \$2.96). *Pediatric*:** 4 mg/kg/day PO in divided doses Q12H.

Indications

1. Pneumocystis jiroveci pneumonia treatment in combination with dapsone (third-line therapy).

TRIMETHOPRIM/SULFAMETHOXAZOLE

Usual Dose

Adult: 8-10 mg TMP/40-50 mg SMX /kg/day in 3-4 divided doses IV (UWHC cost/day \$10.21-12.76) including skin infections with MRSA. For PJP 15-20 mg/kg/day of TMP component in 3-4 divided doses. Dose for prostatitis and UTI may be 160 mg/800 mg orally twice daily. (UWHC cost/day \$0.11) For PJP prophylaxis, give one double-strength tablet 3 times/week - once daily. (UWHC cost/day \$0.06)

Pediatric:** 6-12 mg TMP/30-60 mg SMX/kg/day in divided doses IV Q6H, PO Q12H

Indications

1. Uncomplicated urinary tract infection, including acute prostatitis, caused by susceptible strains of *E coli*, *P mirabilis* and *Klebsiella* spp.

2. Recurrent urinary tract infection prophylaxis.

3. *Pneumocystis jiroveci* pneumonia, as the drug of first choice (15-20 mg TMP/kg/day; 75-100 mg/kg/day divided Q6H IV). Rash or hematologic toxicity is common in patients with AIDS.

4. *Pneumocystis jiroveci* prophylaxis for transplant or HIV + (whose CD₄ has ever been <200) patients.

5. Shigellosis, typhoid fever.

6. Enteropathogenic Escherichia coli infections.

7. Traveler's diarrhea treatment. Resistance has limited utility to infections acquired in Mexico only.

8. Stenotrophomonas maltophilia infections – drug of choice. Dose at 12-15 mg/kg/day of TMP component divided Q6-8H IV.

9. Methicillin-resistant Staphylococcus aureus mild infections (excluding endocarditis and abscesses).

10. MRSA decolonization (eradication of nasal carriage) – in combination with rifampin. Topical mupirocin may also be effective, but is more expensive. MRSA decolonization with rifampin should not be attempted routinely; the Infectious Disease service should be consulted.

11. Selected nontuberculin mycobacterial infections (strains other than *Mycobacterium tuberculosis*), given as part of a combination regimen.

12. Acute otitis media or sinusitis treatment when patient is intolerant to beta-lactams.

13. Step-down therapy for skin or respiratory infections with CA-MRSA.

Comments

Dose adjustment required for renal impairment. See renal dosing guideline on uconnect.

TMP/SMX may no longer be the drug of choice for cystitis due to growing resistance problems when the resistance rate exceeds 15%. UWHC susceptibilities suggest that TMP/SMX has limited activity against coagulase-negative staphylococci. TMP/SMX should NOT be used in patients with SLE because the sulfonamide component induces disease flares. TMP/SMX is not recommended for use in infants less than 2 months old. TMP/SMX should not be used in pregnancy near term. TMP/SMX may induce hyperkalemia when used in high doses for AIDS patients or in normal doses in the elderly. TMP/SMX is the agent of choice for prophylaxis against *P jiroveci* in patients with AIDS or transplant patients. NOTE: Each 10 mL of the injection contains 160 mg of trimethoprim and 800 mg of sulfamethoxazole. The suspension contains 80 mg/400 mg per 10 mL. Oral bioavailability is 90-100%.

TRIMETREXATE

No longer being manufactured and there are no supplies.

TRIZIVIR[®]

For up-to-date information on the use of antiretrovirals, consult an HIV expert or www.aidsinfo.nih.gov/

TRUVADA[®] -- see tenofovir/emtricitabine

UNASYN[®] - see ampicillin/sulbactam

VALACYCLOVIR

Usual Dose

Adult. 1 g TID PO OR 500 mg BID PO (UWHC cost/day \$5.92-17.76).

Indications

1. Herpes zoster (shingles) in immunocompetent individuals (1 g TID PO x 7 days). **Must be started within 72 hours of onset of rash to be effective**, except in immunocompromised hosts.

2. Herpes simplex (genital herpes) – acute recurrence (500 mg BID PO x 3- 5 days).

3. Herpes labialis (cold sores) - initiate therapy at first sign of tingling (2 g BID for 1 day).

Comments

Dose adjustment required for renal impairment. See renal dosing guideline on uconnect.

Valacyclovir, a prodrug, is the L-valyl ester of acyclovir. It is metabolized to acyclovir by hepatic enzymes. The oral bioavailability of valacyclovir is 3 to 5 times higher than that of acyclovir, making lower doses and longer dosing intervals possible. An increasing trend toward mortality from thrombotic thrombocytopenic purpura/hemolytic uremic syndrome (TTP/HUS) was seen in one clinical trial with immunocompromised patients at supranormal doses, making its use in this population questionable. The safety and efficacy of valacyclovir in children have not been established.

VALGANCICLOVIR

Usual Dose

Adult. Induction 900 mg BID PO x 21 days (UWHC cost/day 158.16). Maintenance and prophylaxis 900 mg Q24H PO (UWHC cost/day \$79.08).

Indications

1. Cytomegalovirus (CMV) retinitis, pneumonitis, enterocolitis, esophagitis or bloodstream infections.

2. CMV prophylaxis - oral formulation restricted to prophylaxis of CMV infections in transplant recipients receiving a graft from a seropositive donor or who are seropositive for CMV and in patients receiving anti-rejection therapy.

Comments

Dose adjustment required for renal impairment. See renal dosing guideline on uconnect.

Oral bioavailability is 60%. Patients should be monitored for progression of CMV retinitis and signs and symptoms of adverse effects including granulocytopenia, anemia, thrombocytopenia, seizures, sedation, ataxia, confusion, increased creatinine, diarrhea, nausea, vomiting, fever, headache, insomnia, peripheral neuropathy, paresthesia and retinal detachment. Valganciclovir should not be administered if the absolute neutrophil count is less than 500 cells/mcL, the platelet count is less than 25,000/mcL or the hemoglobin is less than 8 g/dL. The bioavailability of ganciclovir from valganciclovir differs significantly from that of ganciclovir capsules; therefore, valganciclovir tablets cannot be substituted for ganciclovir capsules on a one-to-one basis. Valganciclovir tablets should not be crushed; may use suspension. Patients taking zidovudine and valganciclovir may not be able to tolerate full doses of both drugs because of the myelosuppressive effects of each drug.

Drug Interactions

Probenecid may increase the area under the curve (AUC) of valganciclovir and thus may increase the likelihood of toxicity from valganciclovir. Valganciclovir may increase the AUC of didanosine and increase the potential for didanosine toxicity.

VANCOMYCIN

Usual Dose

Adult. 1 g Q12H IV (15 mg/kg) OR 125 mg Q6H PO (UWHC cost/day IV \$8.12; PO \$3.09) **At UW, the IV formulation is being used for in hospital oral use.**

The UWHC cost for a comparable PO dose given as capsules is \$73.38.

Pediatric:** 40 mg/kg/day IV in divided doses Q6H OR 10-50 mg/kg/day PO in divided doses Q6H.

Meningitis 60 mg/kg/day in divided doses Q6H.

ICU Dosing: Loading dose of 15-25 mg/kg; Maintenance dose of 10 mg/kg Q8H

Note: Dose using IBW. For obese patients (BMI>30 kg/m²) use a dosing weight

(DW) = 0.4 (ABW-IBW) + IBW.

(IBW=Ideal Body Weight; ABW=Actual Body Weight)

Indications

1. Major Gram-positive infections, especially bacteremia or endocarditis, in patients with serious penicillin allergy. Empiric therapy with vancomycin should be promptly discontinued in patients whose cultures are negative for beta-lactamase-producing Gram-positive organisms.

2. Methicillin-resistant *Staphylococcus aureus* (MRSA), methicillin-resistant coagulase-negative *Staphylococcus* or ampicillin-resistant enterococci infections only. **Not for colonization.**

3. Drug for *Clostridium difficile* colitis. **Vancomycin is only effective orally for** *C difficile* **colitis.** Metronidazole is the drug of first choice unless the patient is moderately ill (but can take oral medications), has not responded to metronidazole or is allergic to metronidazole.

4. Bacteremia or endocarditis with beta-lactam resistant Corynebacterium species (especially C jeikeium).

5. Surgical prophylaxis in patients who are allergic to penicillin, are colonized with methicillin-resistant *S aureus* or in patients requiring repeat surgical interventions, especially through the previous incision. Ideally dosed as a <u>single</u> preoperative dose and NOT continued for more than 24 hours following surgery.

6. Cardiovascular or orthopedic prophylaxis when prosthetic material is being implanted. Ideally dosed as a single preoperative dose and NOT continued for more than 24 hours following surgery.

7. Bacterial endocarditis prophylaxis (see Appendix A).

8. Serious infections with Streptococcus pneumonia including meningitis when given in combination with ceftriaxone until penicillin susceptibility documented.

9. Treatment of intraventricular shunt infections in combination with rifampin and/or removal of shunt material.

Comments

Dose adjustment required for renal impairment. See renal dosing guideline on uconnect.

Vancomycin is still a reliable antibiotic for many MRSA infections, or for methicillin-resistant coagulase-negative *Staphylococcus*. Vancomycin is not absorbed orally. To avoid histamine-like reactions, which are not true allergic reactions, administer the drug no faster than over 60 minutes. Pre-operative doses may begin 2 hours before the planned incision time in the OR. Vancomycin infusions should not be administered during patient transport. Trough concentrations are required only for pharmacokinetic dosing in renal failure, burn and obese patients; suspected toxicity; or suspected inefficacy. The unit pharmacist will assist with pharmacokinetic dosing (See Serum Drug Concentration Monitoring Protocol [Appendix G] or on uconnect) Consider dosing at 15 mg/kg/day in obese patients or see Appendix H.

See Vancomycin Serum Concentration Monitoring [Appendix H] or on uconnect.

Trough: 15 minutes to 30 minutes prior to next dose. Monitor long-term therapy by following the serum creatinine concentrations.

Vancomycin use topically or for irrigations is discouraged. Excess use of vancomycin can promote spread of vancomycinresistant enterococci. Organisms with intermediate vancomycin susceptibility have been reported, most commonly in patients on long-term vancomycin therapy.

VORICONAZOLE

Infectious Disease approval is required for all use of voriconazole (See Appendix I). Usual Dose

Adult: 6 mg/kg Q12H IV for 2 doses, then 4 mg/kg Q12H. If a patient is unable to tolerate 4 mg/kg, reduce maintenance dose to 3 mg/kg. Oral therapy: For patients weighing >40 kg, 200 mg PO BID. If response is inadequate, may increase dose to 300 mg PO BID. For patients weighing <40 kg, 100 mg PO BID. If response is inadequate, may increase dose to 150 mg PO BID. (UWHC cost/day IV \$323.54 PO \$82.74).

Pediatric: 6 mg/kg Q12H IV for 2 doses, then 4 mg/kg Q12H. If a patient is unable to tolerate 4 mg/kg, reduce maintenance dose to 3 mg/kg.

Indications

1. Invasive aspergillosis

- 2. Serious fungal infections caused by Scedosporum apiospermum and Fusarium species
- 3. Invasive infections caused by Candida albicans or Candida krusei.

4. Not for routine prophylaxis in hematology or stem cell transplant patients except by special protocol, and not as routine substitution for posaconazole prophylaxis patients with GI side effects.

Comments

The IV formulation is not recommended for patients with moderate-to-severe renal dysfunction (creatinine clearance <50 mL/min) because the intravenous vehicle is excreted renally and will accumulate in these patients. Dose adjustment is necessary in patients with mild-to-moderate hepatic dysfunction (Child-Pugh class A and B). No pharmacokinetics data available for patients with severe hepatic dysfunction (Child-Pugh class C). Transaminase abnormalities occurred in approximately 13% of patients in clinical trials. Serial monitoring of LFTs is recommended. Transient visual disturbances (altered or enhanced visual perception, blurred vision, color vision abnormalities and/or photophobia) occur in approximately 30% of patients, more likely with IV therapy. Omeprazole may occasionally be prescribed with voriconazole in order to increase blood levels.

See guidelines for use on uconnect.

See Guidelines for Antifungal Therapy (Appendix E) or on uconnect

Not for routine anti-fungal therapy in most oncology patients with febrile neutropenia.

See IV-to-PO Interchange Policy (Appendix F) or on uconnect

Drug Interactions

As a cytochrome P450 inhibitor, voriconazole is subject to many drug interactions. Voriconazole is a substrate of the isoenzymes CYP2C19, CYP2C9 and CYP3A4, and has the greatest affinity for CYP2C19. Because of potentially dangerous drug interactions, concomitant use of voriconazole and the following drugs is contraindicated:

- Astemizole -- increased plasma levels leading to QT prolongation
- Carbamazepine -- expected to reduce plasma levels of voriconazole
- Cisapride -- increased plasma levels of cisapride leading to QT prolongation
- Dronaderone increased plasma levels leading to QT prolongation
- Ergot alkaloids -- increased plasma levels of these drugs leading to ergotism
- Long-acting barbiturates -- expected to reduce plasma levels of voriconazole
- Pimozide -- increased plasma levels leading to QT prolongation
- Quinidine -- increased plasma levels leading to QT prolongation
- Rifabutin -- reduces C_{max} and AUC of voriconazole and increased C_{max} and AUC for rifabutin
- Rifampin -- severely reduces the C_{max} and AUC of voriconazole
- Ritonavir -- reduces C_{max} and AUC of voriconazole
- Sirolimus -- increased serum levels of Sirolimus
- St. John's Wort -- reduces C_{max} and AUC of voriconazole
- Terfenadine -- increased plasma levels leading to QT prolongation

Careful monitoring of patients using voriconazole concomitantly with the following drugs is recommended because voriconazole is an inhibitor of cytochrome P450 isoenzymes, including 3A4 and 2C19 and is expected to increase blood levels of these drugs:

Erlotinib

Estrogens

• Etravirine

• Everolimus

HMG-CoA

Maraviroc

Meloxicam

Methadone

• Fentanyl & derivatives

reductase inhibitors

• Erythromycin

• Esomeprazole

- Alfuzosin
- Alosetron
- Amprenavir/Fosamprenavir
- Atazanavir
- Benzodiazepines
- Cinacalcet
- Clarithromycin
- Clopidogrel
- Cyclosporin
- Dasatanib
- Delavirdine
- Dihydropyridine Ca⁺⁺ channel blockers
- Eletriptan
- Eplerenone

- Nelfinavir
 - Nevirapine

- Nilotinib
- Omeprazole
- Oxycodone
- Paracalcitol
- Phenytoin/
 Fosphenytoin
- Romidepsin
- Saquinavir
- Sirolimus
- Sulfonylureas
- Sunitinib & metab
- Tacrolimus
- Temsirolimus
- Vinca alkaloids

Other drugs that should be used cautiously with voriconazole due to the risk of additive QT prolongation are:

- Amiodarone
 Methadone
- Bretylium
- NilotinibPazopanib
- ClarithromycinDofetilide

Erythromycin

- Ranolazine
- Sotalol
- Ibutilide
- Telavancin

Miscellaneous drug interactions with voriconazole include:

- Amprenavir/Fosamprenavir blood levels of either drug may be increased
- Chloramphenicol increases voriconazole blood levels
- Darunavir decreases overall exposure to voriconazole
- Non-nucleoside reverse transcriptase inhibitors may increase voriconazole blood levels
- Phenytoin/Fosphenytoin decrease voriconazole blood levels
- Saquinavir increased blood levels of either drug
- Tretinoin risk of hypercalcemia is increased
- Tipranivir blood levels of either drug may increase or decrease

ZIDOVUDINE

For up-to-date information on the use of antiretrovirals, consult an HIV expert or www.aidsinfo.nih.gov/

ZYVOX[®] -- see linezolid

APPENDIX A: PREVENTION OF INFECTIVE ENDOCARDITIS

American Heart Association Guidelines - 2007

Recommended standard prophylactic regimen for patients at highest risk of infective endocarditis for all dental procedures that involve manipulation of gingival tissue or the periapical region of teeth or perforation of the oral mucosa, for procedures involving incision or biopsy of the respiratory mucosa, or for surgical procedures involving infected skin, skin structures, or musculoskeletal tissue.

Patients at highest risk for infective endocarditis include those with prosthetic cardiac valve, history of infective endocarditis, unrepaired cyanotic congenital heart disease, completely reparied congenital heart defect with prosthetic material or device during the first 6 months after the procedure, repaired congenital heart disease with residual defects at the site or adjacent to the site of a prosthetic patch or device, or cardiac transplantation recipients who develop cardiac valvulopathy.

CONDITION	DRUG	ADULT DOSE	PEDIATRIC DOSE*
Standard oral regimen	Amoxicillin	2 g PO 30 – 60 minutes before procedure	50 mg/kg PO 30 – 60 minutes before
			procedure
Patients unable to take	Ampicillin	2 g IV/IM 30 – 60 minutes before procedure	50 mg/kg IV/IM 30 – 60 minutes before
oral medications			procedure
	Cefazolin or ceftriaxone	1 g IV/IM 30 – 60 minutes before procedure	50 mg/kg IV/IM 30 – 60 minutes before
			procedure
Allergic to penicillins or ampicillin - oral	Cephalexin*†	2 g PO 30 – 60 minutes before procedure	50 mg/kg PO 30 – 60 minutes before
			procedure
	Clindamycin	600 mg PO 30 – 60 minutes before procedure	20 mg/kg PO 30 – 60 minutes before
			procedure
	Azithromycin or	500 mg PO 30 – 60 minutes before procedure	15 mg/kg PO 30 – 60 minutes before
	clarithromycin		procedure
Patients unable to take	Cefazolin or ceftriaxone†	1 g IV/IM 30 – 60 minutes before procedure	50 mg/kg IV/IM 30 – 60 minutes before
oral medications and			procedure
are allergic to penicillins	Clindamycin	600 mg IV/IM 30 – 60 minutes before procedure	20 mg/kg IV/IM 30 – 60 minutes before
or ampicillin			procedure

*Or other first-or second-generation oral cephalosporin in equivalnet adult or pediatric dosage

†Cephalosporins should not be used in an individual with a history of anaphylaxis, angioedema, or urticaria with penicillins or ampicillin

APPENDIX B: UWHC SURGICAL ANTIMICROBIAL PROPHYLAXIS GUIDELINES

Principles of prophylaxis

- 1) Use antimicrobials for surgical procedures where prophylactic antimicrobials have been found to be beneficial.
- 2) Time antimicrobial administration so that the agent is present in the potentially contaminated tissue <u>before</u> the bacteria enter the site (i.e. at the time of surgical incision and persisting in tissues throughout the period of potential contamination). Antimicrobials vary in their distribution pharmacokinetics. The goal is begin delivery of the antimicrobial 30-60 minutes before incision to ensure infusion is complete prior to incision. Vancomycin and ciprofloxacin, which must be infused over 60 minutes, may be begun 120 minutes prior to incision).
- 3) For longer cases, appropriate antibiotics should be redosed according to their t ¹/₂ lives.
- 4) Appropriate antibiotics should be redosed after significant blood loss (4 units or 1000 ml).
- 5) Limit the duration of antimicrobial prophylaxis. Studies document that postoperative antimicrobial administration is not necessary for many surgeries.
- 6) Plan the route of antimicrobial administration, for example, use oral antimicrobials for gut decontamination
- 7) Select an antimicrobial which is active against the most common surgical wound pathogens.

Head and Neck ³	LIKELY PATHOGENS	ANTIMICROBIAL REGIMEN (Adult)	ANTIMICROBIAL REGIMEN (Pediatric)	OR REDOSING	COMMENTS
Basic Case Major head and neck surgical cases where mouth	Normal flora of the mouth, various streptococci (including aerobic and anaerobic species), <i>Staph aureus</i> , <i>Peptostreptococcus</i> , <i>Neisseria</i> and numerous anaerobic Gram- negative bacteria <i>including Porp-</i> <i>hyromonas</i> (<i>Bacteroides</i>), <i>Prevotella</i> (<i>Bacteroides</i>), <i>Fusobacterium and</i> <i>Veillonella</i> . Nasal flora includes <i>Staphylococcus</i> , <i>Streptococcus</i> <i>pyogenes</i> , <i>Strep</i> <i>pneumoniae</i> , <i>Moraxella</i> and <i>Haemophilus</i> species.	 Cefuroxime⁵ 1.5 g IV preop Clindamycin 900 mg IV <u>plus</u> gentamicin 1.7 mg/kg IV preop or Unasyn® (ampicillin/sulbactam) 1.5 g-3 g IV preop 	 Cefuroxime 30mg/kg IV preop (Maximum of 1.5 g) Clindamycin 10mg/kg IV (Maximum of 900mg) <u>plus</u> gentamicin 1.5mg/kg IV (Maximum of 80mg) preop or Unasyn (ampicillin/sulbactam) 37.5mg/kg (provides 25mg/kg of ampicillin) IV (Maximum of 3 g) preop 	 Cefuroxime every 4 hours Clindamycin every 6 hours Unasyn® every 4 hours 	Risk is high for mixed infections of anaerobes, staphylococci and some Gram-negative rods.
or pharynx is entered ³		 Cefuroxime 1.5 g IV plus Metronidazole 500 mg IV pre-op or Cefoxitin⁴ 1 g IV preop (2 g if > 80 kg) 	 Cefuroxime 30mg/kg IV preop (Maximum of 1.5 g) <u>plus</u> Metronidazole 7.5mg/kg IV (Maximum of 500mg) preop or Cefoxitin 25mg/kg IV (Maximum of 1 g) preop 	 Cefuroxime every 4 hours Metronidazole every 6 hours Cefoxitin every 3 hours 	Risk is high for mixed infections of anaerobes and staphylococci but not <i>Pseudomonas</i> .
Gastrointestinal	LIKELY PATHOGENS	ANTIMICROBIAL REGIMEN (Adult)	ANTIMICROBIAL REGIMEN (Pediatric)	OR REDOSING	COMMENTS
---	--	---	---	---	--
GI:Cholecystect omy ³	<i>Escherichia coli</i> and <i>Klebsiella</i> . Streptococci and staphylococci are occasionally isolated. Anaerobic bacteria are uncommon, but <i>Clostridium</i> is possible.	 Cefazolin 1 g IV⁴ pre-op (2 g if > 80 kg) 	Cefazolin 25mg/kg IV preop (Maximum of 1 g)	 Cefazolin every 4 hours 	Bacteria isolated from bile during surgery are those most likely to be associated with wound infections.
GI: Upper Gastroduodenal ³	Most common are nasopharyngeal commensals (streptococci, lactobacilli and diphtheroids)	 Cefazolin⁴ 1 g IV pre-op (<u>2 g if > 80 kg)</u> or Cefuroxime 1.5 g IV pre-op 	 Cefazolin 25mg/kg IV preop (Maximum of 1 g) or Cefuroxime 30mg/kg IV preop (Maximum of 1.5 g) 	 Cefazolin every 4 hours Cefuroxime every 4 hours 	Prophylaxis indicated only for patients with increased pH from the use of H2 receptor blockers, proton pump inhibitors, with gastric obstruction or GI hemorrhage and with complex upper GI procedures such as a Whipple or gastric bypass.
GI: Colorectal ³	Enteric Gram-negative bacilli, anaerobes, with E. coli and Bacteroides fragilis the most common organisms.	 Bowel prep (day before surgery): Metoclopramide 10 mg PO 30 min. prior to GI lavage 1.5 L Q1H until clear (max. 4-6 L). When GI lavage is clear, start neomycin 1 g PO with erythromycin 1 g PO at 1300, 1400, and 2300. Unasyn® (ampicillin/sulbactam) 1.5 g-3 g IV pre-op or Cefoxitin 1-2 g IV pre-op (2 g if > 80 kg) or Ciprofloxacin 400 mg IV pre- op plus Metronidazole 500-750 mg IV pre-op. or Clindamycin 900 mg IV plus gentamicin 1.7 mg/kg IV 30 pre-op 	Bowel prep (day before surgery): Metoclopramide 0.1mg/kg (Maximum of 10mg) PO 30 min prior to GI lavage (see order set for weight based dosing). Then give neomycin 20mg/kg PO x3 doses (Maximum of 1 g) with erythromycin 20mg/kg x3 doses • Unasyn (ampicillin/sulbactam) 37.5mg/kg (provides 25mg/kg of ampicillin) IV (Maximum of 3 g) preop or • Cefoxitin 30mg/kg IV (Maximum of 2 g) preop or • Clindamycin 10mg/kg IV (Maximum of 900mg) plus gentamicin 2mg/kg IV preop (Maximum of 80mg) pre-op	 Unasyn® every 4 hours Cefoxitin every 3 hours Ciprofloxacin: none Metronidazole every 6 hours Clindamycin every 6 hours 	Metronidazole 750 mg may be substituted for erythromycin in erythromycin-sensitive patients. NOTE: 50% of trials evaluated demonstrated <5% post-op infection rate and 90% of trials evaluated demonstrated <10% post-op infection rate with bowel prep alone. Systemic regimens reduce rate of infection beyond that seen with bowel prep as outlined above. If enterococcus is suspected or confirmed, vancomycin 1 g IV would be an alternative in the penicillin-sensitive patient (this regimen would cover Enterococcus). Most primary prophylaxis regimens do not require coverage for Enterococcus or Pseudomonas.

GI: Appendectomy ³	Anaerobic organisms (especially B fragilis) and Gram-negative enteric organisms (predominantly E coli). Staphylococcus, Enterococcus and Pseudomonas species have also been reported.	Uncomplicated: • Cefoxitin ⁴ 1 g IV pre-op (2 g if > 80 kg) <u>Complicated:</u> • Unasyn® (ampicillin/sulbactam) 1.5-3 g IV pre-op	<u>Uncomplicated:</u> • Cefoxitin 30mg/kg IV (Maximum of 2 g) preop <u>Complicated:</u> • Unasyn (ampicillin/sulbactam) 37.5mg/kg (provides 25mg/kg of ampicillin) IV (Maximum of 3 g) preop	 Cefoxitin every 3 hours Unasyn® every 4 hours 	The incidence of infectious complications following appendectomy is dependent on the condition of the appendix at the time of surgery
Gynecologic	LIKELY PATHOGENS	ANTIMICROBIAL REGIMEN (Adult)	ANTIMICROBIAL REGIMEN (Pediatric)	OR REDOSING	COMMENTS
	Lactobacillus sp. Staph aureus Corynebacterium sp. Gram-negative organisms Anaerobes	 Cefazolin⁴ 2 g IV Or Cefoxitin⁴ 2 g IV Or Clindamycin 900 mg Q8H IV plus gentamicin 1.7 mg/kg IV 30 min pre-op for penicillin-allergic patients 	 Cefazolin 25mg/kg IV preop (Maximum of 1 g) Or Cefoxitin 30mg/kg IV (Maximum of 2 g) preop Or Clindamycin 10mg/kg IV (Maximum of 900mg) plus gentamicin 2mg/kg IV (Maximum of 80mg) preop for penicillin-allergic patients 	 Cefazolin every 4 hours Cefoxitin every 3 hours Clindamycin every 6 hours 	

Cardiothoracic	LIKELY PATHOGENS	ANTIMICROBIAL REGIMEN (Adult)	ANTIMICROBIAL REGIMEN (Pediatric)	OR REDOSING	COMMENTS
General Cardiothoracic	Coagulase-negative staph, Staph aureus, Corynebacterium, enteric Gramnegative bacilli.	 Cefuroxime^{4.5} 1.5 g IV preop AND/OR vancomycin 1 g IV (single dose) if implantation of prosthetic/valvular graft (Staphylococcus epidermidis), or if patient is MRSA-positive or Vancomycin 1 g IV, if penicillin allergic 	 Cefuroxime 30mg/kg IV preop (Maximum of 1.5 g) AND/OR vancomycin 15mg/kg IV (Maximum of 1g) if patient is MRSA- positive or if penicillin allergic 	 Cefuroxime every 4 hours or at end of cardiopulmonary bypass. Vancomycin: none; every 6 hours for pediatric patients 	Cefuroxime has enhanced activity against coagulase-negative staphylococci
Left Ventricular Assist Device		 Rifampin 600 mg PO plus Ciprofloxacin 400 mg IV Fluconazole 400 mg IV Vancomycin 15 mg/kg (up to 1 g) IV 	•	 Ciprofloxacin every 12 hours Fluconazole every 12 hours Vancomycin every 12 hours 	
Lung transplant: Cystic Fibrosis patient		Check Infectious Disease Recommendations	Check Infectious Disease Recommendations		

Vascular	LIKELY PATHOGENS	ANTIMICROBIAL REGIMEN (Adult)	ANTIMICROBIAL REGIMEN (Pediatric)	OR REDOSING	COMMENTS
 Abdominal aortic aneurysm: elective or ruptured Thoracoabdo minal aneurysm Aortobifem/ilia c bypass Renal or carotid endarterecto my 	Staph aureus (predominant), also Gramnegative bacilli, coagulase-negative staphylococci and enterococci	 Cefuroxime^{4,5} 1.5 g IV preop <u>AND/OR</u> vancomycin 1 g IV (single dose) if implantation of prosthetic/valvular graft (Staphylococcus epidermidis), or if patient is MRSA-positive or Vancomycin 1 g IV, if penicillin allergic 	 Cefuroxime 30mg/kg IV (Maximum of 1.5g) pre-op AND/OR vancomycin 15mg/kg IV (Maximum of 1g) if patient is MRSA- positive or pencillin allergic 	 Cefuroxime every 4 hours Vancomycin: none; every 6 hours for pediatric patients 	All preoperative antibiotics should be administered within 1 hour of incision
 Below/above knee amputations 					
 Lower extremity bypass (no warfarin) 					
 Transmetatar sal amputation 					
Toe amputation					
• Ist rid resection					

Neurosurgical	LIKELY PATHOGENS	ANTIMICROBIAL REGIMEN (Adult)	ANTIMICROBIAL REGIMEN (Pediatric)	OR REDOSING	COMMENTS
Craniotomy	Staphylococcus aureus, coagulase-negative staphylococci	 Cefazolin⁴ 1 g IV pre-op (2 g if > 80 kg) 	Cefazolin 25mg/kg IV pre- op (Maximum of 1 g)	Cefazolin every 4 hours	Organisms listed represent >85% of post-op infections
Cerebrospinal fluid shunt	Staphylococci account for 75-80% of wound infections following shunt procedures; Gram negative bacteria 1-20%.	 Cefuroxime^{4,5} 1.5 g IV preop OP Vancomycin 1 g IV as a single dose (IF incidence of infections with MRSA >10% in an institution, vancomycin is recommended, otherwise it is optional) 	 Cefuroxime 30mg/kg IV (Maximum of 1.5g) pre-op Or Vancomycin 15mg/kg IV (Maximum of 1 g) pre-op 	 Cefuroxime every 4 hours Vancomycin none; every 6 hours for pediatric patients 	IF incidence of infections with MRSA >10% in an institution, vancomycin is recommended, otherwise it is optional
Orthopedics	LIKELY PATHOGENS	ANTIMICROBIAL REGIMEN (Adult)	ANTIMICROBIAL REGIMEN (Pediatric)	OR REDOSING	COMMENTS
Total joint replacement	Staphylococcus aureus and Staphylococcus epidermidis and various streptococci cause >66% of wound infections.	 Cefazolin^{1.4} 1 g IV preop (2 g if > 80 kg) or Cefuroxime⁵ 1.5 g IV pre- op or Vancomycin (15 mg/kg), up to 1 g IV pre-op if MRSA+ 	 Cefazolin 25mg/kg IV preop (Maximum of 1 g) Or Cefuroxime 30mg/kg IV preop (Maximum of 1.5 g) Or Vancomycin 15mg/kg IV (Maximum of 1 g) preop if MRSA+ 	 Cefazolin every 4 hours Cefuroxime every 4 hours Vancomycin none; every 6 hours for pediatric patients 	Cefuroxime has enhanced activity against coagulase-negative staphylococci Use vancomycin only for severe penicillin allergy or if MRSA+. Some clinicians use clindamycin in penicillin-allergic patients
Hip fracture repair	Staphylococci	 Cefazolin^{1,4} 1 g IV pre-op (2 g if > 80 kg) or Cefuroxime⁵ 1.5 g IV pre- op or Vancomycin (15 mg/kg) up to 1 g IV if MRSA+ 	 Cefazolin 25mg/kg IV preop (Maximum of 1 g) Or Cefuroxime 30mg/kg IV preop (Maximum of 1.5 g) Or Vancomycin 15mg/kg IV (Maximum of 1 g) preop if MRSA+ 	 Cefazolin every 4 hours Cefuroxime every 4 hours Vancomycin none; every 6 hours for pediatric patients 	Use vancomycin only for severe penicillin allergy or MRSA+. Some clinicians use clindamycin in penicillin-allergic patients

Clean orthopedic procedures (other)	Staphylococci	 Minor procedures - None Major procedures - Cefazolin⁴ 1 g IV pre-op, <u>(2</u> <u>g if > 80 kg)</u> or Vancomycin 1 g IV preop if patient is MRSA-positive 	 Minor procedures - None Major procedures - Cefazolin 25mg/kg IV pre- op (Maximum of 1 g) Vancomycin 15mg/kg IV pre-op (Maximum of 1 g) if MRSA+ 	 Cefazolin every 4 hours Vancomycin none; every 6 hours for pediatric patients 	Use vancomycin only for severe penicillin allergy. Some clinicians use clindamycin in penicillin- allergic patients.
Genitourinary	LIKELY PATHOGENS	ANTIMICROBIAL REGIMEN (Adult)	ANTIMICROBIAL REGIMEN (Pediatric)	OR REDOSING	COMMENTS
Transurethral Resection of Prostate ³	E coli as well as other Gramnegative bacilli and enterococci	 Gentamicin 80 mg IV (single dose) <u>plus</u> Ampicillin 500 mg - 1 g IV (single dose) pre-op or Ciprofloxacin 500 mg PO or 400 mg IV pre-op (single dose) 	•	• None	If urine is sterile the role of perioperative prophylaxis is probably of marginal benefit. Continuing antibiotic prophylaxis post TURP is strongly discouraged and will greatly increase the risk of nosocomial UTI with enterococci, resistant Gramnegative bacilli, and candida.
Injury	LIKELY PATHOGENS	ANTIMICROBIAL REGIMEN (Adult)	ANTIMICROBIAL REGIMEN (Pediatric)	OR REDOSING	COMMENTS
Ruptured viscus ³	Enteric Gramnegative bacilli, anaerobes (<i>Bacteroides fragilis</i>) and enterococci.	 Unasyn[®] (ampicillin/sulbactam) 3 g IV pre-op Or Piperacillin/tazobactam 4.5 g IV pre-op Or Clindamycin 900 mg IV plus gentamicin 1.7 mg/kg IV pre-op for penicillin-allergic patients 	 Unasyn (ampicillin/sulbactam) 37.5mg/kg (provides 25mg/kg of ampicillin) IV (Maximum of 3 g) preop Piperacillin/tazobactam 80mg/kg IV pre-op (Maximum of 4.5 g) Clindamycin 10mg/kg IV plus gentamicin 2mg/kg IV (Maximum of 80mg) pre-op for pencillin-allergic patients 	 Unasyn every 4 hours Pip/Tazo every 4 hours Clindamycin every 6 hours Gentamicin every 8 hours 	Use Unasyn [®] for community- based peritonitis. Use piperacillin/tazobactam for peritonitis that develops secondarily in hospitalized patients or patients with prior antibiotic use at risk for resistant bacteria such as <i>Enterococcus</i> and <i>Pseudomonas</i> .

Traumatic Staphylococcus Group A streptor	eureus, occi, Cefazolin ⁴ 1 g IV pre-op (2 g if > 80 kg)	• Cefazolin 25mg/kg IV pre- op (Maximum of 1 g)	 Cefazolin every 4 hours 	Organisms may vary depending on source of injury.
clostridia	 or Cefuroxime^{4,5} 1.5 g IV plus or minus gentamicin 80 mg (or tobramycin 3.3 mg/kg) IV pre-op Add vancomycin 1g IV if MRSA+ 	Or • Cefuroxime 30mg/kg IV (Maximum of 1.5 g) <u>plus or</u> minus gentamicin 2mg/kg IV (Maximum of 80mg) pre- op Or • Add vancomycin 15mg/kg IV (Maximum of 1 g) if MRSA+	Cefuroxime every 4 hours	If wound has been massively contaminated by soil, manure or dirty water, a regimen with activity against <i>P. aeruginosa, S.</i> <i>aureus</i> , and other Gram negative bacilli is recommended.

Footnotes:

- 1. This population is usually elderly and doses should be adjusted accordingly based on renal function.
- 2. Patients receiving vancomycin preoperatively may be given diphenhydramine 50 mg IV just before the vancomycin to reduce the risk of hypotension secondary to histamine release
- 3. Add endocarditis prophylaxis in patients at risk (ampicillin 2 g IV given 30 min prior to incision or vancomycin 1 g IV over 1 hour, completing infusion within 30 min of starting procedure).
- 4. Use clindamycin 600 mg 30 min pre-op for penicillin-allergic patients where the reaction is severe enough (i.e.: hives, angioedema, anaphylaxis) to warrant avoiding cephalosporins
- 5. Use cefazolin 1-2 g IV if cefuroxime is not available.

References:

- 1. Clinical Infectious Diseases 2004;38:1706-15
- 2. Arch Surg 1993; 128: 79-88
- 3. Infect Control Hosp Epidemiol 1999; 20: 250-78
- 4. Clin Pharm 1992; 11: 483-513
- 5. Medical Letter 2004; 2: 27-32
- 6. ASHP Therapeutic Guidelines on Antimicrobial Prophylaxis in Surgery April 21, 1999

APPENDIX C: THERAPY FOR TUBERCULOSIS IN THE ERA OF MULTIDRUG RESISTANCE

This Official Joint Statement of the American Thoracic Society, CDC, and the Infectious Diseases Society of America was approved by the ATS Board of Directors, by CDC, and by the Council of the IDSA in October 2002. This report appeared in the *American Journal of Respiratory and Critical Care Medicine* (2003; 167:603--62) and is being reprinted as a courtesy to the American Thoracic Society, the Infectious Diseases Society of America, and the *MMWR* readership.

The complete treatment document can be found at http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5211a1.htm

Drug	Broporation	Adulte/Children	Doses			
Drug	Freparation	Adults/Children	Daily	1x/wk	2x/wk	3xwk
First-line drugs						
Isoniazid	Tablets (50 mg, 100 mg, 300 mg); elixir	Adults (max.)	5 mg/kg (300 mg)	15 mg/kg (900 mg)	15 mg/kg (900 mg)	15 mg/kg (900 mg)
	(50 mg/5 mL); aqueous solution (100 mg/mL) for intravenous or intramuscular	Children (max.)	10-15 mg/kg (300 mg)		20-30 mg/kg (900 mg)	
	injection					
Rifampin	Capsule (150 mg, 300 mg); powder	Adults‡ (max.)	10 mg/kg (600 mg)		10 mg/kg (600 mg)	10 mg/kg (600 mg)
	may be suspended for oral administration; aqueous solution for intravenous injection	Children (max.)	10-20 mg/kg (600 mg)		10-20 mg/kg (600 mg)	
Rifabutin	Capsule (150 mg)	Adults‡ (max.)	5 mg/kg (300 mg)		5 mg/kg (300 mg)	5 mg/kg (300 mg0
		Children	Appropriate dosing for children is unknown	Appropriate dosing for children is unknown	Appropriate dosing for children is unknown	Appropriate dosing for children is unknown
Rifapentine	Tablet (150 mg, film coated)	Adults		10 mg/kg (continuation phase) (600 mg)		
		Children	The drug is not approved for use in children	The drug is not approved for use in children	The drug is not approved for use in children	The drug is not approved for use in children
Pyrazinamide	Tablet (500 mg,	Adults	See Table 2		See Table 2	See Table 2

Table 1 Dose* of antituberculosis drugs for adults and children†

	1		1	1		
	scored)					
		Children (max.)	15-30 mg/kg (2 g)		50 mg/kg (4 g)	
Ethambutol	Tablet (100 mg, 400	Adults	See Table 3		See Table 3	See Table 3
	mg)	Children8 (max)	15-20 mg/kg daily (1 g)		50 ma/ka (4 a)	
Second-line drug		offildreng (max.)			00 mg/kg (+ g)	
Second-Inte drugs			40.45 # (1.44			—
Cycloserine	Capsule (250 mg)	Adults (max.)	10-15 mg/kg/d (1 g in two	I nere are no data to	There are no data to	There are no data to
			doses), usually 500-750	support intermittent	support intermittent	support intermittent
			mg/d in two doses	administration	administration	administration
		Children (max.)	15-20 mg/kg/d (1 g/d)			
Ethionamide	Tablet (250 mg)	Adults# (max.)	15-20 mg/kg/d (1 g/d),	There are no data to	There are no data to	There are no data to
			usually 500-750 mg/d in a	support intermittent	support intermittent	support intermittent
			single daily dose or two	administration	administration	administration
			divided doses#			
		Children (max.)	15-20 mg/kg/d (1 gm/d)	There are no data to	There are no data to	There are no data to
				support intermittent	support intermittent	support intermittent
				administration	administration	administration
Streptomycin	Aqueous solution (1	Adults (max.)	**	**	**	**
	g vials) for					
	intravenous or	Children (max.)	10-40 mg/kg/d (1 g)		20 mg/kg	
	intramuscular					
	administration					
Amikacin/kanamycin	Aqueous solution	Adults (max.)	**	**	**	**
	(500 mg and 1 g				45.00 //	
	vials) for intravenous	Children (max.)	15-30 mg/kg/d (1 mg)		15-30 mg/kg	
	or intramuscular		Intravenous or			
	administration		intramuscular	يل يل	يك يك	4-4-
Capreomycin	Aqueous solution (1	Adults (max.)	**	~*	**	**
	g vials) for		45.00 # (1.(4.))		45.00 //	
	intravenous or	Children (max.)	15-30 mg/kg/d (1 g) as a		15-30 mg/kg	
	intramuscular		single daily dose			
	administration					1

p-Aminosalicylic acid (PAS)	Granules (4 gm packets) can be mixed with food; tablets (500 mg) are	Adults	8-12 gm/day in two or three doses	There are no data to support intermittent administration	There are no data to support intermittent administration	There are no data to support intermittent administration
	still available in some countries, but not in the United States; a solution for intravenous administration is available in Europe	Children	200-300 mg/kg/d in two to four divided doses (10 gm)	There are no data to support intermittent administration	There are no data to support intermittent administration	There are no data to support intermittent administration
Levofloxacin	Tablets (250 mg, 500 mg, 750 mg); aqueous solution (500 mg vials) for	Adults	500-1,000 mg daily	There are no data to support intermittent administration	There are no data to support intermittent administration	There are no data to support intermittent administration
	intravenous injections	Children	~~	~~	٨٨	٨٨
Moxifloxacin	Tablets (400 mg); aqueous solution (400 mg/250 mL) for intravenous injection	Adults	400 mg daily	There are no data to support intermittent administration	There are no data to support intermittent administration	There are no data to support intermittent administration
			Children	‡ ‡	±‡	±‡

*Dose per weight is based on ideal body weight. Children weighing more than 40 kg should be dosed as adults.

+ For purposes of this document adult dosing begins at age 15 years.

‡ Dose may need to be adjusted when there is concomitant use of protease inhibitors or nonnucleoside reverse transcriptase inhibitors.

§ The drug can likely be used safely in older children but should be used with caution in children less than 5 years of age, in whom visual acuity cannot be monitored. In younger children, ethambutol at the dose of 15 mg/kg per day can be used if there is suspected or proven resistance to isoniazid or rifampin.

¶ It should be noted that, although this is the dose recommended generally, most clinicians with experience using cycloserine indicate that it is unusual for patients to be able to tolerate this amount. Serum concentration measurements are often useful in determining the optimal dose for a given patient.

The single daily dose can be given at bedtime or with the main meal.

** Dose: 15 mg/kg per day (1 gm) and 10 mg/kg in persons more than 59 years of age (750 mg). Usual dose: 750-1000 mg administered intramuscularly or intravenously, given as a single dose 5-7 days/week and reduced to two or three times per week after the first 2-4 months or after culture conversion, depending on the efficacy of the other drugs in the regimen.

^{^^}The long-term (more than several weeks) use of levofloxacin in children and adolescents has not been approved because of concerns about effects on bone and cartilage growth. However, most experts agree that the drug should be considered for children with tuberculosis caused by organisms resistant to both isoniazid and rifampin. The optimal dose is not known.

^{‡‡} The long-term (more than several weeks) use of moxifloxacin in children and adolescents has not been approved because of concerns about effects on bone and cartilage growth. The optimal dose is not known.

Table 2 Suggested pyrazinamide doses, using whole tablets, for adults weighing 40-90 kilograms

	Weight (kg)*					
	40-55	56-75	76-90			
Daily, mg (mg/kg)	1,000 (18.2 – 25)	1,500 (20 – 26.8)	2,000 [†] (22.2 – 26.3)			
Three times weekly, mg (mg/kg)	1,500 (27.3 – 37.5)	2,500 (33.3 – 44.6)	3,000 [†] (33.3 – 39.5)			
Twice weekly, mg (mg/kg)	2,000 (36.4 - 50)	3,000 (40 - 53.6)	4,000 [†] (44.4 – 52.6)			

*Based on estimated lean body weight. [†]Maximum dose regardless of weight.

Table 3 Suggested ethambutol doses, using whole tablets, for adults weighing 40-90 kilograms

	Weight (kg)*				
	40-55	56-75	76-90		
Daily, mg (mg/kg)	800 (14.5 – 20)	1,200 (16 – 21.4)	1,600 [†] (17.8 – 21.1)		
Three times weekly, mg (mg/kg)	1,200 (21.8 – 30)	2,000 (26.7 – 35.7)	2,400 [†] (26.7 – 31.6)		
Twice weekly, mg (mg/kg)	2,000 (36.4 - 50)	2,800 (37.3 – 50)	4,000 [†] (44.4 – 52.6)		

*Based on estimated lean body weight. [†]Maximum dose regardless of weight.

Appendix D: UNIVERSITY OF WISCONSIN HOSPITAL & CLINICS AND CHILDREN'S HOSPITAL BEST PRACTICES FOR BLOOD CULTURING

• SURVEILLANCE CULTURES ARE NOT USEFUL AND SHOULD NOT BE ORDERED.

•	STANDING ORDERS ARE NOT APPROPRIATE FOR BLOOD CULTURES.				
•	<u>WHEN TO OBTAIN CULTURES</u> NEW ONSET OF FEVER (≥38.2°°C)	•	<u>TIMING OF BLOOD CULTURES</u> DRAW ONLY DURING A FEBRILE	•	SITES AND NUMBER Inoculate one culture set from each of
	WITH OR WITHOUT OTHER		EPISODE, ideally before fever abates.		two separate sites.
	SIGNS OF SEPSIS (rigors, hypotension,	•	If patient has endocarditis or intravascular		VENIPUNCTURES ARE
	leukocytosis, mental status change,		device-related sepsis, cultures may be drawn any		PREFERRED BECAUSE OF
	oliguria, hypoxia, tachypnea or metabolic		time.		LOWER CONTAMINATION RATES
	acidosis)	٠	CULTURES MUST BE DRAWN FROM	٠	If venous access is severely limited,
•	REPEATED CULTURING OF		TWO SEPARATE SITES; VENIPUNCTURE		draw one via venipuncture and one
	NEUTROPENIC PATIENTS IS		IS BY FAR THE PREFERRED SPECIMEN		through a line
	UNNECESSARY, UNLESS THERE		BECAUSE LINES ARE TWICE AS LIKELY	٠	If venous access is <u>unavailable</u> , draw one
	IS A NEW ONSET OF FEVER		TO YIELD CONTAMINANTS.		through each of two separate lines
•	"Test of cure" cultures are warranted	•	TWO SETS (40 mL TOTAL) IS THE	٠	When one or both specimens are from
	ONLY if the patient has endocarditis, <i>S</i> .		VOLUME NEEDED TO DIAGNOSIS		lines, specimens must be of equal
	aureus or fungal sepsis or continued		SEPSIS; LARGER VOLUMES ARE		volume, drawn within 10 min of one
	signs and symptoms of sepsis despite		UNNECESSARY		another, and sent together or in
	antiinfective therapy. Begin 48 hour after	•	Surveillance cultures should not be requested		immediate succession.
	discontinue often 2 nogetiue cultures				
	discontinue after 2 negative cultures.				

BLOOD CULTURE FOR BACTERIA AND YEAST (e.g., Candida and Cryptococcus)						
Weight	Patient weight	Blood cu	ulture set 1	Blood culture set 2		
Category	(kg)	Pink (pediatric) bottle	Purple (anaerobic) bottle	Pink (pediatric) bottle	<i>Purple</i> (anaerobic)	
		(mL)	(mL)	(mL)	bottle (mL)	
А	≤1	1.5	0.5	-	-	
В	1.1-2.0	1.5	1.5	1.5	-	
С	2.1-12.7	1.5	3.0	1.5	-	
C' (Special Peds)*	12.8-20.0	1.5	3.0	1.5	3.0	
Weight Category	Patient weight	Blue (aerobic)	Purple (anaerobic) bottle	Blue (aerobic)	Purple (anaerobic)	
	(kg)	bottle (mL)	(mL)	bottle (mL)	bottle (mL)	
D	12.8-36.3	6.5	5.0	6.5	5.0	
E	>36.3	10	10	10	10	

BLOOD CULTURE FOR FILAMENTOUS FUNGI

e.g., Histoplasma capsulatum, Blastomyces dermatitidis, Coccidioides immitis, Fusarium species, Malassezia furfur

- Requires review by Infectious Diseases or Director of Clinical Microbiology
- Draw one 10 mL Isolator tube from each

CULTURE-NEGATIVE ENDOCARDITIS

- The HACEK protocol is no longer required
- For patients suspected of having bloodstream infection with unusual organisms such as *Brucella*, *Bartonella*, *Borrelia*, *Campylobacter*, *Chlamydia*, *Coxiella*, *Ehrlichia/Anaplasma*, *Helicobacter*, *Legionella*, *Leptospira* or *Mycoplasma*, the Director of Clinical Microbiology should be consulted regarding the use of special media or other methods of detection.

ONGOING MONITORS

- Single blood cultures
- Volume of blood collected
- Surveillance cultures
- >4 blood cultures in 48 hr
- Continued culturing after 2 successive days
- Test of cure cultures
- Contamination rate

***Special Peds:** This designation is intended for pediatric patients whose recorded weights may not be accurate because of fluid overload, i.e., BMT, solid organ transplants, dialysis patients and ICU patients. Use ideal body weight or dry weight when calculating blood culture volumes as appropriate.

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UW HOSPITAL & CLINICS AND AMERICAN FAMILY CHILDREN'S HOSPITAL

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BEST PRACTICES FOR BLOOD CULTURING*

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March 2009

*Best Practices for Blood Culturing is located on U-Connect within the "Clinical Guidelines" Worklist in the U-Connect Workroom. Select the "Microbiology Testing Guidelines" link, and then select "Best Practices for Blood Culturing."

Appendix E: UWHC Guidelines for the Appropriate Use of Antifungal Drugs

Guidelines developed by UWHC Antimicrobial Use Subcommittee and the Drug Policy Program (DPP)

Authors: Barry Fox, MD; Dennis Maki, MD; David Andes, MD Coordination: Sara Shull, PharmD, MBA, Manager Drug Policy Program Reviewed by: David Andes, MD; Barry Fox MD; Dennis Maki, MD; Carol Spiegel, PhD; Andrew Urban, MD; Brad Kahl, MD; Walter Longo, MD; Mark Juckett. MD; Natalie Callander, MD

Approved By P&T Committee: September 2003 Last Reviewed: February 2007 Next Scheduled Review Date: June 2011

A. Management of Patients with Documented or Probable Invasive Fungal Infections

- 1.0 *Candida* Infections
 - 1.1 There are no data to indicate that lipid-associated IV amphotericin B is superior therapeutically to conventional amphotericin B in adequate doses (0.3-0.6 mg/kg/day).
 - 1.2 For *Candida* bloodstream infections, echinocandins may be marginally superior to conventional IV amphotericin B.^{1,2,3} Three to ten days of echinocandin therapy with stepdown to oral fluconazole may be considered as one standard of care.
 - 1.3 For *C. albicans* infections, IV fluconazole (400 800 mg/day) generally gives results therapeutically comparable to conventional IV amphotericin B (and presumably echinocandin).^{4,5}
 - 1.4 For non-*albicans Candida* infections, fluconazole may fail because of reduced susceptibility.⁶ Susceptibility testing for Candida glabrata isolated from sterile body sites is automatically sent for susceptibility testing. Other testing is available upon request. An echinocandin or IV amphotericin B may be preferred.^{7,8}
 - 1.5 Voriconazole has recently been approved for the treatment of candidemia, but clinical experience is limited; published data available at the time of approval of this document are limited to salvage therapy.⁹
- 2.0 Deep *Aspergillus* Infections
 - 2.1 There are no data that conclusively show the lipid-associated amphotericin preparations are therapeutically superior to conventional IV amphotericin B in full doses (≥ 1 mg/kg/day).¹⁰ However, since it is essential to use full dose IV amphotericin B for filamentous fungal infections (≥1 mg/kg/d), a dosage which produces substantial nephrotoxicity, in general, lipid-associated preparations of amphotericin B (5 mg/kg/day) are preferable for documented filamentous fungal infection, especially deep *Aspergillus* or *Zygomycetes* infections.
 - 2.2 Voriconazole appears to be superior to all IV amphotericin B products for invasive *Aspergillus* infections and is recommended for initial therapy of probable or documented invasive *Aspergillus* infections.¹¹ Echinocandins have also been shown to be effective for invasive aspergillosis in patients refractory to or intolerant of conventional antifungal therapy.¹²

- 2.3 Recent animal data and some recent clinical data suggest that for documented or highly suggestive invasive *Aspergillus* infections, the *combination* of voriconazole with an echinocandin may be therapeutically superior to the use of either drug alone.¹³⁻¹⁷ However, a randomized trial by the national mycoses study group is in progress and results should be available shortly in 2010. This trial limits combination therapy to 14 days, and not indefinitely.
- 2.4 General comments regarding Lipid-based Amphotericin products: There are no data to suggest that liposomal amphotericin B (AmBisome[®]) is superior to amphotericin B lipid complex (Abelcet[®] ABLC),¹⁸ except for intracranial fungal infections or histoplasmosis,²⁴ where AmBisome[®] may be more effective.¹⁹ There are limited data that indicate that AmBisome[®] is slightly less nephrotoxic than amphotericin B lipid complex. AmBisome[®] is the current UWHC formulary lipid-associated amphotericin product at this time
- 3.0 CNS Cryptococcal Infections
 - 3.1 In general, an amphotericin product plus flucytosine remains the regimen of first choice.^{20,21}
 - 3.2 For patients unable to tolerate this regimen (e.g., patients with advanced AIDS), fluconazole 400-800 mg/day is recommended.²²
 - 3.3 Echinocandins are **not** effective for treatment of cryptococcal infection.
 - 3.4 Data suggest voriconazole or posaconazole may be useful for fluconazole failures but it should not be used as primary therapy.²³
 - 3.5 For indefinite suppressive therapy (e.g., in advanced AIDS), fluconazole is recommended.²⁴
- 4.0 Other filamentous fungal infections/endemic mycoses
 - 4.1 Some fungal species, such as *Zygomycetes, Fusarium* or *Scedosporium*, are resistant to amphotericin B or voriconazole.²⁵ In general, with infections caused by these organisms, *in vitro* susceptibility testing is strongly recommended and ID consultation should be sought.
 - 4.2 For treatment of histoplasmosis, blastomycosis and coccidiomycosis, the treatment of choice for life-threatening infections remains an amphotericin-based product, and AmBisome[®] is preferred at this time for histoplasmosis.²⁶ For less severe infections or for step-down therapy, use of itraconazole for histoplasmosis and blastomycosis is acceptable. For coccidiomycosis, fluconazole should be untilized.²¹
 - 4.3 Data supporting the use of voriconazole or posaconazole for the treatment of endemic mycosis are lacking, but there is some accumulating evidence that voriconazole may be effective.
 - 4.4 Posaconazole has been approved for prophylaxis of invasive fungal infections in patients with hematologic malignancies. It has in vitro activity against Zygomycetes, and may be considered for adjunctive therapy with amphotericin for such infections under the guidance of an infectious disease specialist.^{27,28}

B. Antifungal Prophylaxis for BMT and Hematologic Malignancies

- 1.0 For allogenic BMT patients, fluconazole prophylaxis has been shown to reduce the incidence of deep *Candida* infections.⁴⁰⁻⁴²
- 2.0 Itraconazole may be more effective than fluconazole for prevention of invasive fungal infections but is associated with more frequent GI side effects.⁴³
- 3.0 For patients with hematologic malignancies or solid tumors, no study has shown a clear benefit of antifungal prophylaxis. High-risk patients with prolonged neutropenia, however, can be individually considered for this strategy.⁴⁴
- 4.0 Micafungin has been approved for prophylaxis for stem cell transplant recipients, but the benefit of prophylaxis with this or other echinocandin must be weighed against the potential loss of this class of drug for therapeutic purposes.⁴⁵
- 5.0 Posaconazole has been approved for prophylaxis for patients with hematologic malignancies. While preliminary data is encouraging, difficulties with drug absorption and drug interactions may not make this a suitable prophylaxis alternative for all patients. Voriconazole should not be automatically substituted for patients having difficulty with posaconazole.^{46,47}
- 6.0 Patients with hematologic malignancies with significant GVHD <u>></u>Grade 3 may be considered candidates for prophylaxis with posaconazole, or occasionally voriconazole, although evidence based medicine for the later is lacking.^{48,49}

C. Empiric Antifungal Therapy for the Management of Patients with Febrile Neutropenia

1.0 In patients with granulocytopenia (<500/mcL) who have had persistent fever for more than 3-5 days despite empiric antibiotic therapy (cefepime or piperacillin/tazobactam, with or without tobramycin or ciprofloxacin), the addition of an antifungal drug to the empiric regimen is desirable and can reduce mortality from occult deep fungal infection.²⁹ These patients should ideally be screened for invasive fungal infections through serological and radiographic means.⁴⁹ Patients may be stratified by their risk of invasive fungal infections as noted below.

Low risk = *not high risk*

High risk = febrile patient with one or more of the following:

- Any patient with greater than 21 days of persistent neutropenia after cytotoxic chemotherapy
- Stem cell transplantation with neutropenia of greater than 5 days
- Patients with relapsed leukemia undergoing reinduction therapy with neutropenia/fever greater than 5 days
- Stem cell transplant with GVHD <u>></u>Grade 3 with or without neutropenia/fever
- Any patient with greater than 7 days of neutropenia, unresponsive to 7 days of azole empiric therapy, with high suspicion of filamentous fungal infection
- 2.0 Conventional IV amphotericin B (at a dose of 0.5 mg/kg) and lipid-based amphotericin products (at a dose of 3-5 mg/kg) are both effective.^{30,31} However, in patients who have not been receiving fluconazole prophylactically, fluconazole or itraconazole appear to give comparable results^{32,33} and voriconazole may be considered for high-risk patients.

- 3.0 There is no proven role for the use of voriconazole for routine empiric therapy of neutropenic fever. In a recent multi-center randomized trial, voriconazole was marginally more effective than amphotericin B in high risk patient subgroups only and statistically inferior in other subgroups.³⁴⁻³⁶
- 4.0 Other studies have shown that an echinocandin may be an effective alternative to lipid-based amphotericin products.^{37,38} Echinocandins may be considered for use at UWHC for certain high risk patients with extensive azole experience as outlined below. Use of echinocandins must be weighed against the future risk of drug resistance.³⁹

In trying to decide on the optimal antifungal regimen, also assess whether patients have had prior azole antifungal therapy or prophylaxis (defined as greater than 14 days of the equivalent of 200 mg of fluconazole or itraconazole, 400 mg of voriconazole or 600mg of posaconazole in the past 3 months). Prophylaxis with voriconazole or posaconazole makes the development of invasive fungal infection much less likely.⁵⁰ Specifically also assess whether patients have been receiving posaconazole prophylaxis in a reliable fashion, including assessment of drug levels. Prophylaxis regimens should be discontinued if therapeutic choices are chosen. The suggested regimens are:

No prior azole therapy:	<u>Low Risk</u> fluconazole, itraconazole	<u>High Risk</u> echinocandin, voriconazole AmBisome [®]
Prior fluconazole, itraconazole	echinocandin or AmBisome [®]	echinocandin or AmBisome [®]
Prior posaconazole	no change	no change or AmBisome [®]
Prior voriconazole	posaconazole or AmBisome [®]	AmBisome®

D. Cost Comparison

Drug	Dose (70 kg patient)	Cost per day	Comments
Amphotericin B deoxycholate	1 mg/kg/day IV daily	\$13.54	
Amphotericin B Liposomal	5 mg/kg/day IV daily	\$423.15	Requires ID Section approval
Amphotericin B lipid complex	5 mg/kg/day IV daily	253.65	Nonformulary; requires ID approval
Anidulafungin	Load – 200 mg IV Maintenance – 100 mg IV daily	\$347.86 \$173.93	Nonformulary: requires ID Section approval
Caspofungin	Load – 70 mg IV Maintenance – 50 mg IV daily	\$338.72 \$326.00	Nonformulary; requires ID Section approval
Micafungin	100 mg IV daily 150 mg IV daily	\$86.74 \$130.11	Requires ID Section approval
Fluconazole	Load – 400 mg IV Maintenance – 200 mg IV daily	\$5.37 \$2.68	
Fluconazole	200 mg PO daily	\$0.14	
Itraconazole	Load – 200 mg PO TID Maintenance – 200 mg PO BID	\$33.24 \$22.16	
Posaconazole	200 mg PO Q8h	\$82.28	Requires ID Section approval except for use according to the standard operating procedures of the Hematology Section
Voriconazole	Load – 6 mg/kg IV Q12h x 2 doses Maintenance – 4 mg/kg IV Q12h	\$485.31 \$323.54	Requires ID Section approval
Voriconazole	200 mg PO BID	\$82.74	Requires ID Section approval

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Appendix F: UWHC Guideline for Medication Route Interchange in Adult Patients

Guideline developed by UWHC Center for Drug Policy Coordination: Lee Vermeulen, MS, RPh, FCCP, Director, Center for Drug Policy Last Revised by: Wendy Horton, PharmD, BCPS; Kerry Goldrosen, PharmD Approved by P&T: June 2009 Next Scheduled Review Date: June 2011

A. Background

This guideline outlines the framework and clinical criteria to support the UWHC Medication Route Interchange Protocol.

B. Criteria

To initiate interchanges in the route of medication administration (from parenteral to enteral route, including administration via various feeding tubes), the pharmacist will assess for appropriateness based on the following criteria:

1.0 Parenteral to Enteral

To initiate the parenteral to enteral interchange, which includes medications administered orally or via feeding tubes, the medication must be listed in <u>Table 1</u>. In addition, patients must meet all inclusion criteria and none of the exclusion criteria.

- 1.1 Inclusion Criteria
 - 1.1.1 Patient must have a diet order and be tolerating either a clear liquid or more advanced diet or must be tolerating enteral tube feedings.
 - 1.1.2 Patient must have the ability to adequately absorb medications via the enteral route.

1.2 <u>Exclusion Criteria</u>

- 1.2.1 Patient is unable to swallow, is strict NPO, or refuses oral medications.
- 1.2.2 Severe vomiting or diarrhea has been documented within the past 24 hours or patient has an acute condition that affects gastrointestinal absorption (i.e. gastrointestinal obstruction or bleed, severe diarrhea, ileus, severe vomiting or mucositis).
- 1.2.3 Patient is hemodynamically unstable (sustained heart rate >100 beats/minute, respiratory rate >24 breaths/minute, systolic blood pressure <90 mmHg or on vasopressors).

2.0 Enteral to Parenteral

For a patient to be eligible for the enteral to parenteral interchange the medication must be listed in <u>Table 1</u> and the patient must meet one or more of the following clinical criteria.

2.1 Inclusion Criteria

- 2.1.1 Patient is unable to tolerate oral medications and does not have a feeding tube in place.
- 2.1.2 Patient has an acute condition that affects gastrointestinal absorption (i.e. gastrointestinal obstruction or bleed, severe diarrhea, ileus, severe vomiting or mucositis).
- 2.1.3 Patient is nutritionally compromised and parenteral administration of medication (phenytoin, fluoroquinolones, etc) is clinically warranted to minimize the amount of time the enteral nutrition is interrupted.
- 2.1.4 Patient is hemodynamically unstable (sustained heart rate >100 beats/minute, respiratory rate >24 breaths/minute, systolic blood pressure <90 mmHg or on vasopressors).
- 2.1.5 Patient has had an NPO order for greater than two days.
- 2.1.6 Patient has failed a swallow study and does not have a feeding tube in place.

- 2.1.7 Patient is without placement of a feeding tube and is somnolent and unable to protect airway.
- 2.1.8 Patient is at risk for aspiration and does not have a feeding tube in place.
- 2.1.9 Patient requires continuous gastric suctioning.

3.0 Enteral (Oral to Feeding Tube – Feeding Tube to Oral)

All medication orders with an enteral route of administration are eligible for this interchange. An initial medication order must be documented in the medical record to initiate this protocol. The pharmacist will modify the medication order based on the below inclusion criteria and evaluation of assessment criteria.

3.1 Feeding Tube to Oral Inclusion Criteria

To initiate a feeding tube to oral interchange the patient must have passed a swallow study.

3.2 Oral to Feeding Tube Inclusion Criteria

To qualify for the oral to enteral interchange an enteral feeding tube must be in place and cleared for use with documentation of appropriate placement.

- 3.3 Assessment Criteria
 - 3.3.1 Evaluation of available alternative dosage forms including an assessment of formulation appropriateness.
 - 3.3.2 Assessment of pharmacokinetic parameters including the site of drug action, bioavailability, absorption characteristics and the effects of food on drug absorption.
 - 3.3.3 Evaluation of the type of feeding tube and placement location within the gastrointestinal tract.
 - 3.3.4 Assessment and modification of dosage and/or frequency if therapeutically warranted (i.e. phenytoin capsules to phenytoin suspension). A pharmacist is also permitted to modify an extended release product for an immediate release product. (i.e. depakote to valproic acid solution; mycophenolate sodium EC tablet to mycophenolate mofetil suspension)

C. Documentation

- 4.1 Medication orders meeting the above criteria for the change in the route of administration are subject to interchange as soon as the patient meets the established criteria.
- 4.2 Once a patient meets the criteria, the pharmacist will discontinue the current medication order and automatically convert the medication to the appropriate corresponding dosage form by placing an order in the electronic medical record.
- 4.3 The pharmacist will document this change in the administration instruction section of the medication order by indicating "Modification made per medication route interchange protocol".
- 4.4 Orders will be processed using the per protocol without cosign ordering mode.

Table 1: Medications Approved for Parenteral and Oral Route Interchange

Medications Approved for Parenteral and Oral Route Interchange for Adults

Parenteral Regimen	Parenteral Dose/Frequency	Oral Regimen	Oral Dose/Frequency	Notes	
Ampicillin/Sulbactam	1.5 gm IV q6h	Amoxicillin/	500 mg/125 mg orally twice daily		
	3 gm IV q6h	Clavulanate	875 mg/125 mg orally twice daily		
Azithromycin	250 mg IV q24h	Azithromycin	250 mg orally daily	1 to 1 dosing	
	500 mg IV q24h		500 mg orally daily		
Cefazolin	1 gm IV q8h	Cephalexin	500 mg orally four times daily		
	2 gm IV q8 h		1000 mg orally four times daily		
Cefuroxime	750 mg IV q8h	Cefpodoxime	200 mg orally twice daily		
	1.5 gm IV q8h or q12h	Cefpodoxime	400 mg orally twice daily		
Ciprofloxacin	200 mg IV q12h	Ciprofloxacin	250 mg orally twice daily		
	400 mg IV q12h		500 mg orally twice daily		
	400 mg IV q8h OR 600mg IV q12h		750 mg orally twice daily		
Dexamethasone	2 mg IV	Dexamethasone	2 mg orally	1 to 1 dosing	
	4 mg IV		4 mg orally		
	6 mg IV		6 mg orally		
Disevia	10 mg IV	Disevia	10 mg orally		
Digoxin	125 mcg IV q24n	Digoxin	125 mcg orally daily	1 to 1 dosing	
	250 mcg IV q24h		250 mcg orally daily		
Doxycycline	100 mg IV q12h	Doxycycline	100 mg orally twice daily	1 to 1 dosing	
Fosphenytoin	18-20 mg IV PE/kg (loading)	Phenytoin	18-20 mg/kg in 2-3 divided doses orally (given 2-4 hours apart use suspension or chew tabs)	Increase IV/suspension/chew tab dose by 10% and round to	
	4-6 mg IV PE/kg/day		 4-6 mg/kg/day in 2 divided doses orally when using chew tabs or suspension; 1-2 divided doses orally when using capsules (once daily if dose < 400 mg) 	capsule strength when converting to capsules. Round to nearest 25 mg for chew tab and 50 mg for suspension.	
Fluconazole	100 mg IV q24h	Fluconazole	100 mg orally daily	1 to 1 dosing	
	200 mg IV q24h		200 mg orally daily		
	400 mg IV q24h		400 mg orally daily		

Parenteral Regimen	Parenteral Dose/Frequency	Oral Regimen	Oral Dose/Frequency	Notes
Levetiracetam	500-1500 mg IV twice daily	Levetiracetam	500-1500 mg orally twice daily	1 to 1 dosing
Levothyroxine	80 mcg IV q24h	Levothyroxine	100 mcg orally daily	Parenteral dose should be approximately 80% of oral dose.
Linezolid	600 mg IV q12h	Linezolid	600 mg orally twice daily	Use of linezolid is restricted to ID approval 1 to 1 dosing
Metoclopramide	10 mg IV q6h	Metoclopramide	10 mg orally q6h	1 to 1 dosing
Metronidazole	500 mg IV q8h	Metronidazole	500 mg orally three times daily	1 to 1 dosing
Methylprednisolone	4 mg IV	Prednisone	5 mg orally	
Moxifloxacin	400 mg IV q24h	Moxifloxacin	400 mg orally daily	1 to 1 dosing
Pantoprazole	40 mg IV	Pantoprazole	40 mg orally	1 to 1 dosing
Phenobarbital	15-20 mg/kg IV (loading)	Phenobarbital	Na	Status epilepticus
	1-3 mg/kg/day IV (2 divided doses)		1-3 mg/kg/day orally in 1-2 divided doses	
Potassium Chloride	10 mEq - 40 mEq IV	Potassium Chloride	10 mEq - 40 mEq orally	Only if patient is asymptomatic and K >3.2 mmol/L 1 to 1 dosing
Ranitidine	50 mg IV q8h	Ranitidine	150 mg orally twice daily	
Rifampin	600 mg IV q24h	Rifampin	600 mg orally daily	1 to 1 dosing
TMP/SMZ	320/1600 mg q12h 160/800 mg q12h	TMP/SMZ	320/1600 mg q12h 160/800 mg q12h	
Valproic Acid	10-15mg/kg/day IV (divided q 6 hrs)	Divalproex	Immediate release 3-4x orally daily; delayed release 2-3 x orally daily; 10-15mg/kg/day	Round dose to nearest tablet strength
Voriconazole	Maintenance dose - 4 mg/kg IV q12h	Voriconazole	100 mg twice daily if pt weight <40 kg 200 mg twice daily if pt weight >40 kg	Use of voriconazole is restricted to ID approval

Medications Approved for Parenteral and Oral Route Interchange for Adults

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APPENDIX G: Serum Drug Concentration Monitoring Protocol

UWHC Protocol For Inpatient Serum Drug Concentration Monitoring By Clinical Pharmacists Protocol developed by UWHC Center for Drug Policy (CDP)

Author: Cindy Gaston, RPh Coordination: Lee Vermeulen, MS, RPh, FCCP, Director, CDP

Reviewed by: Pharmacokinetics Committee Approved By P&T: July 2001 Last Reviewed: April 2007 Next Scheduled Review Date: April 2009

A. Background

This protocol outlines the procedure of therapeutic monitoring of serum drug concentrations (SDC) by clinical pharmacists and gives the authority to the pharmacist to order serum drug concentrations as necessary. Serum drug concentrations are useful to identify the causes of unwanted or unexpected responses, improve clinical outcomes, and prevent unnecessary diagnostic testing. Monitoring concentrations is important when pharmacologic and toxic effects correlate with SDC and therapeutic endpoints are difficult to assess clinically. Abnormalities in absorption, distribution, or elimination can be detected by SDC monitoring. A serum drug concentration may be necessary to evaluate an inadequate response to treatment, toxicity, and the impact of drug interactions. However, SDC should not be the only means for determining appropriate dose regimens. Accurate assessment and clinical judgment must be used to evaluate SDCs and determine appropriate dosing regimens.

Timing of the SDC is important. Route of administration, dosage regimen, dosage form, pharmacokinetic characteristics of the drug, drug interactions, and alterations in elimination will determine the optimum time to obtain the serum sample. The drug should be allowed to distribute thoroughly throughout the body before samples are obtained. Concentrations obtained during the distributive phase are variable and do not correlate with the usual therapeutic range. To obtain the most useful information SDC should be obtained at steady state. Steady state is reached in 4 to 5 half-lives for drugs following first order kinetics. If a concentration is not at steady state, then the SDC does not reflect the drug's clearance. It may be necessary to obtain a SDC before steady state if toxic or sub-therapeutic concentrations are a concern at that time. Improper sampling times can lead to misleading SDC and incorrect therapeutic adjustments.

B. Policy and Procedure

1.0 Policies

- 1.1 Only SDC that can accurately and readily be measured and be correlated with therapeutic or toxic effects will be ordered.
- 1.2 The clinical pharmacist is responsible for reviewing each patient's drug therapy and the need for SDC, and if appropriate, ordering a serum drug concentration. In advance of ordering serum drug concentrations, the pharmacist will consider the therapeutic goal of the specific medication.
- 1.3 Indications for SDC include:
 - 1.3.1 Questionable drug efficacy
 - 1.3.2 Patient exhibiting signs of possible drug-related toxicity
 - 1.3.3 Noncompliance is suspected
 - 1.3.4 Concomitant disease states that can alter drug elimination
 - 1.3.5 Drug-drug interactions
 - 1.3.6 Establishing a baseline value after a patient exhibits a therapeutic response to drug therapy
 - 1.3.7 Changing dosage formulations or regimens

- 1.3.8 Sub-therapeutic response to drug therapy
- 1.4 The clinical pharmacist is responsible for determining the sample time of the SDC.
- 1.5 The order for a SDC may be overridden, at any time, by the prescriber writing "Serum Drug Concentration as Written" or other equivalent orders.
- 1.6 The clinical pharmacist is responsible for interpreting and evaluating the results of the SDC and making appropriate recommendations. When evaluating the results of the SDC, the pharmacist should take into consideration factors such as the indication for use of the drug, the target serum concentration, the acute or chronic nature of the drug therapy, and the patient's clinical status. See the <u>UWHC Adult</u> <u>Pharmacokinetic Guideline</u> for assistance in interpreting concentrations.
- 2.0 Procedure for Managing the Ordering of Serum Drug Concentrations
 - 2.1 The pharmacist is responsible for monitoring drug therapy and SDC on a routine basis.
 - 2.2 If a patient is receiving a drug routinely monitored by SDC, the pharmacist will determine the need for a SDC.
 - 2.3 If a SDC is indicated, the pharmacist will:
 - 2.3.1 Determine the appropriate time of SDC by referring to the <u>UWHC Adult</u> <u>Pharmacokinetics Guideline</u>, <u>UWHC Lab Handbook</u>, <u>MICROMEDEX</u>[®], or current literature.
 - 2.3.2 Write an order for the SDC along with the indication for the concentration and the appropriate sample time and date.
 - 2.3.3 The order shall state, "Serum Drug Concentration per protocol" and be signed by the pharmacist.
 - 2.4 If the physician orders a SDC and indicates "SDC as written," then this information will be recorded on the pharmacy monitoring notes. The pharmacist will indicate the appropriate sampling time on the original order if not already indicated.
 - 2.5 If the physician orders "SDC per pharmacist" or "levels per pharmacist", the clinical pharmacist shall determine the indication for the concentration(s), date and time. The pharmacist shall document this in the patient's orders and sign, date, and time the order. If the pharmacist determines that no SDC is indicated, they shall discuss the indication with the ordering physician. If there is agreement that no SDC is required, then the pharmacist will write an order to discontinue the SDC. If there is not agreement and the ordering physician is a resident who requests a SDC even though protocol indicates otherwise, then an order by the attending physician is required to overrule the pharmacist and the protocol.
 - 2.6 The results and assessment of the SDC will be recorded in the pharmacy monitoring note and the patient's chart.
 - 2.7 If a change in dose is indicated as a result of the SDC, the pharmacist will verbally contact the physician to initiate the change and record this information in the pharmacy monitoring notes and the patient's chart on the same shift that the results become available.

APPENDIX H: Guidelines for Monitoring of Vancomycin Serum Concentrations in Adult Patients

Guidelines developed by UWHC Department of Pharmacy Author: Cindy Gaston, RPh, PharmD Reviewed by: Antimicrobial Subcommittee, Pharmacokinetics Committee Approved by P&T Committee: December 2003 Last Reviewed: June 2009 Next Scheduled Review Date: June 2011

Vancomycin, a glycopeptide antibiotic with bactericidal activity against gram-positive infections, has been used clinically since the 1950s and has a wide therapeutic index. Since vancomycin exhibits concentration-independent killing, bacterial growth is inhibited as long as the unbound concentration is above the minimum inhibitory concentration (MIC) of the organism at the site of the infection.^{1, 2} Vancomycin diffuses well into most body tissues, but distribution to lung tissue and the central nervous system is variable and dependent upon disease process.¹ Lung penetration is suboptimal at routine doses and as a result higher serum concentrations are generally targeted in the treatment of pneumonia.^{1, 3-5} Distribution into the cerebral spinal fluid is poor unless the meninges are inflamed.⁶ The inoculum size at the site of infection may also impact the activity of vancomycin. In vivo and mathematical models indicate that inoculum size may also have an impact on the efficacy of vancomycin.^{7, 8}

Sparse data exist correlating efficacy and toxicity with vancomycin trough or peak concentrations. Historically, monitoring of vancomycin concentrations was minimized because pharmacokinetics are predictable and toxicity did not correlate with serum concentrations.^{9, 10} Peak concentrations of vancomycin are of little value since bactericidal activity is independent of peak serum concentrations. Limited animal and human data indicate that the ratio of area under the curve (AUC) to MIC (AUC/MIC) is predictive of clinical outcome when treating methicillin-resistant Staphylococcus aureus (MRSA).^{1, 11, 12} Calculation of the AUC/MIC is cumbersome since it involves serial vancomycin concentrations; therefore, trough concentrations are recommended as a surrogate marker.¹³ Trough concentrations are drawn within 30 minutes of the next dose and should be maintained above 10 mcg/mL for uncomplicated infections and 15 to 20 mcg/mL for organisms with a MIC greater than 1 mcg/mL, hospital-acquired pneumonia, healthcare-associated pneumonia and ventilator associated pneumonia.^{5, 13} The Infectious Diseases Society of America (ISDA) Guidelines for the Treatment of Endocarditis recommend trough concentrations of 10 to 15 mcg/mL; whereas, other guidelines specify target concentrations of 15 to 20 mcg/mL for S. aureus endocarditis.^{13, 14} The 2004 ISDA Guidelines for Meningitis recommend trough concentrations of 15 to 20 mcg/mL with intermittent vancomycin dosing.¹⁵ Others have treated meningitis with a continuous infusion of high doses of vancomvcin and targeting concentrations of 20 to 30 mcg/mL.⁶ Vancomvcin Continuous Infusion for Meningitis

Prolonged and low exposure of vancomycin can select out resistant mutants and maintaining the sufficient concentrations throughout the dosing interval may prevent resistance.^{2, 16, 17} Some institutions have recognized a trend of increased MICs for vancomycin among *S. aureus* isolates, while others have noted a superior clinical response in treatment of MRSA pneumonia and bacteremia with lower vancomycin MICs.¹⁸⁻²⁰ In January 2006 the Clinical and Laboratory Standards Institute established lower MIC breakpoints for *S. aureus* to improve detection of heterogeneously resistant isolates.²¹ Bacteremic patients with MRSA isolates with a MIC of 2 mcg/mL require a significantly longer treatment period and have a lower likelihood of bacterial eradication, and alternatives to vancomycin should be considered under these unusual circumstances.²² A trial of patients with MRSA bacteremia demonstrated higher rates of treatment failure with MICs ≥ 1 mcg/mL.²³ Since low vancomycin concentrations are associated with increasing MICs, resistance and treatment failure of *S. aureus*, it is important to maintain trough concentrations greater than 10 mcg/mL.¹³

When first released in the 1950's vancomycin was associated with nephrotoxicity. This was subsequently attributed to impurities in the product and after product purification the incidence was considered to be less than 5%.^{24, 25} The occurrence of nephrotoxicity with vancomycin, however, increases when co-administered with aminoglycosides or furosemide.^{26, 27} With increasing MIC concentrations, aggressive dosing and higher targeted trough concentrations, there is concern for an increased incidence of

nephrotoxicity. A retrospective cohort study determined nephrotoxicity, defined as an increase in serum creatinine of 0.5 mg/dL or 50%, was significantly higher in patients on four grams or more per day, with a total body weight of 101.4 kilograms or more, a creatinine clearance of 86.6 mL/min or less, or ICU status.²⁸ Likewise, a recent retrospective cohort study of patients with health-care associated MRSA pneumonia demonstrated that nephrotoxicity is significantly higher with concurrent administration of nephrotoxic drugs, trough concentrations of 15 to 20 mcg/mL and treatment for greater than 8 days.²⁹

Similar to nephrotoxicity, ototoxicity was associated with initial product impurities and is rarely reported in the literature.^{9, 25} It is somewhat elusive however, since it is more difficult to detect. Baseline and followup audiograms were used to detect high-frequency hearing loss in a case-controlled, retrospective analysis of patients with target vancomycin concentrations of 10 to 20 mcg/mL.³⁰ Of the 89 patients, 11 (12%) experienced high-frequency hearing loss. Independent predictors were abnormal baseline audiograms and age over 53 years. Long-term follow up and correlation of trough vancomycin concentration were not evaluated in the study, but are important considerations.

Minimizing toxicity and resistance while improving outcomes is best accomplished by aggressive, empiric dosing based on renal function and actual body weight (table 1), tailoring therapy to MICs and monitoring vancomycin and creatinine concentrations. ^{13, 31-40} A loading dose of 20 to 25 mg/kg should be considered for critically ill patients in an effort to attain therapeutic concentrations quickly.^{13,38, 41} Patients with pneumonia, meningitis, endocarditis, organisms with MIC \geq 1 mcg/mL, sepsis, large volumes of distribution, body mass index \geq 30 kg/m², prolonged therapy, renal insufficiency and dialysis require monitoring of trough concentrations to ensure adequate concentrations throughout the dosing interval and minimize toxicity.¹³

Creatinine Clearance*	Initial Dose (ABW) [†]	Maintenance Dose(ABW) [†]
≥100 mL/min	15 - 25 mg/kg	10 mg/kg Q 8 h
80 - 99 mL/min	15 - 25 mg/kg	15 mg/kg Q 12 h
56 - 79 mL/min	15 - 25 mg/kg	10 mg/kg Q 12 h
40 - 55 mL/min	15 - 25 mg/kg	15 mg/kg Q 24h
30 - 39 mL/min	15 - 25 mg/kg	10 mg/kg Q 24 h
20 - 29 mL/min	15 - 25 mg/kg	15 mg/kg Q 48 h
<20 mL/min	15 - 20 mg/kg	Monitor serum concentrations
Hemodialysis	15 – 20 mg/kg or 1 g	500 - 750 mg after dialysis or monitor serum concentration as indicated in sections 7 below
CRRT	15 – 20 mg/kg	1 g Q 12 – 24 h Monitor serum concentrations

Table 1. Adult vancomycin dosing nomogram

Adult Vancomycin Dosing Nomogram^{38,40}

ABW – actual body weight, CRRT – continuous renal replacement therapy

* Dosing recommendations are based on decreasing creatinine clearance, which can be measured directly or estimated with equations such as the Cockcroft-Gault equation. In obese patients with a BMI > 30 kg/m², the Salazaar-Corcoran equation is more precise and less biased.⁴² For more information; please consult the protocol for renal-based dose adjustments. <u>Renal Function-Based Dose Adjustment in Adults</u>

[†] Round doses down to the nearest 500 mg, 750 mg, 1 g, 1.25 g or 1.5 g dose. If higher single doses are calculated, then consider giving a smaller dose more frequently. <u>Maximum</u> infusion rate is 10 mg/min or over 1 hour, whichever is longer. Minimum dilution is 5 mg/mL in a peripheral line.

- Patients with large volumes of distribution may require higher milligram per kilogram doses and serum concentrations are necessary to adjust doses as the volume of distribution changes. Initial loading doses of 20 to 25 mg/kg are useful to achieve and maintain therapeutic concentrations sooner. Patient conditions that can have larger volumes of distribution are sepsis, recent cardiac or trauma surgery, burns over 20% of the total body surface area or pregnancy.^{41, 43} The usual volume of distribution varies from 0.4 to 1 liter/kg.¹
- 2. In patients with normal renal function the half-life ranges from 6 to 12 hours; as a result it can take up to 60 hours to reach steady state in patients with normal renal function and even longer in patients with renal compromise.¹
- 3. Trough concentrations are recommended for patients with aggressive dosing, targeting serum concentrations of 15 to 20 mcg/mL, obesity (BMI >30 kg/m²), at high risk for nephrotoxicity, with unstable renal function or on dialysis.¹³ Patients with targeted trough levels of 15 mcg/mL or greater should have trough levels drawn approximately every three days and serum creatinine levels approximately every other day. The unit pharmacist may order a serum creatinine without a physician's cosignature for the purposes of drug concentration monitoring. Patients with rapidly changing renal function where vancomycin kinetics may be difficult to predict may be candidates for alternatives to vancomycin.
- 4. All patients receiving vancomycin therapy for prolonged therapy (at least 4 days) should have at least one steady-state concentration drawn. Concentrations should be drawn weekly on patients with stable hemodynamic and renal function and more frequently on unstable patients. Patients on more than 4 weeks of therapy can have a decrease in vancomycin clearance, thus it is important to monitor concentrations at this point in therapy.⁴⁴ Infectious Disease guidance should strongly be considered for patients requiring more than 4 grams of vancomycin per day, and if the patient is on the Infectious Disease consult service, the ID attending physician should be consulted.

Treatment population	Desired Concentrations
All patients ¹³	> 10 mcg/mL
Endocarditis ^{13, 14}	10 – 20 mcg/mL
An infection with a MIC \geq 1 mcg/mL, hospital-acquired pneumonia, healthcare-associated pneumonia, ventilator-associated pneumonia, meningitis with intermittent dosing ^{5, 13, 15}	15 – 20 mcg/mL
Meningitis, continuous infusion ⁶	20 – 28 mcg/mL

5. Target trough concentrations (within 30 minutes of the next dose):

- 6. If a steady-state concentration is outside the target therapeutic range, then proportionate dosage adjustments should be made in 250-mg increments and/or consider changing the dosing interval.
- High-flux hemodialysis (HD) is now the primary means of HD at UWHC and removes a significant amount of vancomycin.⁴⁵ The average amount of vancomycin removed by high flux HD during a 3- to 4-hour session is 30 to 38%.⁴⁶
 - 7.1. Most patients will require a vancomycin dose after each dialysis session. One method for dosing patients on a regular HD schedule (of three times per week) is to give an initial loading dose of 15 to 20 mg/kg and then empirically give 500 to 750 mg during the last hour of each HD session.^{46, 47} If greater than three days of treatment is planned, then serum concentration monitoring is recommended.
 - 7.2. A second method of dosing with HD is to draw a concentration 2 hours after the end of dialysis (to allow for vancomycin redistribution) and then give a supplemental dose to attain the desired target concentration.

- 7.3. Patients on a regular dialysis schedule will likely require the same dose of vancomycin after each dialysis session.
- Continuous renal replacement therapy (CRRT) clears vancomycin more quickly than peritoneal or HD. Usually patients on CRRT require a vancomycin dose (1 g) every 12 to 24 hours and trough serum concentrations are used to ensure adequate dosing.⁴⁹
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APPENDIX I: Infectious Diseases Approval of Restricted Antimicrobials

PURPOSE: To describe a mechanism for obtaining Infectious Diseases Section Approval of orders for restricted antimicrobials.

POLICY: Designated physicians from the Infectious Diseases Section will review for approval all orders for restricted antimicrobials. The designated physician will be contacted via a centralized paging system.

PROCEDURE:

- 1.0 The Pharmacy and Therapeutics Committee will determine which antimicrobial agents require Infectious Diseases approval before dispensing.
- 2.0 The Department of Pharmacy will maintain a list of current restricted antimicrobials as part of the UWHC formulary.
- 3.0 The Infectious Diseases Section will designate a physician or physicians to be responsible for the approval of restricted antimicrobials.
- 4.0 A designated physician will be contacted whenever an order for a restricted antimicrobial is written.
 - 4.1 When the order for the restricted antimicrobial is written, the pharmacist will inform the ordering, covering or attending physician of the existence of this policy (Pharmacy Policy #13.19) and that Infectious Diseases approval is required before the drug can be dispensed.
 - 4.1.1 If a patient is admitted on a restricted antimicrobial, Infectious Diseases approval is still required unless previous ID approval for the specific drug has been obtained for the current course of therapy.
 - 4.2 Between the hours of 0700 and 2300, the ordering physician or his/her physician designee will contact either the Infectious Diseases designated physician via pager **#3333.** The Infectious Diseases Fellow may be contacted as a backup for approval at his or her assigned pager if there is no response at the #3333 pager.
 - 4.3 The ordering physician will provide information to the Infectious Diseases designated physician including patient MR#, unit, clinical condition and clinical rationale for the use of the restricted antimicrobial.
 - 4.4 If the request is made between 2300 and 0700, **or** if a delay in approval of greater than one hour is anticipated, the pharmacy may dispense a single dose of the restricted antimicrobial. However, Infectious Diseases approval is required before any subsequent doses may be dispensed.
 - 4.5 The Infectious Diseases designated physician will discuss the appropriateness of the request with the ordering physician or designee and make a decision on whether or not to approve the order. The prescribing physician will notify the unit pharmacist when approval is given and inform the pharmacist of the name of the physician who gave the approval. The unit pharmacist will contact the Infectious Diseases designated physician to verify that approval has been given.
 - 4.5.1 If the attending physician and the designated Infectious Disease physician do not agree, a single dose of the drug may be dispensed until a formal or informal ID consultation is obtained. A second ID staff physician may serve as an arbitrator for the case.
- 4.5.1.1 To assist with the resolution of these cases, a formal ID consultation may be requested by the attending physician.
- 4.5.1.2 If a formal consultation is not requested, an informal antimicrobial consultation will take place for which the ID recommendations and rationale will be documented in the patient's medical record. These cases will be followed-up by the UWHC MUE and P&T Committees for quality improvement purposes.
- 4.6 The decentral pharmacist will document the name of the ID physician who approved the order in the comments section of the medication order in the pharmacy order entry computer system.
- 4.7 This policy does not apply to orders written by ID Section physicians.

Antimicrobials restricted to ID Approval

Formulary antimicrobials:

Aztreonam (Azactam[®]) Daptomycin (Cubicin[®]) Ertapenem (Invanz[®]) Levofloxacin (Levaquin[®]) – with some exceptions Linezolid (Zyvox[®]) Liposomal amphotericin B (Ambisome[®]) Meropenem (Merrem[®]) - with some exceptions Micafungin (Mycamine[®]) Posaconazole (Noxafil[®]) Rifampin, intravenous only Tigecycline (Tygacil[®]) Voriconazole (Vfend[®])

Nonformulary antimicrobials:

Anidulafungin (Eraxis[®]) Caspofungin (Cancidas[®]) Quinupristin/Dalfopristin (Synercid[®])

APPENDIX J: UWHC Guidelines For the Use of Beta-Lactam Antibiotics in Patients with Reported Allergies to Penicillin

Please address questions, comments, and suggestions regarding this guideline to Lee Vermeulen, MS, RPh, FCCP, Director, Center for Drug Policy at 608/262-7537.

Guidelines developed by UWHC Center for Drug Policy Author: Jeffrey Fish, PharmD Reviewed by: Infectious Disease Section and Allergy Section, UW Hospital and Clinics Coordination: Lee Vermeulen, MS, RPh, FCCP, Director, CDP Approved by P&T: May 2004 Last Review Date: May 2009 Next Scheduled Update: May 2011

A. Principles and Background

The reported penicillin allergy rate for inpatients and outpatients is 10%.¹⁻⁵ Of these patients, 80-90% will not have positive penicillin skin testing, which test for IgE-mediated reactions only.^{6,7} The patient may state they are allergic to a medication, but the reaction could be an adverse drug reaction (i.e. GI intolerance) or attributed to the disease being treated (i.e., rash caused by viral infection while on amoxicillin).⁶ The positive penicillin skin test also decreases 10% annually after a penicillin allergic reaction and 78% of penicillin allergic patients have negative skin tests after 10 years of avoidance.⁸

The different types of allergic drug reactions are classified as follows by the Gell and Coombs classification.^{2-4,6,7,9-11}

- 1.0 Type 1: IgE-mediated
 - 1.1 Immediate reactions (onset <1 hour after drug administration): systemic manifestations of anaphylaxis
 - 1.1.1 Urticaria (hives), pruritus, bronchospasm, laryngeal edema, hypotension, and/or cardiac arrhythmias
 - 1.1.2 Life-threatening
 - 1.1.3 Tested by minor determinant of penicillin skin test
 - 1.1.4 Immediate reactions occurring greater than one hour after infusion, or during sustained therapy, even in the presence of urticaria, are rare
 - 1.2 Accelerated reactions (onset 1-72 hours after drug administration)
 - 1.2.1 Urticaria, angioedema, laryngeal edema, wheezing
 - 1.2.2 Rarely life-threatening
 - 1.2.3 Determined by penicillin skin test
 - 1.3 Usually associated with beta-lactam antibiotics
- 2.0 Type 2: Cytotoxic/antibody-mediated (IgG-,IgM- complement-mediated)
 - 2.1 Hemolysis, thrombocytopenia, neutropenia, or interstitial nephritis
 - 2.2 Usually associated with quinidine, methyldopa and penicillins
 - 2.3 IgG and IgM antibodies don't induce allergic reactions
 - 2.3.1 Only IgE binds to mast cells and basophils to produce allergic reactions
- 3.0 Type 3: Immune complex (IgG, IgM immune complexes)
 - 3.1 Serum sickness
 - 3.2 Fever, rash, urticaria, lymphadenopathy, and arthralgias
 - 3.3 Usually associated with antisera, penicillin, sulfonamides and phenytoin

- 4.0 Type 4: Cellular immune-mediated/delayed hypersensitivity reaction
 - 4.1 Contact dermatitis
 - 4.1.1 Example: health care workers involved in the manufacturing and dispensing of offending agents
 - 4.2 Delayed nonurticarial rashes caused by aminopenicillins
- 5.0 Unknown mechanism: erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, fixed drug reaction, pulmonary infiltrates (nitrofurantoin), autoimmune disease (vasculitis, lupus), drug fever, drug-induced hypersensitivity syndrome (antiepileptics)
 - 5.1 Penicillin skin testing will not detect these type of reactions
 - 5.2 Desensitization should not be performed due to the risk of reactivate of the reaction

Switching to another class of antibiotics due to a reported patient allergy may adversely affect patient care due to the different antibiotic:^{6,12,13}

- Being less effective
- Having more adverse effects
- Being more broad-spectrum, leading to increased resistance
- Being more expensive

Since beta-lactam antibiotics share a common beta ring, there is a risk of cross-reactivity.¹⁻²⁰ An explanation for not having higher cross-reactivity is that the alpha rings between the different classes vary. Penicillins have a thiazolidine ring, cephalosporins have a dihydrothiazine ring, carbapenems have a modified thiazolidine ring and monobactams are missing the alpha ring.^{3-5,11}, Some of the antibiotics share common side chains (see section D) which also may contribute to cross-reactivity.^{4,7,14,15} This degree of cross-reactivity appears to be greater amongst the same class of antibiotics than between classes.¹⁴ The greatest risk of cross-reactivity is amongst penicillins.¹⁴⁻¹⁶

Prior to 1980, the cross-reactivity between penicillins and cephalosporins was reported to be 10-20%. This was probably due to the fact that the cephalosporins used at the time, cephalothin and cephaloridine, share a similar side chain with benzyl penicillin.⁷ Also during this time, some cephalosporins were contaminated with trace amounts of penicillin.⁷ Since 1980, reaction rates in penicillin history-positive and skin test-positive patients who received cephalosporins decreased to between 1.1 and 4.4%.^{3,7,15,16} A review of cross-reactivity and postmarketing studies of second- and third-generation cephalosporins revealed no increase in allergic reactions in those patients with a history of penicillin allergy.⁸ If a patient is penicillin history-positive, but skin test-negative, they are at no increased risk of cephalosporin cross-reactivity.^{5,16} If patients with a history of penicillin allergies aren't skin tested, the risk of a reaction when given a second or third generation cephalosporin is about 1%, but most of these reactions are anaphylaxis.⁷

The estimated cross-reactivity between carbapenems and other beta-lactams varies depending on the type of study. Retrospective studies show a cross-reactivity rate of about 9-11%.^{5,17-21} Issues with these retrospective studies were they didn't verify the penicillin allergies with skin testing, they didn't limit the definition for allergic reactions to IgE mediated reactions, and they based their results on chart documentation.²¹ Prospective studies had a cross-reactivity rate of 0.9-47.4%.²¹ The study showing a 47.4% cross-reactivity rate was a positive skin test to imipenem or its metabolites performed in nineteen penicillin skin-test positive patients. None of the patients received systemic imipenem.²¹ Three other prospective studies showed crossreactivity rates of 0.9-1%. These studies included penicillin skin-test positive patients who received a carbapenem skin test, but not any carbapenem metabolites. Patients who were carbapenem skin test negative then received a systemic carbapenem via a graded challenge. None of the the patients had an allergic reaction to the systemic carbapenem.²¹ Cross-reactivity with aztreonam and other beta-lactams, except ceftazidime (see Section D), is low and it may be used safely in beta-lactam allergic patients.^{5,11,21} Also, patients with a history of penicillin allergy are three times more likely to have an adverse reaction to any additional antibiotics (including cephalosporins and sulfa).^{8,22}

Penicillin is the only drug class with a valid skin test. Degradation products of other antibiotics are not known or commercially available. Under physiologic conditions, penicillin degrades to reactive intermediates that act as haptens. These haptens bind to self-proteins and elicit an immune response. Approximately 95% of penicillin degrades to the penicilloyl moiety which is the major determinant. The rest degrades to penicilloate and penicillanyl moieties which are the minor determinants. The risk of having an adverse reaction to a penicillin skin test is <1% and the reaction is usually only urticaria. Prior to conducting skin testing, patients should be instructed to hold antihistamines, beta-blockers and tricyclic antidepressants. Penicillin skin test to both the major and minor determinants will not have an immediate type 1 reaction. Skin test-negative patients may safely receive penicillin. Skin test-positive patients should avoid all penicillin compounds. These patient's should be desensitized when an alternative class of antibiotics may not be substituted (i.e.: treatment of syphilis during pregnancy)^{2-5,7,11,16}

B. Objectives

1.0 To develop a guideline for prescribers and pharmacists to help with ordering and processing beta-lactam antibiotics in penicillin-allergic patients.

C. Guideline

- 1.0 When an order for a beta-lactam antibiotic is initiated it should be determined if the patient has any medication allergies.
 - 1.1 The order may be processed if the patient does not have an allergy to betalactam antibiotics.
 - 1.2 In the case of a reported allergy:
 - 1.2.1 The presciber or pharmacist should investigate and determine the type and severity of the reaction (see Section F).
 - 1.2.2 If a rash is described, the health care professional should ascertain the characteristics of the rash. Types of rashes include:
 - 1.2.2.1 Urticaria (IgE-mediated) rashes are an intensely pruritic, circumscribed, raised and erythematous eruption with central pallor.
 - 1.2.2.2 Maculopapular or morbilliform rashes (non-IgE-mediated) begin in dependent areas and generalize, often with associated mucous membrane erythema, and are pruritic.
 - 1.2.3. An order for that class of beta-lactam may be processed if:
 - 1.2.3.1. The patient has received that class of beta-lactam in the past without a reaction.
 - 1.2.3.2. The patient or family does not recall the reaction.
 - 1.2.3.3. A non-severe, non-IgE-mediated reaction is described and the prescribed beta-lactam and the beta-lactam the patient is allergic to have different side chains. (see section D)
 - 1.2.3.4. The health care professional can ascertain that the rash is non-urticarial and the prescribed beta-lactam and the beta-lactam the patient is allergic to have different side chains. (see section D)
 - 1.2.3.5. A graded challenge may be tried if some concern about cross-reactivity exists. (see section E)

- 1.2.3.5.1. Prescriber should be contacted prior to initiating graded challenge
- 1.2.3.5.2. Anaphylaxis treatment medications should be available
- 1.2.4. The pharmacist should contact the prescriber if:
 - 1.2.4.1. The type of rash cannot be ascertained, in which case it should be assumed to be urticarial (IgG mediated).¹¹
 - 1.2.4.2. The patient's history is positive for an IgE-mediated (type 1) reaction.
 - 1.2.4.3. The reaction is a severe, non-IgE-mediated reaction.

- 1.2.5. The prescriber and pharmacist should determine the next course of action:
 - 1.2.5.1. Use an antibiotic from another class.
 - 1.2.5.2. Initiate a graded challenge (see section E) if the risk of reaction is felt to be low.
 - 1.2.5.3. Penicillin skin testing.
 - 1.2.5.3.1. Patients with a history of severe, non-IgE mediated reactions should not be skin tested.

D. Side Chains

1.0 If the order is for a beta-lactam antibiotic that has the same side chain as the antibiotic the patient is allergic to, the prescriber should be contacted for another antibiotic choice due to increased risk of cross-reactivity.^{4,14-16} Cefazolin does not share a common side chain with any other beta-lactams.¹⁴ The following table lists beta-lactams with common side chains:

Agent	Agents with Common Side Chains					
Amoxicillin	Ampicillin	Cefaclor	Cefadroxil	Cefprozil	Cephalexin	Cephradine
Ampicillin	Amoxicillin	Cefaclor	Cefadroxil	Cefprozil	Cephalexin	Cephradine
Aztreonam	Ceftazidime					
Cefaclor	Amoxicillin	Ampicillin	Cefadroxil	Cefprozil	Cephalexin	Cephradine
Cefadroxil	Amoxicillin	Ampicillin	Cefaclor	Cefprozil	Cephalexin	Cephradine
Cefamandole	Cefotetan					
Cefdinir	Cefixime					
Cefepime	Cefotaxime	Cefpodoxime	Ceftizoxime	Ceftriaxone		
Cefixime	Cefdinir					
Cefotaxime	Cefepime	Cefpodoxime	Ceftizoxime	Ceftriaxone	Cephalothin	
Cefotetan	Cefamandole					
Cefoxitin	Cefuroxime	Cephalothin	Penicillin G			
Cefpodoxime	Cefepime	Cefotaxime	Ceftizoxime	Ceftriaxone		
Cefprozil	Amoxicillin	Ampicillin	Cefaclor	Cefadroxil	Cephalexin	Cephradine
Ceftazidime	Aztreonam					
Ceftibuten	Ceftizoxime					
Ceftizoxime	Cefepime	Cefotaxime	Cefpodoxime	Ceftibuten	Ceftriaxone	
Ceftriaxone	Cefepime	Cefotaxime	Cefpodoxime	Ceftizoxime		
Cefuroxime	Cefoxitin					
Cephalexin	Amoxicillin	Ampicillin	Cefaclor	Cefadroxil	Cefprozil	Cephradine
Cephalothin	Cefotaxime	Cefoxitin	Penicillin G			
Cephradine	Amoxicillin	Ampicillin	Cefaclor	Cefadroxil	Cefprozil	Cephalexin
Penicillin G	Cefoxitin	Cephalothin				

E. Graded Challenge

- 1.0 A graded challenge is cautiously administering a medication to a patient who is unlikely to be allergic to it. It does not entail modification of the immune response. Since lower doses are initially used, if an allergic reaction happens, hopefully it will be minor and easily treated. Patient's should have beta-blockers discontinued to prevent treatment resistant anaphylaxis if it occurs.^{2,7,11}
- Procedure: give 1%, then 10%, then 100% of therapeutic dose at 30 minute intervals if no reaction develops at each dosage increment
 - 1.1.1 If a reaction develops, the patient should be desensitized

- 1.2 Anaphylaxis medications should be available
 - 1.2.1 Epinephrine 0.2-0.5 mg IM or SC Q5 minutes as needed 1.2.1.1 Pediatrics: 0.01 mg/kg (maximum 0.3mg)
 - 1.2.2 Diphenhydramine 25-50 mg IV
 - 1.2.2.1 Pediatrics: 1-2 mg/kg
 - 1.2.3 Albuterol 2.5-5 mg nebulized

F. Patient Interview

- 1.0 Potential questions to ask a patient/family member when investigating a medication allergy include:⁶
 - 1.1 Patient's age at the time of the reaction
 - 1.2 Patient's recall of the reaction or who informed them of it
 - 1.3 Time of onset of the reaction after beginning the penicillin (e.g., after 1 dose or several days)
 - 1.4 Signs/symptoms of the reaction
 - 1.4.1 Was an antidote given
 - 1.4.2 Did it require a visit to emergency room
 - 1.4.3 Was there a loss of consciousness
 - 1.5 Route of administration (oral or IV)
 - 1.6 Indication for penicillin (or cephalosporin)
 - 1.7 Concurrent medications
 - 1.8 Did the reaction abate after the penicillin (or cephalosporin) was discontinued
 - 1.9 Had the patient taken other penicillins (or cephalosporins) before or after the reaction
 - 1.9.1 If yes, what was the outcome

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Appendix K UWHC Guidelines for Cost-Effective Antimicrobial Selection

Guidelines developed by UWHC Center for Drug Policy (CDP) Authors: Lizbeth Hansen, Doctor of Pharmacy Candidate; Sarah Bland, RPh Coordination: Lee Vermeulen, MS, Director, CDP Reviewed by: Antimicrobial Use Subcommittee

A. Background

Between the years of 2000 and 2001 the national spending on retail prescription drugs increased 17.1% (by \$22.5 billion). The shift in use from generic drugs to more expensive branded products accounted for 24% of this increase. In addition, broad-spectrum antibiotics were a major contributor to this increase, growing 8.8% (\$686 million) during this period.¹ Large, well-designed studies have demonstrated that older, generic medications are as safe and effective as their branded counterparts and can be as safe and effective as new and significantly more expensive products.²

We have compiled from the UWHC Antimicrobial Use Guidelines (AMUG) various low cost options for treating common infections. Other therapeutic alternatives may exist and can be found in the main section of the AMUG. In certain circumstances, more expensive alternatives may be preferred over lower cost agents, and these alternatives are listed in the comments section in Table 1 of this appendix.

B. Antimicrobial Options (Table 1)

- 1.0 Almost all of the medications in this table should (after adding an appropriate dispensing fee) be accessible to cash-paying patients for under \$15.
- 2.0 In certain situations an inexpensive or generic drug is not an appropriate therapeutic choice and this is noted with a dollar sign (\$), to indicate that the recommended drug exceeds this expense.
 - 2.1 In these situations, the in-house patient assistance program should be contacted (if program is not available, contact the drug manufacturer).
 - 2.2 If a specific infection needing treatment is not found on this table, contact the pharmacy.

C. Caveats

- 1.0 Applicability of this guideline will depend on local antimicrobial resistance patterns and drug availability.
- 2.0 Prices are based on Maximum Allowable Cost (MAC) for the Wisconsin Medicaid system. The MAC system is commonly used to establish reimbursement levels for generic medications.
- 3.0 At the time this guideline was written, generic ciprofloxacin, fluconazole and amoxicillin/clavulanate were still in their first 6 months of availability and remained relatively costly. Following the first 6-month period after the release of these generic products, the prices have decreased substantially.
- 4.0 The recommendations in this guideline apply only to immunocompetent patients. In many cases, immunocompromised patients may require higher-cost brand-name medications.

Infection	Treatment	Comments
Otitis media		
Otitis media w/bulging tympanic membrane ^{3,4}	Children: Amoxicillin 80-100 mg/kg per day in two or three divided doses for 7 days Adults: Amoxicillin 500 mg PO BID or TID	-For otitis media without bulging tympanic membrane suggest delayed antibiotic prescribing strategy as follows: initiate treatment with full-dose acetaminophen (up to 2.6 g per day in children less than 12 years), provide a prescription for amoxicillin to be used only if otalgia or fever persists or if there is no clinical improvement after 48-72 hours ³
Resistant bacterial otitis ^{3.4}	Cefuroxime axetil 30 mg/kg twice a day for 7 days	-Treatment failure is defined as lack of improvement in clinical signs and symptoms after 3 days of therapy
Gastroenteritis/GI		
<i>H. pylori</i> infection ⁵	Bismuth subsalicylate 525 mg PO four times daily plus metronidazole 250 mg PO four times daily plus tetracycline 500 mg PO four times daily for 2 weeks plus ranitidine 150 mg PO twice daily for 4 weeks	
Traveler's Diarrhea – Mild (1-2 stools/24 hours with minor symptoms) ⁶	Fluids only or loperamide hydrochloride 4 mg PO initially, then 2 mg PO after each loose stool to a maximum of 8 mg per day or bismuth subsalicylate 4 tablets PO every half hour, maximum 8 doses	-Do not use loperamide if diarrhea is associated with fever or blood in stool
Traveler's Diarrhea – Moderate (more than 2 stools within 24 hours) ⁶	If no distressing symptoms: fluids and loperamide or bismuth subsalicylate – if worsening consider single dose ciprofloxacin 500 mg PO If distressing symptoms or critical trip:	-Resistance to fluoroquinolones in <i>Campylobacter</i> is increasingly common -Fluoroquinolones may not be
	BID for 1-3 days; avoid loperamide	
Urogenital System		
Acute (uncomplicated) Lower Urinary Tract Infection in Women ⁷	Trimethoprim-sulfamethoxazole 160/800 mg PO BID for 3 days	-The efficacy of trimethoprim is similar whether it is used alone or in combination with

		sulfa and can be prescribed to patients with a sulfa allergy
Uncomplicated Acute Pyelonephritis in Women ⁷	Ciprofloxacin 500 mg PO BID for 10 days (preferred) or trimethoprim- sulfamethoxazole 160/800 mg PO BID for 14 days	
Chlamydial Infection ^{8,9}	Doxycycline 100 mg PO BID for 7 days	-If compliance is an issue single-dose azithromycin 1 g (\$) may be more cost-effective choice
Gonococcal Infection ^{8,10}	Ciprofloxacin 500 mg single dose -if treated of acquired in Hawaii, Asia or Pacific use cefixime 400 mg PO single dose	Chlamydial infection accompanies 10-30% of gonococcal infections so routine dual therapy may be cost-effective
Genital Herpes – First Episode or Episodic Antiviral Treatment ¹¹	Acyclovir 200 mg PO five times daily for five days	
Bacterial Vaginosis ^{8,12}	Metronidazole 500 mg PO BID for 5-7 days or metronidazole 2 g PO immediately	
Vulvovaginal Candidiasis ^{8,13}	Clotrimazole 1% cream 5 g intravaginally daily for 7-14 days (\$) or clotrimazole 100 mg one vaginal tablet daily for 7 days or two vaginal tablets daily for 3 days (\$) or fluconazole 150 mg oral tablet single dose	
Trichomonas vaginalis ^{8,14}	Metronidazole 2 g PO single dose or metronidazole 500 mg PO BID for 5-7 days	
Acute or Chronic Bacterial Prostatitis ^{15,16}	Ciprofloxacin 500 mg PO BID for 28 days	
Respiratory Infections		
Bronchitis ^{17,18}	Routine antibiotic treatment is not justified unless pertussis infections is suspected or in the situation of acute exacerbation of chronic bronchitis	
Pharyngitis (due to group A streptococci) ^{19,20}	Penicillin V 250-500 mg PO 3-4 times daily for 10 days	-Limit antibiotic prescribing to patients who are most likely to have pharyngitis due to infections with Group A beta- hemolytic <i>Streptococcus</i> (GABHS) as evidenced by diagnostic testing and/or two

		or more of the following symptoms: history of fever, tonsillar exudates, no cough, and tender anterior cervical lymphadenopathy ¹⁹ -Group A streptococcal pharyngitis is usually self- limiting with symptoms disappearing spontaneously within 3-4 days of onset, even without antibiotics ¹⁹ -Antibiotic therapy can safely be postponed for up to 9 days after onset of symptoms and still prevent occurrence of the major nonsuppurative sequela, acute rheumatic fever ¹⁹
Community-Acquired Pneumonia ^{21,22}	 -Previously healthy patient given no recent antibiotic therapy: doxycycline 100 mg PO BID for 10-14 days or erythromycin 500 mg PO BID for 10-14 days -Previously healthy patient given recent antibiotic therapy: respiratory quinolone (\$) or advanced macrolide and beta-lactam (\$) or telithromycin 800 mg PO daily for 7-10 days (\$) -Patient with comorbidities (COPD, diabetes, renal or congestive heart failure, or malignancy) given no recent antibiotic therapy: respiratory quinolone (\$) or advanced macrolide (\$) or telithromycin 800 mg PO daily for 7-10 days (\$) -Patient with comorbidities given no recent antibiotic therapy: respiratory quinolone (\$) or advanced macrolide (\$) or telithromycin 800 mg PO daily for 7-10 days (\$) -Patient with comorbidities given recent antibiotic therapy: respiratory quinolone (\$) or advanced macrolide and beta-lactam (\$) or telithromycin 800 mg PO daily for 7-10 days (\$) -Suspected aspiration with infection: clindamycin 300 mg PO four times daily for 10 days (\$) or amoxicillin/clavulanate extended-release two tablets PO BID for 10 days (\$) -Influenza with bacterial 	 -Respiratory quinolones are Levofloxacin 750 mg PO daily for 5 days Or moxifloxacin 400 mg PO daily for 10 days -Advanced macrolides are Azithromycin 500 mg PO on day one then 250 mg PO daily on days 2-5 Or clarithromycin 500 mg PO BID for 10-14 days Beta-lactams are Amoxicillin 1 g PO TID for 10 days Amoxicillin/clavulanate extended-release (Augmentin XR[®]) two tablets PO BID for 10 days (equals 2 g of amoxicillin plus 125 mg clavulanate per dose)

	superinfection: amoxicillin 1 g PO TID for 10 days or amoxicillin/clavulanate extended-release two tablets PO BID for 10 days (\$)	
Acute Bacterial Sinusitis ²³	Amoxicillin 500 mg PO TID for 10 days	-Antibiotic therapy should be reserved for patients with moderately severe symptoms lasting at least 7-10 days who have maxillary pain or tenderness in face or teeth (symptomatic treatment preferred for patients with mild symptoms)
Skin Infections		
Impetigo ^{24,25}	Topical mupirocin 2% TID for 7 days (\$)	
Mild to Moderate Inflammatory Acne ²⁶	Topical benzoyl peroxide 5% plus erythromycin 2% solution applied BID for 8-12 weeks	-Treatment continued until no new lesions develop and then should be slowly discontinued -Use OTC benzovl peroxide
		and generic topical erythromycin preparation
Inflammatory Acne ²⁶	Topical benzoyl peroxide 5% plus erythromycin 2% solution applied BID for 8-12 weeks or oral tetracycline 500 mg BID for 6-8 weeks (preferred) or doxycycline 100 mg PO BID for 6-8 weeks	
Severe Papulonodular Acne ²⁶	No anti-infective strategies suggested	
Early Lyme Disease ^{27,28}	Doxycycline 100 mg PO BID for 10 days	-Therapeutic choice is appropriate for the treatment of early localized or early disseminated Lyme disease associated with erythema migrans, in the absence of neurological involvement or third-degree atrioventricular heart block

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Appendix L: Child-Pugh Grading of Liver Disease and Liver Disease Dosing

No single lab test can adequately access liver function. A common way to access metabolic ability is to determine the Child-Pugh score which evaluates lab tests and clinical symptoms to determine the extent of liver dysfunction. A patient with a score of 5 has normal function, while a score of 15 represents severe hepatic failure and dysfunction.

Grade	Cognitive/Motor	Behavior		
1	Mild tremor, altered handwriting	Anxiety, insomnia, mild confusion		
2	Dysarthria	Lethargy, disorientation		
3	Seizure, muscle twitching	Delirium, bizarre behavior		
4	Posturing	Coma		

Scale for Assessing the Depth of Hepatic Encephalopathy

Child-Pugn Grading of Liver Disease				
Clinical & Biochemical	Points Scored for Increasing Abnormality*			
Measurements	1	2	3	
Encephalopathy	None	1 and 2	3 and 4	
Ascites	Absent	Slight	Moderate	
Bilirubin (mg/dL)	<2	2-3	>3	
Albumin (G/dL)	>3.5	2.8-3.5	<2.8	
PT (sec prolonged over control)	1-3	4-6	>6	
or more currently used:				
INR (sec prolonged over control)	<u><</u> 1.7	1.8-2.2	<u>></u> 2.3	

Child-Pugh Grading of Liver Disease

- INR (International Normalized Ratio) is an expression of prothrombin time (PT), corrected by the sensitivity of the reaction to anticoagulants, and should be validated as an alternative to PT in liver insufficiency.
- Each row is given a point value of 1, 2, or 3. The sum of each row's score provides the overall score that is converted to a "grade of A, B, or C"
- Grade A = 5-6 points Grade B = 7-9 points Grade C \geq 10 points

For drugs with \geq 60% hepatic metabolism general initial dosing recommendations can be made and subsequently titrated as clinically indicated. Close clinical monitoring for efficacy and adverse reactions is imperative.

Initial Dosing of Drugs with \geq 60% Hepatic metabolism

(unless otherwise indicated by manufacturer)

Child-Pugh Score	Liver Dysfunction	Dosage Adjustment
8-9	Moderate	Decrease dose by 25% of initial dose
<u>></u> 10	Severe	Decrease dose by 50% of initial dose

An alternative method of measuring severity of liver disease and prognosis is the Model of End-Stage Liver Disease (MELD) score, for which an on-line calculator can be found at http://www.mayoclinic.org/meld/mayomodel7.html. However, no recommendations for dose adjustments specific to MELD scores have been published.

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Appendix M: Guidelines for the Prophylaxis and Management of Intraabdominal, Biliary, and Appendiceal Infections

University of Wisconsin Hospital and Clinics Intraabdominal Infections – Prophylaxis and Management

Guidelines developed by: Barry Fox, MD Reviewed and approved by: Surgical QA Committee, Antimicrobial Use Subcommittee Approved by P&T: Scheduled for Review

- A. Background
- B. Surgical Prophylaxis
- C. Source Control
- D. Categorization
- E. Treatment by Category
- F. Cholangitis and Cholecystitis
- G. Duration of therapy
- H. Necrotizing Pancreatitis

A. Background

This guideline is intended to provide evidence-based guidance for surgical prophylaxis and the treatment of intraabdominal infections. It is based on the 2009 revision of the Infectious Diseases Society of America/Surgical Infection Society update of their joint guideline.¹ The guideline is stratified according to the severity of infection and risk of treatment failure, and antimicrobial recommendations are targeted accordingly.

B. Surgical Prophylaxis

The UWHC Antimicrobial Use Guidelines (AMUG) include a section on surgical antimicrobial prophylaxis.² Use of the appropriate antimicrobial regimen for the appropriate duration is of paramount importance in gastrointestinal surgeries. Table 1 shows the prophylaxis regimens recommended in the AMUG.

Castrointostinal				COMMENTS
GI:Cholecystectomy	Escherichia coli and Klebsiella. Streptococci and staphylococci are occasionally isolated. Anaerobic bacteria are	• Cefazolin 1 g IV ⁴ pre-op (<u>2 g if > 80 kg</u>)	Cefazolin every 4 hours	Bacteria isolated from bile during surgery are those most likely to be associated with wound infections.
GI: Upper Gastroduodenał GI: Colorectał	is possible. Most common are nasopharyn geal commensals (streptococci, lactobacilli and diphtheroids) Enteric Gram -negative <u>Deciming metorboog</u> min E.	-op (2 g if > 80 kg) or • Cefuroxime 1.5 g IV pre-op Bowel preo (day before surgery):	Cefazolin every 4 hours Cefuroxime every 4 hours	Prophylaxis indicated only for patients with increased pH from the use of H2 receptor blockers, proton pump inhibitors, with gastric obstruction or GI hemorrhage. and with complex procedures suche as a Whipple or a gastric humase
	coli and Bacteroides fragilis the most common organisms.	Metoclopianide for fig PO 30 min, prior to GI lavage 1.5 L Q1H until clear (max. 4-6 L). When GI lavage is clear, start neomycin 1 gPO with erythromycin 1 g PO at 1300, 1400, and 2300. Unasym® (ampicillin/sulbactam) 1.5 g-3 g IV pre-op or Cefoxitin 1-2 g IV pre-op (2 g if > 80 kg) or Ciprofloxacin 400 mg IV pre-op plus Metronidazole 500-750 mg IV pre-op. or Clindamycin 900 mg IV plus gentamicin 1.7 mg/kg IV 30 pre-op	 Unasyn® every 4 hours Cefoxitin every 3 hours Ciprofloxacin: none Metronidazole every 6 hours Clindamycin every 6 hours 	Metronidazole 750 mg may be substituted for erythromycin in erythromycin -sensitive patients. NOTE: 50% of trials evaluated dem - onstrated <5% post - op infection rate and 90% of trials evaluated demonstrated <10% post - op infection rate with bowel prep alone. Systemic regimens reduce rate of infection beyond that seen with bowel prep as outlined above. If enterococcus is suspected or confirmed, vancomycin 1 g IV would be an alternative in the penicillin - sensitive patient (this regimen would cover Enterococcus). Most primary prophylaxis regimens do not require coverage for Enterococcus or Pseudomonas.
GI: Appendectomy	Anaerobic organisms (especially B fragilis) and Gram-negative enteric organisms (predominantly E coli). Staph ylococcus, Enterococcus and Pseudomonas species have also been reported.	Uncomplicated: • Cefoxitin ⁴ 1 g IV pre-op (2 g if > 80 kg) <u>Complicated (adult):</u> • Unasyn® (ampicillin/sulbactam) 1.5-3 g IV pre-op <u>Complicated (children):</u> • Unasyn® (ampicillin/sulbactam) 12.5-25 mg/kg pre-op	Cefoxitin every 3 hours Unasyn® every 4 hours	The incidence of infectious complications following appendectomy is dependent on the condition of the appendix at the time of surgery

Table 1. GI Surgical Prophylaxis Regimens

C. Source Control

A procedure to control the source of infection is required in nearly all patients with intraabdominal infections

- Percutaneous drainage of abscesses and/or fluid collections is preferable
 where possible
- Patients with diffuse peritonitis should have emergency surgery and not be deferred until they are stabilized
- Hemodynamically stable patients without organ failure may have surgery delayed up to 24 hours with appropriate antibiotics and monitoring
- Mandatory or scheduled relaparotomy is not recommended in patients with severe peritonitis unless there is intestinal discontinuity, loss of abdominal fascia preventing wall closure or intraabdominal hypertension
- Selected patients with well-defined foci of infection and minimal physiological disruption may be managed with antimicrobials alone, provided close follow-up is available

D. Categorization

Patients should be stratified before choosing the initial antibiotic by the severity of infection and whether they have come in from the community or likely have a healthcare-associated infection. There are three general categories of patients:

- Community-acquired, mild-to-moderate infection
- Community-acquired, severe infection/immunocompromised/high-risk
- · Healthcare-acquired

E. Treatment by Category

Each category of patient has specific organisms that should be targeted with antimicrobial therapy. Empiric coverage for each category takes into account the relative risk for resistant organisms. The following factors contribute to a patient's being "high-risk."

Clinical Factors Predicting Failure of Source Control

- Delay in initial intervention >24 hours
- High degree of severity of illness (defined as APACHE II score >15)
- Increasing age
- Comorbidities and organ dysfunction
- Low serum albumin
- Poor nutritional status
- Degree of peritoneal involvement or diffuse peritonitis
- · Inability to achieve adequate debridement or control of drainage
- Presence of malignancy

1. Community-acquired, mild-to-moderate infection

- Cefoxitin
- Metronidazole PLUS cefazolin, cefuroxime or ceftriaxone
- Metronidazole PLUS ciprofloxacin
 - Less desirable because *Pseudomonas* coverage is not needed
- Piperacillin/tazobactam, ertapenem,* meropenem*
 - Less desirable due to excessively broad coverage
 - *- ID approval required
- Moxifloxacin, tigecycline*
 - Less desirable due to excessively broad coverage unless severe beta-lactam allergy
 - *- ID approval required
- Ampicillin/sulbactam, cefotetan and clindamycin are no longer recommended
- Yeast and Enterococcus coverage is not required

For adults recovering from intraabdominal infections who are able to tolerate an oral diet, completion of the antimicrobial course with oral forms of moxifloxacin, ciprofloxacin or levofloxacin plus metronidazole, an oral cephalosporin with metronidazole, or amoxicillin/clavulanic acid is acceptable provided resistant organisms have not been isolated.

Cultures are not routinely needed unless patients have been on an antibiotic within the last three months; then cultures should be considered and the prior antibiotic should be taken into account in the empiric antibiotic selection.

If a lower-risk patient with a community-acquired infection is improving on empiric therapy and source control it is not necessary to adjust therapy if unsuspected and untreated pathogens are reported later.

2. Community-Acquired Severe Infection/High-Risk/Immunocompromised

- Piperacillin/tazobactam
- Metronidazole PLUS cefepime or ciprofloxacin
- Meropenem,* ertapenem,* moxifloxacin, tigecycline*
 - o Less desirable due to broad spectrum or cost
 - o *-ID restricted

Cultures from the site of infection should be obtained routinely especially if the patient has had prior antibiotic exposure or is more likely to have resistant organisms.

Empiric coverage for yeast and/or MRSA is not recommended in the absence of evidence of infection with these organisms. Empiric coverage for *Enterococcus* is recommended for severe infections:

- Ampicillin
- Piperacillin/tazobactam
- Vancomycin

For transplant and severely immunocompromised patients, also refer to the Healthcare-Associated Infection section

3. Healthcare-Associated Infection

- Piperacillin/tazobactam
- Metronidazole PLUS cefepime or ciprofloxacin
- Meropenem,* ertapenem*
 - o *-ID restricted
 - Carbapenems do not cover the enterococci well

Empiric coverage for *Enterococcus* is recommended; give full course of therapy if found in cultures:

- Ampicillin
- Piperacillin/tazobactam
- Vancomycin

Empiric coverage for VRE is not routinely recommended unless the patient is known to be colonized with VRE and moderately ill, or extremely high risk for VRE, e.g., liver transplant patient with sepsis in the ICU. Coverage would usually be for 72 hours to rule out VRE.

Empiric coverage for MRSA is indicated for patients known to be colonized with MRSA:

- Vancomycin
- Daptomycin*
- Linezolid*
 - *- ID restricted

Empiric coverage for yeast may be appropriate, especially if yeast is seen on the Gram stain; give full course of appropriate therapy if found in cultures:

- Fluconazole
- Micafungin*
 - *ID-restricted
 - For non-albicans yeast

F. Cholangitis, Cholecystitis and Appendicitis

- In general, cholangitis and cholecystitis follow recommendations for the three categories of infections
- Anaerobic coverage is not mandatory unless there is a biliary-enteric anastomosis
- Routine coverage for *Enterococcus* is not required except for liver transplant patients
- Antibiotics should be discontinued within 24 hours unless there is evidence of infection outside the gallbladder
- In general, appendicitis should follow recommendations for communityacquired infections

G. Duration of Therapy

The following recommendation is taken directly from the published guideline:

Evidence presented in the previous guidelines suggested that a duration of therapy no greater than 1 week was appropriate for most patients with intra-

abdominal infection, with the exception of those who had inadequate source control Within this window, resolution of clinical signs of infection should be used to judge the termination point for antimicrobial therapy. The risk of subsequent treatment failure appears to be quite low in patients who have no clinical evidence of infection at the time of cessation of antimicrobial therapy [This usually implies that the patients are afebrile, have normal white blood cell counts, and are tolerating an oral diet]. Therefore:

Antimicrobial therapy of established infection should be limited to 4–7 days, unless it is difficult to achieve adequate source control. Longer durations of therapy have not been associated with improved outcomes.

The previous guidelines also outlined a number of conditions for which a duration of therapy beyond 24 h was not believed to be necessary. In such patients, the primary goal of therapy is prophylaxis against a surgical site infection, as opposed to treatment of an established infection. These conditions included traumatic or iatrogenic bowel injuries operated on within 12 h, upper gastrointestinal perforations operated on within 24 h, and localized processes, such as nonperforated appendicitis, cholecystitis, bowel obstruction, and bowel infarction, in which the focus of inflammation or infection is completely eliminated by a surgical procedure and there is no extension of infection beyond the organ in question when source control is achieved within 24 h, prophylactic anti-infective therapy directed at aerobic gram-positive cocci for 24 h is adequate .

Bowel injuries attributable to penetrating, blunt, or iatrogenic trauma that are repaired within 12 h and any other intraoperative contamination of the operative field by enteric contents should be treated with antibiotics for 24 h. Acute appendicitis without evidence of perforation, abscess, or local peritonitis requires only prophylactic administration of narrow spectrum regimens active against aerobic and facultative and obligate anaerobes; treatment should be discontinued within 24 h.

Patients with persistent or recurrent signs of peritoneal irritation, failure of bowel function to return to normal, or continued fever or leukocytosis are at high risk of an intra-abdominal or other infection that may require additional intervention to achieve source control. In general, patients with a persistent or new intra-abdominal infection, an organ-space infection, or a superficial or deep surgical-site infection can be identified through a careful physical examination supplemented by appropriated laboratory and imaging investigations. CT of the abdomen is usually the most accurate method by which to diagnose an ongoing or recurrent intra-abdominal infection.

Transplant patients, and the patients identified above with uncontrolled or persistent infection, are candidates for longer durations of antibiotic therapy.

H. Necrotizing Pancreatitis

The published guideline made special reference to the use of antibiotics in necrotizing pancreatitis:

The administration of prophylactic antibiotics to patients with severe necrotizing pancreatitis prior to the diagnosis of infection is not recommended

Broad-spectrum antibiotic therapy has been used by some clinicians for the treatment of patients with necrotizing pancreatitis, in an effort to prevent an infection in the inflammatory phlegmon and thereby improve patient outcome. In a guideline on the management of severe pancreatitis, however, the authors concluded that this approach was not justified on the basis of available data. A meta-analysis of trials performed in this area have shown that positive results were attributable to poor study design and that well-designed studies did not demonstrate benefit .This practice is not recommended without clinical or culture evidence of an established infection in patients with necrotizing pancreatitis. In those patients with established pancreatic infection, the agents recommended for use with community-acquired infection of higher severity and health care–associated infection are the preferred agents. Because of the difficulty of achieving adequate source control in patients with infected pancreatic and peripancreatic phelgma, a longer duration of therapy may be needed.

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- 2. UWHC Antimicrobial Use Guidelines 20th Edition. Appendix B. Surgical Prophylaxis. 2009.

Appendix N: Antimicrobial Duration of Therapy

The information contained in the following chart represents the recommended duration of treatment for specific infections based on guidelines published by or with the Infectious Diseases Society of America. In situations where the IDSA did not have guidelines, the most relevant national group was sought for guidance (e.g. Society of Critical Medicine for sepsis recommendations). This chart is intended to serve as a *guide* for the appropriate duration of treatment and its use should be combined with clinical judgment taking into account patient specific responses to therapy. Infectious Disease service is often consulted for complex patients, especially those with aspergillosis, blastomycosis, and cryptococcal disease and duration of antimicrobial therapy can vary widely from the recommendations. For electronic access to the guidelines, please visit http://www.idsociety.org.

Infection		Length of Therapy
Catheter related infection ¹		Last Guideline: 2009 / Projected Update: Fall 2010
Short-term central or peripheral infection, NEG BCx, cath tip POS with <i>S. aureus</i>		5-7 days
Short-term central or	CoNS	5-7 days PLUS remove catheter or 10-14 days PLUS abx lock without catheter removal
peripheral infection,	S. aureus	≥ 14 days PLUS remove catheter
POS BCx, cath tip POS, uncomplicated	<i>Enterococcus</i> or Gram neg bacilli	7-14 days PLUS remove catheter
	Candida spp.	14 days after first NEG BCx PLUS remove catheter
	CoNS	10-14 days PLUS abx lock without catheter removal
	S. aureus	4-6 weeks PLUS remove catheter
Long-term central or	Enterococcus	7-14 days PLUS abx lock without catheter removal (consider catheter removal if deterioration or persistent bacteremia)
uncomplicated	Gram neg bacilli	7-14 days PLUS remove catheter or 10-14 days PLUS abx lock without catheter removal (remove if no response and r/o endocarditis)
	Candida spp.	14 days after first NEG BCx PLUS remove catheter
Tunnel infection/Port abscess, POS BCx, complicated		7-10 days PLUS remove catheter
Septic thrombosis, er	ndocarditis,	4-6 weeks PLUS remove catheter
osteomyelitis, POS B	Cx, complicated	6-8 weeks PLUS remove catheter for osteomyelitis
Tunneled HD cath, resolution of	CoNS or Gram neg bacilli	10-14 days PLUS abx lock with or without guidewire exchanged
bacteremia or	S. aureus	3 weeks (with negative TEE) PLUS remove catheter
fungemia and fever	C. albicans	14 days after first NEG BCx and guidewire exchange
Persistent bacterem fever	ia or fungemia and	4-6 weeks PLUS remove catheter
Clostridium difficile	2	Last Guideline: 2010 / Projected Update: Unknown
Initial episode, mild or moderate	WBC < 15,000 and SCr < 1.5 times the premorbid level	Initial episode, mild or moderate
Initial episode, severe	WBC \geq 15,000 and a SCr \geq 1.5 times the premorbid level	Initial episode, severe
Initial episode, severe, complicated	Hypotension or shock, ileus, megacolon	Initial episode, severe, complicated
First recurrence		Same as initial episode
Second recurrence		Vancomycin in a tapered and/or pulsed regimen (example: vancomycin 125mg po four times per day for 10-14 days, then 125mg po BID for 7 days, then 125mg po daily for 7 days, and then 125mg po every 2 or 3 days for 2-8 weeks)
Diabetic foot ulcer ³		Last Guideline: 2004 / Projected Update: Summer 2010
Soft Tissue Only		1-2 weeks: mild (\geq 2 manifestations of inflammation, cellulitis \leq 2 cm, infection limited to the skin/SQ)

		2-4 weeks: moderate to severe		
		2-5 days: s/p amputation with no residual tissue		
Bone or Joint		2-4 weeks: s/p amputation with residual soft tissue (no bone)		
		4-6 weeks: s/p amputation with residual tissue and viable but infected bone		
		> 12 weeks: no amputation or s/p amputation with residual dead bone		
Endocarditis ⁴		Last Guideline: 2005 / Projected Update: Unknown		
		PCN susceptible (MIC \leq 0.12 mg/L)		
		4 weeks: PCN or Ceftri mono*		
		OR		
		2 weeks: PCN or Ceftri PLUS GENT		
	Native Valve	PCN int (MIC >0.12 to \leq 0.5 mg/L)		
Streptococci,		4 weeks: PCN or Ceftri mono* PLUS		
S. bovus		2 weeks: GENT		
		PCN resist (MIC >0.5 mg/L)		
		Treat like Enterococcal Endocarditis		
		<u>PCN suscep (MIC \leq 0.12 mg/L)</u>		
		6 weeks: PCN or Ceftri*		
	Prosthetic Valve	± 2 weeks: GENT		
		PCN Int/Resist (MIC > 0.12 mg/L)		
		6 weeks: PCN or Cettri* PLUS GEN1		
		<u>PCN susceptible (MIC $\leq 0.1 \text{ mg/L}$)</u>		
C. mmouring				
S. prieumoniae		PCN Int (MIC >0.1 to $\geq 2 \text{ mg/L}$)		
		4 weeks: high dose PCN or Cettri (without meningitis)		
		4 weeks with/meningitis: consider vanco PLUS ritampin		
S. pyogenes		4 Weeks: PON G or Celazolin or Cellin 4 Gweeke: DON er Cefezelin er Cefezi - 2 weeke: CENT		
Groups B,C,G strep		4-0 WEEKS. PCIN OF CEId20IIII OF CEILIT ± 2 WEEKS. GEINT		
Methicillin Sensitive	Native Valve	* 3-5 daye' GENIT**		
Stanhylococci		MSSA = > 6 weeks: Nafcillin PLUS rifampin PLUS 2 weeks: GENT		
Claphylococol	Prosthetic Valve	CoNS – 4-6 weeks: Nafcillin* PLUS rifampin PLUS 2 weeks: GENT		
	Native Valve	6 weeks: VANCO (linezolid or TMP/sulfa + rifampin alternatives)		
Methicillin Resistant		MRSA – \geq 6 weeks: VANCO PLUS rifampin PLUS 2 weeks: GENT		
Staphylococci	Prostnetic Valve	CoNS - 6 weeks: Vanco PLUS rifampin PLUS 2 weeks: GENT†		
	PCN/AG/Vanco	4-6 weeks: PCN (AMP alt) PLUS		
	Sensitive	4-6 weeks: GENT (TID dosing)*		
	PCN/Vanco	1 6 wooks: PCN (AMP alt) PI US		
	Sensitive, GENT	4-6 weeks: strentomycin*		
	resistant			
Enterococcus –	Vanco/AG	6 weeks: AMP or Vanco PLUS Gent		
Native and	Sensitive, PCN	(depending on β -lactamase activity)		
Prostnetic valves	resistant			
	DCN/ACA/anao	<u>E. Idecium</u>		
	PCN/AG/Valico Resistant			
	Resistant	<u>E. Idecalis</u> 8 weeks: Iminenem/cilastatin or Ceftri PI US AMP		
HACEK				
(Haemophilus	Native Valve	4 weeks: Ceftri or Amp/Sulbactam (FQ as alternative)		
Actinogacillus.				
Cardiobacterium.				
Eikenella, Kingella	Prosthetic Valve	6 weeks: Ceftri or Amp/Sulbactam (FQ as alternative)		
sp.)				
Pseudomonas sp.	•	≥6 weeks: extended spectrum β-lactam PLUS tobra		
Fungal		Induction: Ampho B to clinical response, then life-long –azole suppression		
(*Vanco can be substi	tuted for PCN in cas	e of allergy)		
** Vanco, then B-lacta	m desensitization			
tor susceptible AG or	• FQ			

Intra-abdominal Infection ⁵	Last Guideline: 2010 / Projected Update: Unknown		
Complicated intra-abdominal infections	4-7 days: (> 7 days if unable to achieve adequate source control)		
Acute stomach & proximal jejunum perforations	≤ 24 hours: assumes adequate source control (focus of inflammation or infection is completely eliminated surgically and no extension of infection beyond the organ in question) and antibiotic therapy within 1 hour prior to operation.		
Bowel injuries (penetrating, blunt, or iatrogenic trauma)	<u>< 24 hours: Repair</u> 4-7 days: Repair	air <12 hours and antibiotics within 1 hour before operation) > 12 hours	
Acute appendicitis (without perforation, abscess, or local peritonitis)	<u> < 24 hours: Prophylactic therapy with narrow spectrum aerobic and facultative anaerobic coverage (administer within 1 hour before operation) </u>		
Cholecystitis, bowel obstruction and bowel infarction	24 hours: assumes adequate source control (focus of inflammation or infection is completely eliminated surgically and no extension of infection beyond the organ in question)		
Severe necrotizing pancreatitis <i>prior</i> to the diagnosis of infection	No antibiotic ther	apy recommended	
Meningitis ⁶			
Neisseria meningitides and Haemophilus influenzae	7 days		
Streptococcus pneumoniae	10-14 days		
Streptococcus agalactiae	14-21 days		
Aerobic gram-negative bacilli	21 days		
Listeria monogytogenes	≥ 21 days		
Pneumonia ^{7,8}	eumonia ^{7,8} Last Guideline: 2007 and 2005 / Projected Up		
Community Acquired Pneumonia	5 days PLUS afebrile x48-72hrs and clinically stable (*clinical instability defined by tachycardia, tachypnea, hypotension, O ₂ desaturation, NPO status, and/or mental status changes from baseline)		
	>5-7 days: initial therapy not active or complicated by extrapulmonary infection		
Hospital Associated Pneumonia/Ventilator Associated	7 days: initial antimicrobial selection correct and good clinical response		
	>7 days: <i>P. aeru</i>	ginosa	
Sepsis ⁹	I = ··· ·	Last Guideline: 2008 / Projected Update: Unknown	
Good source control	7-10 days		
Poor source control	>10 days: slow c	linical response, undrainable foci, immunologic deficiency	
Skin and Skin structure infection ¹⁰	[= ··· · •	Last Guideline: 2005 / Projected Update: Spring 2010	
	7-14 days: Gram	Negative Bacteria	
Neutropenia	7-10 days: Gram	Positive Bacteria	
	7-14 days: Secon	ndary Infection with antibiotic-resistant bacteria	
	2 12 months		
	3-6 weeks	Atvnical mycobacteria	
Immune-compromised with cellular	8-12 weeks	Cryptococcus species	
immunity deficiency (lymphomas, BMT,	8-12 weeks	Histoplasma species	
solid organ transplants, corticosteroid	7-10 davs	Varicella-zoster virus	
and other immunosuppressant use)	7 days	Herpes simplex virus	
	21 days	Cytomegalovirus	
Impetigo (due to Staphylococcus & Streptococcus species)`	~7 days, depending on clinical response		
Animal bites	3-5 days prophylaxis for moderate to severe wound, have crush injury, associated edema, are on the hands, or are close to bones/joints, or are in compromised hosts		
	5-10 days if asso	ciated cellulitis and abscess	
Human bites	4 weeks	Septic Arthritis	
	6 weeks	Osteomyelitis	

Candidemia or candidiasis ¹¹		Last Guideline: 2009 / Projected Update: Unknown		
Non-neutropenic	w/out metastatic complications	2 weeks after documented clearance from the bloodstream and resolution of symptoms attributable to candidemia PLUS catheter removal strongly recommended		
Neutropenia	w/out metastatic complications	2 weeks after documented clearance from the bloodstream, resolution of symptoms attributable to candidemia, and resolution of neutropenia PLUS catheter removal		
Chronic Dissemina	ted Candidiasis	until lesions have resolved (usually months) and should continue through periods of immunosuppression		
Osteomyelitis		6-12 months: fluconazole		
Septic Arthritis		6 weeks: fluconazole		
CNS Candidiasis		Until all signs and symptoms, CSF abnormalities have resolved		
Aspergillosis ¹²		Last Guideline: 2008 / Projected Update: Unknown		
Duration of therapy considerations 1. Duration of therapy for most aspergillosis infection, extent of disease, level of imme 2. Should be determined by resolution of cl antigenemia		is conditions has not been optimally defined. Duration is dependent on: site of nune suppression & ability to reverse immune suppression slinical & radiological findings with or without normalization of galactomannan		
Invasive Pulmonary Aspergillosis		6 - ≥12 weeks: Therapy should be continued throughout the period of immunosuppression and until lesion resolution		
Osteomyelitis &	Immunocompetent	≥ 6-8 weeks		
	Immunocompromised	Long-term suppressive therapy or treatment throughout immunosuppression		
Blastomycosis ¹³		Last Guideline: 2008 / Projected Update: Unknown		
Pulmonary Blastomycosis	Moderately severe to severe disease	1-2 weeks (or until improvement): Lipid amphotericin 3-5mg/kg/day or AmB deoxycholate @ 0.7-1 mg/kg/day then 3 days: Itraconazole 200mg PO TID then 6-12 months: Itraconazole 200mg PO BID		
	Mild to moderate disease	3 days: Itraconazole 200mg PO TID then 6-12 months: Itraconazole 200mg PO BID		
Disseminated Extrapulmonary	Moderately severe to severe disease	 1-2 weeks (or until improvement): Lipid amphotericin 3-5mg/kg/day or AmB deoxycholate @ 0.7-1 mg/kg/day then 3 days: Itraconazole 200mg PO TID then 6-12 months: Itraconazole 200mg PO BID 		
Blastomycosis	Mild to moderate disease	3 days: Itraconazole 200mg PO TID then 6-12 months: Itraconazole 200mg PO BID		
	Osteoarticular	≥ 12 months of antifungal therapy		
CNS Blastomycosi	S	Lipid AmB @ 5mg/kg/day for 4-6 weeks then Oral azole therapy with either fluconazole, itraconazole, or voriconazole		
Blastomycosis in Immunosuppressed Patients		 1-2 weeks (or until improvement): Lipid amphotericin 3-5mg/kg/day or AmB deoxycholate @ 0.7-1 mg/kg/day then 3 days: Itraconazole 200mg PO TID then ≥12 months: Itraconazole 200mg PO BID Consider lifelong suppressive therapy for oral itraconazole 200mg per day if immunosuppression cannot be reversed & in patients with relapses despite adequate treatment 		
Cryptococcal Disease ¹⁴		Last Guideline: 2010 / Projected Update: Unknown		
Cryptococcal Meningoencepalitis	HIV-Infected	Induction: AmB deoxycholate or lipid AmB plus flucytosine for 2 weeks or AmB deoxycholate or lipid AmB (for flucytosine-intolerant patients) for 4-6 weeks Consolidation:		
		Fluconazole for 8 weeks <u>Maintenance</u> : Fluconazole (preferred-superior) or itraconazole or AmB deoxycholate for ≥1 year		

		Induction: Lipid AmB plus flucytosine for 2 weeks or AmB deoxycholate or lipid AmB (without flucytosine) for 4-6 weeks	
Organ Transplant Recipients		Consolidation: Fluconazole for 8 weeks	
		Maintenance: Fluconazole for 6 months-12 months	
	Non-HIV and Non- transplant	Induction: AmB deoxycholate plus flucytosine for 2-≥4 weeks or • 2 weeks for low risk patients (early diagnosis, no uncontrolled underlying condition or sever immunocompromised state) with excellent clinical response to therapy • 4 weeks for patients with meningitis who have no neurological complications, no significant underlying disease or immunosuppression, and for whom CSF culture @ 2 weeks of txtment does not yield yeast • ≥ 4 all other patients not included in 2-4 week categories AmB deoxycholate (for fluctyosine-intolerant patients) for ≥6 weeks or Lipid AmB (for AmB deoxycholate-intolerant patients) with flucytosine for ≥4 weeks Consolidation: Fluconazole for 8 weeks Maintenance: Fluconazole for 6-12 months	
Pulmonary Cryptococcal	Mild-to-Moderate Infection (absence of diffuse pulmonary infiltrates, absence of severe immunosuppression, & lack of dissemination)	Fluconazole for 6-12 months	
	Severe Infection	Same as CNS Disease above	
Cryptococcemia		Same as CNS Disease above	
Non CNS disease, no fungemia, single site of infection, & no immunosuppressive risk factors		Fluconazole for 6-12 months	

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University of Wisconsin Hospital and Clinics

UWHC Guidelines For the Use of Prolonged Infusions of Beta-Lactams

Please address questions, comments, and suggestions regarding this guideline to Sara Shull, Manager, Drug Policy Program at 608/262-1817.

Guidelines developed by UWHC Center for Drug Policy Author: *Jeffrey Fish, PharmD, Brian Moilien, PharmD candidate* Updated by: Lucas Schulz, PharmD Reviewed by: Barry Fox, MD, Sarah Bland, RPh, Jeffrey Fish, PharmD Antimicrobial Subcommittee, Pharmacokinetic Committee Coordination: Lee Vermeulen, M.S., Director, CDP Approved by P&T: Update:

- A. Principles and Background
- B. Objectives
- C. Guideline
- D. Dose of Antibiotic
- E. References

A. Principles and Background

As a result of continuously developing antimicrobial resistance and a shortage of novel antimicrobial development, new dosing strategies have been proposed to optimize the pharmacodynamics of existing antimicrobials. Antimicrobial activity can be separated into two broad categories: time-dependent or concentration-dependent killing. Time-dependent antimicrobials demonstrate maximum efficacy when the percent of time above the minimum inhibitory concentration (%T>MIC) is optimized. The efficacy of concentration-dependent antimicrobials is dependent on the ratio of the area under the concentration-time curve and the minimum inhibitory concentration (AUC/MIC). Piperacillin/tazobactam, cefepime and meropenem all exhibit time-dependent killing. Theoretically, prolonged and continuous infusions of beta-lactams should increase the time of antimicrobial exposure above the MIC and, as a result, improve their efficacy. Prolonged infusions have beneficial effects over continuous infusions including not needing a dedicated line/catheter and usually using a lower total daily dose.

Piperacillin/Tazobactam

Kim et al. used a Monte Carlo simulation model of serum concentration-time profiles at steady state for piperacillin/tazobactam dosed by prolonged infusion regimens, conventional intermittent dosing regimens and continuous infusions.¹ The probability of achieving 50% unbound time above the MIC (fT>MIC) for 470 *P. aeruginosa* isolates with intermittent dosing was 74.7% (3.375g every 6 hours), 79.9% (4.5g every 6 hours), and 85.6% (4.5g every 4 hours). For prolonged infusions, probability of 50% fT> MIC was 83.3% (3.375g every 8 hours; 4-hour infusion), 87.1% (4.5g every 8 hours; 4-hour infusion), and 89.6% (4.5g every 6 hours; 3-hour infusion). For continuous infusions, probability of 50% fT>MIC was 82.3% for 10.125 g/day, 86.5% for 13.5 g/day and 90% for 20 g/day. Prolonged and continuous infusions achieved cumulative fractions of response and probabilities of target attainment greater than those observed with a 30 minute intermittent infusion. However, prolonged infusions of 3.375g every 8 hours at MICs of 16, 32, and 64 mcg/ml, respectively.

Lodise et al. compared mortality rates and median length stay for patients receiving prolonged infusion (over 4 hours) versus conventional infusion (over 30 minutes) of piperacillin/tazobactam in a retrospective cohort study of patients with documented *P. aeruginosa* infection.² Patients were excluded if the *P. aeruginosa* was documented as being intermediate or resistant to

piperacillin/tazobactam. There were 102 patients who received the prolonged infusion of piperacillin/tazobactam dosed 3.375g every 8 hours. There were 92 patients who received the conventional infusion of piperacillin/tazobactam dosed 3.375g every 4 hours (4 patients) or 6 hours (88 patients). There was no difference in baseline characteristics between the two groups. The 14-day mortality rate was 8.8% in the prolonged infusion group versus 15.2% in the conventional infusion group (p=0.17). The median length of stay after sample collection was 18 days in the prolonged infusion group versus 22.5 days in the conventional infusion group (p=0.09). However, in the subgroup of patients with an Acute Physiological and Chronic Health Evaluation-II (APACHE-II) score ≥17, the prolonged infusion group (n=41) had a significantly lower 14 day mortality (12.2% vs. 31.6% [p=0.04]) and decreased median length of stay (21 days vs. 38 days [p=0.02]) verses the conventional infusion group (n=38). However, there was not a significant improvement in mortality (p=0.5) or median length of stay (p=0.5) in patients with an APACHE-II score<17. The authors suggested the differences found with respect to APACHE-II score may have been because more critically ill patients with P. aeruginosa infection are most dependent on drug exposure for good clinical outcome. The Trauma Life Center uses APACHE-IV scoring for patient stratification and there is no direct correlation between APACHE-II and APACHE-IV. It is estimated that most patients in TLC who receive systemic antibiotics would have an APACHE-II score > 17.

A retrospective study was conducted in TLC after implementing prolonged infusions of piperacillin-tazobactam and meropenem. The study showed statistically significant decreased ventilator days (16.8 days to 9.6 days, 95% CI: -12.4 to -2.4), ICU length of stay (15.3 days to 10.7 days, 95% CI: -8.3 to -1.4), and hospital length of stay (30.9 days to 22.4 days, 95% CI: -18.7 to -1.2) between the intermittent infusion and the prolonged infusion group. There was also a decrease in mortality in the prolonged infusion group (20.7% to 12.4%, OR 0.54 (95% CI 0.18-1.66)) that didn't reach statistical significance. The use of the prolonged infusion was also associated with an estimated \$10,000 cost savings for the 54 patients included in the prolonged infusion group.

Meropenem

Mattoes et al. reviewed the pharmacodynamic data of several alternative dosing regimens for meropenem including continuous infusions, prolonged infusions, increased frequency of administration, and higher doses.³ The authors reported that for severe infections caused by meropenem susceptible pathogens with higher MICs, equivalent bactericidal activity was achieved with 500mg every 8 hours over 3 hours, 1000mg every 8 hours over 30 minutes, and 500mg every 6 hours over 30 minutes. For treatment of mild to moderate infections caused by pathogens with low MICs (such as *E coli and K pneumoniae*), prolonged infusions would only have a slight benefit over conventional 30 minute infusions. For clinical situations with a higher risk of antibiotic resistant, gram-negative pathogens, treatment with meropenem 1g every 8 hours as a 3-hour infusion, or 2g every 8 hours as either a 30-minute or 3-hour infusion would optimize pharmacodynamic parameters. One study reported that for an MIC of 4mg/L, the %T>MIC achieved with a 30-minute infusion of 500mg and 2000mg every 8 hours was 30% and 58%, respectively. Increasing the infusion time to 3 hours every 8 hours achieved a %T>MIC of 43% and 73% for the 500mg and 2000mg doses, respectively. Currently, there are no clinical trials comparing prolonged versus intermittent dosing for meropenem.

An internal audit of organisms recovered during calendar year 2008 revealed that 85% of common gram-negative species had MIC values less than or equal to 2 mcg/ml to meropenem. There were 15 isolates (a single Acinetobacter, and 14 Pseudomonas) that had MIC values greater than 2 mcg/ml. Pharmacokinetic and pharmacodynamic data suggest that equal outcomes would be achieved with 500mg every 8 hours infused over 3 hours for organisms with MIC less than 2 mcg/ml. A yearly audit will continue to be conducted.

To address 3-hour infusions of meropenem in renal dysfunction, Dr. Drusano (personal communication) ran a Monte Carlo simulation for estimated CrCl = 40 ml/min (500mg Q6H), 30 ml/min (500mg Q8H) and 17 ml/min (500mg Q12H). The results are in the following table for percent of patients with meropenem > MIC for 40% of the dosing interval.

MIC (mg/L)	Est CrCl = 40 ml/min	Est CrCl = 30 ml/min	Est CrCl = 17 ml/min
2	99%	99%	96%
4	92%	88%	75%

Based on these results, the guidelines renal dosing protocol appears valid.

<u>Cefepime</u>

Lee, et al. used a Monte Carlo simulation to evaluate pharmacodynamic principles of cefepime using various dosing regimens including intermittent infusions, prolonged infusions and continuous infusions.⁵ By using the parameter 50% fT>MIC, for organisms with an MIC \leq 4 mcg/ml, all regimens evaluated achieved this target goal. If the MIC is increased to 16 mcg/ml, 2g every 6-8 hours given by 30 minute infusions, 2g every 6-8 hours given by 3-4 hour infusions and 4-6g/day given by continuous infusions, cefepime will continue to be dosed as a thirty minute infusion.

B. Objective

Prolonged infusions of piperacillin/tazobactam and meropenem will be used at UWHC in patients with appropriate parenteral access to maximize pharmacodynamic principles and potentially decrease mortality, length of stay, and antimicrobial resistance.

C. Guideline

All patients prescribed meropenem or piperacillin/tazobactam will automatically be dosed with prolonged infusions (3 or 4 hours) *after* the first dose. The first dose will be infused over the conventional 30 minutes to obtain therapeutic levels quickly and potentially decrease mortality.⁶ Adult cystic fibrosis patients may receive prolonged infusions for pipercillin/tazobactam and meropenem at the discretion of the Advanced Pulmonary service, but are not limited to doses specified in this guideline.. Patients receiving continuous renal replacement therapy will be excluded from prolonged infusions and will be given the CRRT dose. Patients with CNS infections will also be excluded from the trial since these patients usually will need higher doses of the prescribed antibiotic. Finally, neutropenic patients will receive prolonged infusion, but will not be eligible for meropenem dose reduction and will continue to receive high-dose prolonged infusion meropenem.

If a prescriber writes for a different dosing regimen, the pharmacist will automatically change to the prolonged infusion regimen. The prescriber may write 'Do not change to prolonged infusion'. The pharmacist and nurse should make all efforts to continue to use prolonged infusion; however, if intravenous access becomes problematic, the pharmacist will change to the renally-dosed 30 minute infusion.

D. Dose of Antibiotic

1. Piperacillin/tazobactam⁷

Estimated CrCI	Dose	
<u>></u> 20 ml/min	3.375G IV Q8H infused over 4 hours	
< 20 ml/min and HD/PD patients	3.375G IV Q12H infused over 4 hours	

2. Meropenem

All patients prescribed meropenem will initially receive 500mg IV every 6 hours infused over 3 hours (adjusted based on renal function). IF after 72 hours no organism is recovered or the organism recovered has an MIC that is $\leq 2 \text{ mcg/ml}$, the dose of meropenem will be dose reduced to 500mg IV every 8 hours infused over 3 hours (adjusted based on renal function). IF organisms with an MIC > 2 mcg/ml are recovered, the meropenem dose will be kept at every 6 hours infused over 3 hours (adjusted based on renal function) until the meropenem is discontinued. This practice will ensure that organisms with higher MICs are appropriately treated prior to identification.

Estimated CrCl	Initial Dosing	Deescalated Dosing
<u>></u> 36	500mg IV Q6H over 3 hours	500mg IV Q8H over 3 hours
26-35	500mg IV Q8H over 3 hours	500mg IV Q8H over 3 hours
10-25	500mg IV Q12H over 3 hours	500mg IV Q12H over 3 hours
<10 / HD	500mg IV Q24H over 3 hours	500mg IV Q24H over 3 hours

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Compatibility:

Piperacillin/Tazobactam

Compatible	Incompatible	No Information
Amikacin	Acyclovir	
Calcium	Amiodarone	
Cisatracurium (*)	Amphotericin (all formulations)	
Clindamycin	Azithromycin	
Cyclosporin	Ciprofloxacin	
Daptomycin	Diltiazem	
Dexamethasone	Dobutamine	
Dexmedetomidine	Doxycycline	
Diazepam	Droperidol	
Digoxin	Drotrecogin	
Diphenhydramine	Gancyclovir	
Dopamine	Gentamicin	
Enalaprilat	Haloperidol	
Epinephrine	Hydralazine	
Esmolol	Insulin	
Fenoldopam	Labetalol	
Fentanyl	Midazolam	
Fluconazole	Phenytoin	
Fosphenytoin	Tobramycin	
Furosemide	Vancomycin	
Heparin	Vecuronium	
Hydrocortisone		
Hydromorphone		
Lidocaine		
Linezolid		
Lorazepam		
Magnesium		
Mannitol		
Methylprednisolone		
Metoclopramide		
Metoprolol		
Metronidazole		
Milrinone		
Morphine		
Naloxone		
Nitroglycerin		
Nitroprusside		
Norepinephrine		
Ondansetron		
Pantoprazole		
Phenylephrine		
Potassium Chloride		
Potassium Phosphate		
Ranitidine		
Sodium Bicarbonate		
Sodium Phosphate		
Sulfamethoxazole-		
trimethoprim		
Tacrolimus		

TNA	
Vasopressin	
Voriconazole	

Meropenem

Compatible	Incompatible	No Information
Atropine	Acyclovir	Amiodarone
Daptomycin	Amphotericin (all formulations)	Azithromycin
Dexamethasone	Diazepam	Calcium
Dexmedetomidine	Doxycycline	Ciprofloxacin
Digoxin	Fenoldopam	Cisatracurium
Diltiazem	Metronidazole	Droperidol
Diphenhydramine	Mannitol	Drotrecogin
Dobutamine	Ondansetron	Esmolol
Dopamine	Pantoprazole	Fentanyl
Enalaprilat	Sodium Bicarbonate	Fosphenytoin
Fluconazole		Ganciclovir
Furosemide		Haloperidol
Gentamicin		Hydralazine
Heparin		Hydrocortisone
Hydromorphone		Labetalol
Insulin		Lidocaine
Linezolid		Methylprednisolone
Lorazepam		Metoprolol
Magnesium		Micafungin
Metoclopramide		Midazolam
Milrinone		Naloxone
Morphine		Nitroglycerin
Norepinephrine		Nitroprusside
Potassium Chloride		Phenylephrine
Ranitidine		Potassium Phosphate
Tacrolimus		Propofol
TNA		Sodium Phosphate
Vancomycin		Tobramycin
Vasopressin		
Voriconazole		
UWHC Guidelines for the Use of Daptomycin (Cubicin®)

Guidelines developed by: Antimicrobial Use Subcommittee; UWHC Drug Policy Program (DPP) Authors: Barry Fox, MD, Sarah E. Bland, RPh Updated by: Lucas Schulz, PharmD Coordination: Sara Shull, PharmD, MBA, Manager, DPP Reviewed by: David Andes, MD; Barry Fox, MD; Dennis Maki, MD, Antimicrobial Use Subcommittee; Carol A. Spiegel, PhD, Marie Pietruszka, PharmD Originally Approved by P&T Committee: July 2010 Updated: February 2011 Scheduled For Review: February 2013

A. Background

Antimicrobial resistance among Gram-positive organisms, particularly the sharply rising incidence of life-threatening infections caused by methicillin-resistant staphylococci (MRSA) and vancomycin-resistant enterococci (VRE), has become a major concern. New antimicrobial drugs that are effective against these organisms are available; however, to preserve their utility, minimize their unique toxicities and provide cost-effective therapy, it is essential to ensure that these newer agents are used selectively and appropriately. Daptomycin (Cubicin[®], Cubist Pharmaceuticals) is the first antibiotic in the new cyclic lipopeptide class. It is bactericidal in a concentration-dependent manner against a wide variety of Gram-positive organisms, including those resistant to vancomycin.

B. Appropriate Indications

Appropriate use of daptomycin for extended therapy will usually require a culture/susceptibility test with identification of an organism that exhibits resistance to other possible antimicrobial agents. Based on the potential for bacterial resistance associated with the use of daptomycin, the UW Pharmacy and Therapeutics Committee has approved its use in the following conditions:

1.0 For patients with bacteremia with suspected MRSA, (i.e., coagulase-positive grampositive cocci in a blood culture with identification and sensitivities not yet completed) with daptomycin dosed at 6 mg/kg. Step-down therapy to vancomycin should usually be made if the vancomycin MIC of the organism is \leq 1.5 mcg/mL. Under certain circumstances approved by Infectious Diseases, daptomycin may be continued unless the vancomycin MIC is \leq 1.0 mcg/mL, usually in more serious staphylococcal infections.

2.0 Life-threatening infection, usually septic shock, endocarditis, complex deep skin and soft tissue infections (SSTIs) or intraabdominal sepsis, where there is strong suspicion that the patient is infected by MRSA or VRE (e.g., the patient is known to have been or is currently colonized by these organisms). If the cultures do not confirm MRSA or VRE infection within 72 hours, daptomycin should be switched to vancomycin or other antibiotics.

3.0 Invasive infections caused by vancomycin-resistant *Enterococcus faecium* such as bacteremia, intraabdominal infection, or deep SSTIs.

4.0 SSTIs or osteomyelitis caused by MRSA with a vancomycin MIC >1.5 mcg/mL. Under certain circumstances approved by Infectious Diseases, daptomycin may be continued unless the vancomycin MIC is \leq 1.0 mcg/mL.

5.0 Other MRSA/VRE indications :

5.1 Unable to tolerate vancomycin therapy. Combination therapy may be warranted if gram-negative organisms are present. A history of vancomycin "red man syndrome" (the histamine-release reaction) should generally *not* be considered a reason to use daptomycin for primary treatment; in that circumstance,

pretreatment with an H1-histamine blocker, such as diphenhydramine, and slowing the infusion rate can allow vancomycin to be used safely.

5.2 When the infecting MRSA strain is known to have a vancomycin MIC >1.5 mcg/mL.

5.3 Single-dose procedural prophylaxis in patients known to be colonized with VRE or with an MRSA isolate with vancomycin MIC \geq 2.0 mcg/mL, in a normally sterile body site undergoing an invasive interventional radiology or surgical procedure of that site (dose =4 mg/kg).

C. Inappropriate Uses

- 1.0 Daptomycin should not be used to treat pneumonia.
- 2.0 Daptomycin should not be used for empiric therapy of non-life-threatening infections where there is little evidence that MRSA or VRE are infecting or colonizing microorganisms.
- 3.0 Daptomycin should generally not be used for treating coagulase-negative staphylococcal infections where vancomycin is the drug of choice. Daptomycin may be considered if the vancomycin MIC is ≥4 mcg/mL
- 4.0 Daptomycin should not be used for inpatients for the simple convenience of oncedaily dosing. (except for transition of patients on vancomycin to daptomycin at or near the time of discharge to facilitate once-daily outpatient therapy).
- 5.0 Daptomycin should not be used to treat asymptomatic catheter or non catheterassociated bacteriuria.
- 6.0 MSSA infections, unless there are serious reactions to all appropriate betalactams, and the vancomycin MIC is >1.5 mcg/mL, or concomitant serious adverse reaction to vancomycin.
- 7.0 Under most circumstances, SSTIS or osteomyelitis with MRSA where the vancomycin MIC is \leq 1.5 mcg/mL
- 8.0 Antimicrobial prophylaxis for surgical procedures in patients colonized with MRSA, in the absence of a severe vancomycin allergy.

D. Contraindications

1.0 Daptomycin is contraindicated in any person with a known hypersensitivity to daptomycin or any of the product components.

E. Precautions

- 1.0 Concomitant use of daptomycin and HMG-CoA reductase inhibitors may increase the risk of the development of myopathy. HMG-CoA inhibitors may be considered for temporary suspension.
- 2.0 The use of antimicrobial agents may promote the overgrowth of nonsusceptible organisms. Appropriate measures should be taken if superinfection occurs during the course of treatment.
- 3.0 Development of diarrhea following administration of daptomycin may indicate the complicating pseudomembranous colitis.

- 4.0 Dose adjustment is required in renal insufficiency. Patients with creatinine clearances of less than 30 mL/min should receive the normal dose, but the dosing interval should be increased to once every 48 hours.
- 5.0 Avoid using except in cases of strongly suspected or documented infection to reduce the development of resistant organisms

F. Adverse Effects / Drug Interactions

- 1.0 Daptomycin has been associated with myalgia, increased creatine kinase and rhabdomyolysis.
- 2.0 Gastrointestinal side effects associated with daptomycin in clinical trials may include diarrhea, nausea, constipation and vomiting.
- 3.0 Other side effects observed in clinical trials (> 2% of patients) include headache, insomnia, rash, dizziness and fever.
- 4.0 Less common side effects in clinical trials (at least 1% of patients) include hypotension, pruritus, rash, hyperkalemia, hypokalemia, anemia, increased liver function tests, dizziness, headache, insomnia, renal failure, dyspnea and fungal infection.
- 5.0 Therapeutic levels of daptomycin may falsely prolong prothrombin time and elevate INR. If abnormal results are obtained, a specimen should be drawn just prior to the next daptomycin dose and tested for PT/INR. If the results are still abnormal, further investigation as to the cause is warranted.

G. Monitoring Parameters/Documentation

- 1.0 Therapeutic
 - 1.1 Culture and susceptibility of pathogen from site of infection
 - 1.2 White blood cell count with differential
 - 1.3 Physical exam to monitor for resolution of signs/symptoms of infection
- 2.0 Toxic
 - 2.1 CBC and blood chemistry periodically
 - 2.2 Baseline serum CPK and recheck at least weekly while on therapy

H. Infectious Disease Authorization

- 1.0 Use of daptomycin generally requires approval by Infectious Diseases.
- 2.0 The physician wishing to prescribe daptomycin for an adult patient will contact pager #3333 between the hours of 0700 and 2200 to reach the ID physician on call. If ID approval is given, the ordering physician will then inform the unit pharmacist that approval has been given. A formal consult is not required, but the prescribing physician or the pharmacist should document the name of the authorizing Infectious Diseases physician in the appropriate questions field when entering the order into HealthLink.
- 3.0 The physician wishing to prescribe daptomycin for a pediatric patient will contact the Pediatric Infectious Disease physician on call between the hours of 0700 and 2200 for approval of the order for daptomycin. If ID approval is given, the ordering physician will then inform the unit pharmacist that approval has been given. A

formal consult is not required, but the prescribing physician or the pharmacist should document the name of the authorizing Infectious Diseases physician in the appropriate questions field when entering the order into HealthLink.

4.0 In the event of an emergency or if there is an expected delay in the approval process, such as an order written between 2200 and 0700, a single dose of drug may be dispensed, if the appropriate criteria for treatment are met, by the Pharmacy without ID approval. Subsequent doses will not be dispensed until ID approval has been obtained.

I. Dose and Administration

- 1.0 Doses of daptomycin are administered every 24 hours and should be based on ideal body weight (IBW) to reduce the risk of myopathy.
- 2.0 If the dose entered is not based on IBW, the pharmacist is authorized to change the dose to one based on IBW unless the prescriber indicates "Dose as written" or the Infectious Diseases physician's note indicates that the dose is to be based on a weight other than IBW.
- 3.0 If patient's actual body weight is less than IBW (ABW < IBW), dose based on ABW.
- 4.0 For MRSA and MSSA bacteremia, endocarditis, 6 mg/kg, based on IBW, for 2-6 weeks.
- 5.0 Vancomycin-resistant *Enterococcus faecium* infections involving bacteremia: 6 mg/kg IV, based on IBW, every 24 hours for up to 14 consecutive days.
- 6.0 Vancomycin-resistant *Enterococcus faecium* infections NOT with bacteremia, such as urinary tract infections and SSTIs: 4 mg/kg IV, based on IBW, every 24 hours for up to 14 days.
- 7.0 Shorter courses of therapy (i.e., 3-7 days) may be suitable for other types of infections. Complicated skin and skin structure infections due to MRSA may be treated with 4 mg/kg, based on IBW, IV every 24 hours for a maximum of 8 to10 consecutive days.
- 8.0 Doses greater than 6 mg/kg, based on IBW, are not recommended at this time. In unusual circumstances, larger doses may rarely be indicated. Practitioners requesting the use of larger doses must get authorization through the #3333 pager.
- 9.0 Dosing during inpatient hemodialysis is 4mg/kg after HD for SSTIs or 6 mg/kg after HD for bloodstream infections. For inpatients, doses are given after the patient returns from HD.
- 10.0 For outpatients receiving HD, a 20% increase (~1mg/kg) may be given during the last 30 minutes of each HD session (5 mg/kg or 7 mg/kg). A dose increase on the HD session prior to 68 hour intra-dialytic period (Friday on a Monday, Wednesday, Friday schedule or Saturday on a Tuesday, Thursday, Saturday schedule) is NOT necessary but may be prescribed at the physicians discretion. Alternative dosing, see #13.
- 11.0 Patients receiving HD with residual renal function (≥ 100ml in 24 hours) should strongly be considered for an increased dose (50%) before an inter-dialytic period greater than 48 hours (ie. 4/4/6 or 6/6/9).

- 12.0 Dosing during continuous veno-venous hemodialysis (CVVHD) is 8mg/kg every 48 hours or 4mg/kg every 24 hours. Both regimens yield similar AUC/MIC ratios (PK/PD characteristic associated with efficacy) at steady-state; however, the 8mg/kg dose lower minimum concentration (PK parameter associated with safety). Dosing in alternative continous renal replacement therapies has not been studied.
- 13.0 Daptomycin injection should be administered over a period of 30 minutes. Do not use the intravenous infusion bag in series connections. Concomitant drugs should be administered separately. Diluents containing dextrose should not be used.
- 14.0 In the outpatient setting, a two-minute infusion may be used and is preferred.
- 15.0 The IV line should be flushed before administration of any other medications.
- 16.0 **Important Note:** Daptomycin may take 60 90 minutes to prepare due to the amount of time it takes to go into solution. Therefore, a STAT dose may not be available for 90 minutes or longer after the order is entered.

J. Cost

Drug	Route, Dose	Cost/Day (\$)	Cost/14 Days (\$)
Daptomycin	4 mg/kg IBW IV Q24h 6 mg/kg IBW IV Q24h	122.06 per 65 kg 183.09 per 65 kg	1708.84 per 65 kg 2563.34 per 65 kg
Vancomycin	1 g IV Q12h	8.12	113.62
Linezolid	600 mg IV Q12h	192.34	2692.76
Linezolid	600 mg PO Q12h	148.12	2073.68
Linezolid	600 mg IV Q12h x 7 days plus 600 mg PO Q12h x 7 days	170.23	23.83.22
Quinupristin / Dalfopristin (nonformulary at UWHC)	500 mg IV Q8h	456.99	6397.86

1.0 Cost* comparison of linezolid, quinupristin/dalfopristin, daptomycin and vancomycin

*Costs current as of 1/11/11

K. References

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