

TABLE OF CONTENTS

• Antiretrovirals in Adults and Adolescents	1
• Immunizations in Adults	1-2
• Influenza Immunizations in Children	2
• American College of Physician Statement on HIV Screening	2-3
• Clinical Care Guidelines: Piperacillin-tazobactam Extended Infusion in Adults	3-5
• P&T Committee Formulary Actions	5

Antiretrovirals in Adults and Adolescents

An update of the guidelines, "Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents", was released in November by the Panel on Antiretroviral Guidelines for Adults and Adolescents of the Department of Health and Human Services. Highlights of these changes include a new format, new rating system, and new content. The new format includes important tables and references throughout the document with larger tables in the appendix; all tables may be viewed at the AIDSinfo website (www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf). The new rating system is consistent with other infectious disease guidelines where the strength of recommendations is rated as "A", "B", or "C", with "A" being a strong recommendation; "D" and "E" have been removed. Quality of evidence was revised so that "I" includes not only randomized controlled trials with clinical endpoints, but also with validated laboratory outcomes such as viral load; "II" includes non-randomized trials or well-designed observational cohort studies with long-term clinical outcomes; and "III" remains based on expert opinion.

The new content includes recommendations and a timeline for baseline and laboratory monitoring of antiretroviral therapy for efficacy and safety. A new recommendation (BII) is to consider resistance testing at viral loads of 500 to 1000 copies/mL, although it may not be reliable at all times. Regarding treatment initiation in antiretroviral-naïve patients, a combination regimen should consist of either 1 non-nucleoside reverse transcriptase inhibitor (NNRTI) + 2 nucleoside reverse transcriptase inhibitor (NRTIs), or a protease inhibitor (PI) preferably boosted with ritonavir + 2 NRTIs.

- The preferred NNRTI is efavirenz (A1).
- The preferred PIs are now ritonavir-boosted darunavir, lopinavir, or atazanavir once daily (A1), or ritonavir-

boosted fosamprenavir twice daily (B1).

- The preferred dual NRTIs are tenofovir + emtricitabine (A1); abacavir + lamivudine moved from preferred to alternative (B1) due to large, observational cohort studies which raised concern of an increased risk of myocardial infarction in patients with cardiac risk factors, as well as concern for virologic potency when baseline viral loads are over 100,000 copies/mL.
- For combinations, unboosted atazanavir + didanosine + emtricitabine (or lamivudine) is not recommended due to efficacy concerns (B1), and nevirapine + tenofovir + emtricitabine (or lamivudine) should be used with caution and close monitoring of virologic responses due to reports of early virologic failure in several small studies (CII).
- A section was added on regimen simplification for virologically-suppressed patients under management of the treatment-experienced patient.
- Regimen simplification, or change in effective established therapy to reduce pill burden and frequency of dosing, improve tolerability, or reduce particular food and fluid requirements, may be performed in patients on therapies no longer recommended as preferred or alternative initial choices, with incomplete data on resistance or interactions, or prior to availability of easier or more tolerable options.
- The impetus for regimen simplification is to improve quality of life and medication adherence, and to prevent long-term toxicities and risk of virologic failure.

Immunizations in Adults

Of diseases that can be prevented with vaccines, 95% occur in adults. These vaccine-preventable diseases lead to mortality in >46,000 individuals yearly and cost billions of dollars to treat according to the Centers for Disease Control and Prevention (CDC). Only 26% to 69% of adults get recommended vaccines. Many are simply naïve as to the risk of preventable diseases, booster doses necessary

to maintain immunity, or availability of novel vaccines. Two medical societies, the American College of Physicians (ACP) and the Infectious Diseases Society of America (IDSA), released a joint statement endorsed by 17 other medical organizations regarding the importance of vaccinations in adults. These groups offer the following 5 proposals:

- Current immunization status should be reviewed during medical visits and patients educated on the importance of vaccinations.
- Patients should be provided with or referred appropriately for recommended vaccinations.
- Vaccine administration should be documented in the medical record, as well as those received in other settings, patient refusals, and contraindications.
- Immunization status should be documented by the physician when patients are referred for vaccinations.
- Physicians and staff should be vaccinated according to the CDC recommendations, including annual influenza immunizations.

Subspecialists who see patients with a chronic disease on a regular basis, such as infectious disease physicians treating patients with human immunodeficiency virus (HIV), also have the opportunity to provide immunization administration or referral. Although specific recommendations differ according to factors such as age, immunizations that should be addressed are influenza, pneumococcal, tetanus-diphtheria-pertussis, hepatitis A, hepatitis B, measles-mumps-rubella, chickenpox (varicella), meningococcal, human papillomavirus, and shingles (zoster). More information can be found in the CDC Adult Immunization Schedule (www.cdc.gov/vaccines/recs/schedules/adult-schedule.htm), ACP Adult Immunization Website (www.acponline.org/running_practice/quality_improvement/projects/adult_immunization), and IDSA Adult Immunization Website (www.idsociety.org/adultimmunization.htm).

Influenza Immunizations in Children

An update by the American Academy of Pediatrics (AAP) of the current recommendations regarding influenza immunization in children for 2008 to 2009 was published in November. The AAP recommends annual influenza vaccination for all children aged 6 months to 18 years, household contacts and out-of-home care providers of children with high-risk conditions and healthy children aged <5 years, females who will be pregnant during the influenza season, and healthcare professionals.

Expansion of the recommended age range targets all school-aged children, healthy or with risk factors (chronic medical conditions or immunosuppression), since they have the greatest disease burden and a significantly higher risk of requiring medical care versus healthy adults. Reducing the incidence of influenza in children will reduce transmission to household and community contacts.

Vaccinating close contacts of high-risk children will reduce the incidence of influenza in these children at increased risk of infection, hospitalization, and complications. In healthy

children <24 months, the risk of hospitalization for influenza is at least that of high risk groups. In children aged 2 to 5 years, influenza-related morbidity is increased, including outpatient visits and antibiotic use. Vaccination is neither approved nor recommended in those aged <6 months.

In children receiving the influenza vaccine for the first time, those aged ≥ 9 years require only 1 dose while those aged <9 require 2 doses separated by ≥ 4 weeks. In children aged <9 who received only 1 dose in their first vaccination season, 2 doses should be administered in the season immediately following.

Recommendations regarding antiviral chemoprophylaxis or treatment with oseltamivir or zanamivir have not been modified; amantadine or rimantadine are ineffective and should not be used.

Children aged 6 months to 18 years should be identified and parents informed when the annual influenza vaccine is due. All children should be offered the influenza vaccine immediately after it is made available and throughout the entire influenza season, which may extend beyond March and have >1 peak of activity. Therefore, vaccination up through May 1 can still be protective and allows for a second dose in children who require it.

A collaborative effort between healthcare professionals, vaccine organizers, and public health agencies should be initiated to develop plans to achieve the recommended vaccination rate of all children ages 6 months through 18 years starting no later than the 2009 through 2010 influenza season. In the event of a shortage or delayed availability of influenza vaccines, these groups need to work with the vaccine manufacturers, distributors, and payers to prioritize administration.

The 3 influenza strains in the 2008 to 2009 vaccines are different from the previous year's strains based on global surveillance. According to the CDC website, influenza activity for the 2008 to 2009 influenza season thus far has been "sporadic" in the state of Illinois through the week ending November 29, 2008. Throughout the United States, no areas have reported regional or widespread activity. Influenza rates normally peak in February; therefore, the time frame for vaccination extends beyond the customary fall season.

American College of Physicians Statement on HIV Screening

Of the 1 to 1.18 million people with HIV/Acquired Immune Deficiency Syndrome (AIDS) in the United States, an estimated 24% to 27% are undiagnosed. The 25 to 44 year old age group has the highest proportion of newly diagnosed cases. At least 20,000 patients yearly are infected from others who were unaware of their HIV status. Since 38% of patients develop AIDS within 1 year of diagnosis, many people are likely infected for many years prior to diagnosis.

In order to ensure maximal benefit from treatment, early diagnosis is necessary.

A guidance statement was developed by the American College of Physicians (ACP) based on critical appraisal of HIV screening guidelines from the Centers for Disease Control and Prevention (CDC) and the U.S. Preventive Services Task Force (USPSTF), and was endorsed by the HIV Medicine Association. This guideline applies to adults and adolescents aged >13 years seen in healthcare settings.

This critical appraisal evaluated each guideline in 6 domains by scoring 23 questions. According to the USPSTF 2007 update, all adults and adolescents at increased risk of HIV infection should be screened, as well as all pregnant women (strong recommendations). The risk factors considered are men who have had sex with men after 1975; men and women who have unprotected sex with multiple partners; past or present injection drug use; men and women who exchange sex for money or drugs or have sexual partners who do; persons whose past or present sexual partners were infected with HIV, were bisexual, or were injection drug users; persons being treated for sexually transmitted diseases (STDs); and persons with a history of blood transfusion between 1978 and 1985. However, routine screening of adults and adolescents at no increased risk is not addressed (no recommendation for or against). Anyone who requests screening is also recommended for testing, as well as patients in a clinical setting with a high prevalence or high risk. The high risk clinical settings are considered STD clinics, correctional facilities, homeless shelters, tuberculosis clinics, clinics serving men who have sex with men, and adolescent health clinics with a high prevalence of STDs. Although most adults are willing to disclose high-risk behaviors when the concern is raised by their physician, 10% to 25% of those who test positive report no such behaviors. Effects of HIV screenings on transmission rates have not been directly examined. It is unknown to what degree counseling reduces high-risk behavior and treatment reduces viral load and subsequent infectivity. However, one-third to one-half of infected patients remain untreated.

According to the CDC 2006 guideline, healthcare providers should initiate routine screening in all patients aged 13 to 64 years, unless the documented prevalence of undiagnosed HIV infection in their patient population is or becomes <0.1%. Routine screening should also take place in all patients initiating tuberculosis treatment or seeking STD treatment, including all patients who present to an STD clinic with a new complaint, as well as in all pregnant women. The CDC states that risk-based screening is ineffective in preventing HIV transmission; universal testing strategies (i.e., pregnant women, blood supply) are very effective; and patients subsequently reduce high-risk behaviors when they test positive.

The cost-effectiveness of HIV screening has been

evaluated. One study demonstrated a 1.52-year increase in life-expectancy with early identification and treatment, and suggests that 1 screening could decrease lifetime transmission from a mean of 1.12 partners to 0.95 among men who have sex with men, to 0.35 among heterosexual men, and to 0.12 among heterosexual women. The cost-effectiveness ratio was \$50,000 per quality-adjusted life-year (QALY) gained, even at a prevalence rate as low as 0.05%. Screening inpatients would be cost effective at a 0.1% prevalence rate. Similarly, the incremental cost-effectiveness of 1 screening was \$36,000, \$38,000, and \$113,000 per QALY gained in populations with a 3%, 1%, and 0.1% prevalence rate, respectively. When the benefit of reduced transmission is included, screening is cost-effective at a 0.2% prevalence rate. Screening patients aged 65 to 75 with a sexual partner at risk would cost <\$60,000 per QALY gained at a 0.1% prevalence. Therefore, HIV screening is cost-effective, even at low prevalence rates of 0.1% to 0.2%.

In conclusion, the ACP recommends 2 guidance statements:

- Guidance Statement 1: ACP recommends that clinicians adopt routine screening for HIV and encourage patients to be tested. This is based on the fact that early identification and treatment significantly extends patients' lifespans and may reduce transmission through behavior changes and viral load suppression. Also, risk-based screening is largely ineffective in early disease identification. Prenatal screening has been successful in nearly eliminating mother-to-child transmission in the United States. Even if HIV prevalence is low, screening has been demonstrated to be cost-effective. If prevalence is known, a 0.1% threshold for routine screening is reasonable. Clinicians should educate patients on HIV risk factors, particularly adolescents and older patients. Due to a relatively high rate of false positives with the oral rapid HIV test, positive results with this method require confirmation with traditional testing.
- Guidance Statement 2: ACP recommends that clinicians determine the need for repeat screening on an individual basis. The need for repeated testing depends on the status of ongoing risk factors and clinical judgment. The CDC recommends annual testing in high-risk patients, including those mentioned above as well as their sexual partners and heterosexual persons who have had or whose sexual partners have had >1 sexual partner since their most recent HIV test.

Clinical Care Guidelines: Piperacillin-Tazobactam Extended Infusion in Adults

These systematically developed statements have been created to assist the practitioner in the formulation of health care decisions in specific clinical circumstances. They are not to be construed as an inflexible set of correct procedures or protocols. In each clinical circumstance the exercise of individual judgment is essential. Guidelines are based upon statistical averages and opinions of practicing clinicians. Variation from these guidelines does not constitute improper care or improper professional judgment. Evaluation of these variations requires detailed analysis of the facts and circumstances surrounding the individual patient's care.

Objective

To provide healthcare professionals with a guideline for the implementation of extended (4-hour) infusion piperacillin-tazobactam in order to optimize microbiologic response and improve patient outcomes throughout the hospital.

Definitions

Minimum Inhibitory Concentration (MIC): the minimum amount of drug necessary to inhibit the bacterial growth.

Time-dependent killing: microbiologic response dependent on the amount of time spent above the MIC.

Position Statement

Piperacillin-tazobactam (Zosyn®) is a commonly prescribed antibiotic at the UIMCC due to its broad spectrum of activity and anti-pseudomonal coverage. It exerts its antimicrobial effect in a time dependent manner with maximal response when drug concentrations remain above the MIC for at least 50% of the dosing interval.

Retrospective cohort and computerized modeling studies have shown increased drug exposure above the MIC, decreased mortality and shorter length of hospital stay with the use of extended 4 hour infusions of piperacillin-tazobactam. This is of particular importance given the emergence of *Pseudomonas aeruginosa* strains with multiple mechanisms of resistance and high MICs toward anti-pseudomonal agents. The extended infusion will optimize therapy by producing sustained drug levels above the MIC for susceptible organisms, which may lead to improved efficacy and clinical outcomes.

The traditional piperacillin-tazobactam regimen of 3.375 grams every 6 hours infused over 30 minutes will be replaced by an extended infusion regimen of 3.375 grams every 8 hours infused over 4 hours.

Pediatric patients and patients in pediatric nursing units are excluded from this guideline.

Procedure

I. Adult Dosing

A. Dosing regimens for all adult patients are as follows:

1. Recommendations for both empiric therapy and treatment dosing are in table 1.

Table 1. Adult dosing regimens

Antimicrobial Agent	CrCL = 20 mL/min	CrCL < 20 mL/min or ESRD	Continuous Renal Replacement Therapy
Piperacillin-tazobactam	3.375 gm Q8H	3.375 gm Q12H	3.375 gm Q8H

NOTE: The only available piperacillin-tazobactam dose will be 3.375 grams. Every 6 hours dosing of piperacillin-tazobactam will no longer be given at UIMCC.

2. Select the appropriate dosing regimen from the established order sentence in Cerner based on the patient's renal function.
3. The piperacillin-tazobactam 3.375 gram dose will be supplied in a 100 mL IVPB. The 100 mL dose

will be infused over 4 hours at a rate of 30 mL/h per label instructions. The default administration time will be set for every 8 hours at 5am, 1pm, and 9pm.

- B. "NOW" or "STAT" doses: If piperacillin-tazobactam therapy needs to be initiated at a time outside of the established dosing schedule, give a "NOW" or "STAT" dose of piperacillin-tazobactam 3.375 grams infused over 4 hours followed by the scheduled dose infused over 4 hours. This may result in 8 hours of piperacillin-tazobactam infusion.

1. However, please use clinical judgment when considering the necessity of a "NOW" or "STAT" dose. If the scheduled dose is due in 1 hour, do NOT give a "NOW" or "STAT" dose. If the scheduled dose is due in 2 hours, therapy should not be held and a "NOW" or "STAT" dose would be appropriate.

2. When the 2nd dose overlaps with a "NOW" or "STAT" initial dose, the "NOW" or "STAT" dose should be infused over 4 hours. After completing the initial dose, immediately follow with the 2nd dose infused over 4 hours resulting in 8 hours of piperacillin-tazobactam infusion.

- II. Exemptions from a 4 hour infusion: If piperacillin-tazobactam is required for the OR, a one-time dose of the antibiotic may be infused over 30 minutes intra-operatively. The extended infusion regimen must be resumed once returning to the floor.

III. Limitations of extended infusion

A. A compatibility chart (See Table 3) will be available at all nursing stations and at the patient bedside to assist with questions about compatibility of piperacillin-tazobactam and common intravenous medications. Additional questions about compatibility with other medications that require intravenous infusion should be directed to the pharmacist (PharmD On-Call #4958).

B. Should issues concerning intravenous access arise, a central line should not be placed for the sole purpose of piperacillin-tazobactam administration.

C. If a 4 hour infusion is not feasible, do not give piperacillin-tazobactam. Alternatively, cefepime +/- metronidazole (if anaerobic coverage is needed) may be used for broad antimicrobial therapy including *Pseudomonas*.

IV. Discharge considerations: Home administration

A. If possible, the patient may continue either continuous infusion or a 4 hour extended infusion regimen, depending on the home care healthcare provider. Otherwise, the FDA-approved piperacillin-tazobactam usual adult dose should be used.

B. Select the appropriate regimen based on the patient's renal function from table 2.

Table 2. Home administration dosing regimens

Piperacillin-tazobactam Regimen	CrCL = 20 mL/min	CrCL < 20 mL/min or ESRD	Bolus dose
Intermittent 4 hour infusion (dose in 100 mL D ₅ W or NS)	3.375 gm Q8H	3.375 gm Q12H	None
Continuous Infusion (dose in 250 mL D ₅ W or NS)	10.125 gm infused over 24 H daily	3.375 gm infused over 12 H twice daily	3.375 gm infused over 30 minutes

Addenda

The list in table 3 does not include compatibility data for all medications. For information on other medications, please search Micromedex using the "IV Compatibility" tab. Please contact the pharmacist for additional information on IV Compatibility (PharmD On-call #4758).

Table 3. Y-site compatibility for piperacillin-tazobactam

COMPATIBLE	
Amikacin	Methylprednisolone
Calcium Chloride	Metoclopramide
Calcium Gluconate	Metoprolol
Daptomycin	Metronidazole
Diazepam	Milrinone
Dopamine	Morphine
Enalaprilat	Naloxone
Epinephrine	Nitroglycerin
Esmolol	Nitroprusside
Fentanyl	Norepinephrine
Fluconazole	Ondansetron
Fosphenytoin	Pentobarbital
Furosemide	Phenylephrine
Heparin	Potassium Chloride
Hetastarch (Hextend)	Potassium Phosphate
Hydrocortisone	Sodium Bicarbonate
Hydromorphone	Sodium Phosphate
Linezolid	Tacrolimus
Lorazepam	TPN (without insulin)
Magnesium Sulfate	Vasopressin
INCOMPATIBLE	
Amiodarone	Haloperidol
Azithromycin	Insulin, regular
Caspofungin	Labetalol
Diltiazem	Levofloxacin
Dobutamine	Midazolam
Drotrecogin alfa	Nicardipine
Esomeprazole	Phenytoin
Famotidine	Vecuronium
CONTACT PHARMACY	
Amphotericin Lipid Complex	Tobramycin
Gentamicin	Vancomycin

P&T Committee Formulary Action**Line extensions**

- Cefepime 1gm/50mL injection
- Cefepime 2gm/50mL injection
- Thrombin 5000 units topical (epistaxis kit)

Deletions

- Erythromycin ethylsuccinate 400mg/5mL oral suspension
- Amoxicillin 25mg/mL oral suspension
- Amoxicillin-clavulanate 25mg/mL oral suspension
- Ampicillin 25mg/mL oral suspension
- Cephalexin 25mg/mL oral suspension
- Dexamethasone 0.5mg/5mL elixir
- Ferrous sulfate 44mg/mL elixir
- Penicillin VK 25mg/mL oral suspension
- Zinc sulfate 1mg/mL oral suspension

Authors: Jennifer Banovic, PharmD, BCPS;
Lynley Heinrich, PharmD

Editor: Jennifer Banovic, PharmD, BCPS