

ASHP Therapeutic Guidelines for Nonsurgical Antimicrobial Prophylaxis

The ASHP Therapeutic Guidelines for Nonsurgical Antimicrobial Prophylaxis,¹ which have provided practitioners with standardized effective regimens for the rational use of prophylactic antimicrobials, have been revised as described in this document on the basis of new clinical evidence and additional concerns. Recommendations are provided for adult and pediatric patients (1 to 21 years of age), including infants (one month to 2 years of age). Geriatric patients, newborns (premature and full-term), and patients with renal or hepatic dysfunction are not specifically addressed (with the exception of neonatal prevention of human immunodeficiency virus [HIV] infection). Therefore, the guidelines may not be applicable to these patients, or certain adjustments to the recommendations may be necessary. The higher occurrence of resistant organisms and the importance of controlling health care costs are also considered.

Prophylaxis refers to the prevention of an infection and can be characterized as primary prophylaxis, secondary prophylaxis (suppression), or eradication. Primary prophylaxis is the prevention of an initial infection. Secondary prophylaxis is the prevention of recurrence or reactivation of a preexisting infection (e.g., a latent herpes simplex virus [HSV] infection). Eradication is the elimination of a colonized organism to prevent the development of an infection (e.g., eliminating methicillin-resistant *Staphylococcus aureus* [MRSA] from the nares of health care workers). These guidelines focus on primary prophylaxis. Secondary prophylaxis and eradication are not addressed (with the exception of secondary prophylaxis with antiviral agents in granulocytopenic patients).

Antimicrobial prophylaxis is indicated in selected patients to prevent certain infections that are not a direct result of a surgical procedure. The following guidelines address (1) prevention of infection in specialized settings, including endocarditis in patients at risk who are undergoing dental, respiratory, gastrointestinal (GI), or genitourinary (GU) procedures; nosocomial pneumonia in mechanically ventilated patients; and meningitis after nonpenetrating head trauma associated with a basilar skull fracture, (2) prevention of infection in anticipation of or after defined exposures, including influenza A in patients at risk; malaria and traveler's diarrhea in persons traveling abroad; tuberculosis (TB); and HIV infection in occupational exposure, (3) prevention of perinatally acquired infection, including HIV, HSV-2, and group B streptococcal disease, and (4) prevention of opportunistic infections in the immunocompromised host, including afebrile granulocytopenic cancer patients, afebrile bone marrow transplant recipients, and HIV-infected persons.

The following guidelines review the persons at risk for infection, the efficacy of prophylaxis, and the current recommendations regarding patient eligibility and drug selection. The duration of prophylaxis is addressed only in cases for which data are available. Antimicrobial selection for specific patients should consider not only efficacy but also the agents' adverse-effect profiles, comparative costs, and the patient's drug allergies. Discussion of the adverse-effect profile of the antimicrobials is beyond the scope of these guidelines. Patient preference may also play an important

role in the use of prophylaxis. Examples are perinatal prophylaxis to prevent HIV infection, perinatal prophylaxis to prevent group B streptococcus, prophylaxis for occupational exposure to HIV, and prevention of influenza A.

Guideline Development and Use

These guidelines were prepared by the Rocky Mountain Poison and Drug Center under contract to ASHP. The project was coordinated by a drug information pharmacist who worked with a multidisciplinary consortium of writers and consulted with six physicians on staff at the University of Colorado Health Sciences Center. The project coordinator worked in conjunction with an independent panel of eight clinical pharmacy specialists with expertise in either adult or pediatric infectious disease. The panel was appointed by ASHP. Panel members and contractors were required to disclose any possible conflicts of interest before their appointment. The guidelines underwent multidisciplinary field review to evaluate their validity, reliability, and utility in clinical practice. The final document was approved by the ASHP Commission on Therapeutics and the ASHP Board of Directors.

The recommendations in this document may not be appropriate for use in all clinical situations. Decisions to follow these recommendations must be based on the professional judgment of the clinician and consideration of individual patient circumstances and available resources.

These guidelines reflect current knowledge (at the time of publication) on nonsurgical antimicrobial prophylaxis. Given the dynamic nature of scientific information and technology, periodic review, updating, and revision are to be expected.

Strength of Evidence for Recommendations. The primary literature from the previous ASHP Therapeutic Guidelines on Nonsurgical Antimicrobial Prophylaxis¹ was reviewed together with the primary literature published between the date of the previous guidelines and August 1997, identified by a MEDLINE search. Particular attention was paid to study design, with greatest credence given to randomized, controlled, double-blind studies. Established recommendations by experts in the area (i.e., the American Heart Association's [AHA's] recommendations on bacterial endocarditis, recommendations of the Centers for Disease Control and Prevention [CDC], and the U.S. Public Health Service [USPHS] and Infectious Diseases Society of America [IDSA] Prevention of Opportunistic Infections Working Group recommendations for the HIV population) were also considered.

Guideline development included consideration of the following characteristics: validity, reliability, clinical applicability, flexibility, clarity, and a multidisciplinary nature as consistent with ASHP's philosophy on therapeutic guidelines.² Recommendations for the use of an antimicrobial are substantiated by the strength of evidence that supports the recommendation. The strength of evidence represents only support for or against prophylaxis and does not apply to the antimicrobial choice, dose, or dosage regimen. The strength

of evidence supporting the recommendations for the use of an antimicrobial was classified as follows:

- Level I:** (evidence from large, well-conducted randomized, controlled clinical trials or a meta-analysis)
- Level II:** (evidence from small, well-conducted randomized, controlled clinical trials)
- Level III:** (evidence from well-conducted cohort studies)
- Level IV:** (evidence from well-conducted case-control studies)
- Level V:** (evidence from uncontrolled studies that were not well conducted)
- Level VI:** (conflicting evidence that tends to favor the recommendation)
- Level VII:** (expert opinion)

This system has been used by the Agency for Health Care Policy and Research (AHCPR), and ASHP supports it as an acceptable method for organizing strength of evidence for a variety of therapeutic or diagnostic recommendations.² Each recommendation was assigned a category corresponding to the strength of evidence that supports the use or nonuse of antimicrobial prophylaxis:

- Category A:** (levels I–III)
- Category B:** (levels IV–VI)
- Category C:** (level VII)

A category C recommendation represents a consensus of the expert panel based on the clinical experience of individual panel members and a paucity of quality supporting literature. In cases for which opinions were markedly divided, the recommendations indicate that a substantial number of panel members supported an alternative approach.

Pediatrics. Pediatric patients are subject to many prophylaxis opportunities that are similar to those for adults. Although pediatric-specific prophylaxis data are sparse, available data have been evaluated and are presented in this document. However, in most cases, the pediatric recommendations have been extrapolated from adult data.

Clinical studies to determine the optimal dosages of antimicrobials used for pediatric prophylaxis are essentially nonexistent. In contrast, there are sufficient pharmacokinetic studies for most agents used such that appropriate pediatric dosages can be estimated that provide similar systemic exposure, and presumably efficacy, as that demonstrated by the adult efficacy trials. It is also common clinical practice to use antimicrobial prophylaxis in pediatric patients in a similar, if not identical, manner as in adults. Therefore, the pediatric dosages provided in these guidelines are based largely on pharmacokinetic equivalence and the generalization of the adult efficacy data to pediatric patients.^{3,4} Because pediatric trials have generally not been conducted, a strength of evidence has not been applied to these recommendations. With few exceptions (e.g., aminoglycoside dosages), pediatric dosages should not exceed the maximum adult recommended dosages. If dosages are calculated on a milligram-per-kilogram basis for children weighing more than 40–50 kg, the calculated dosage will exceed the maximum recommended dosage for adults; thus adult dosages should be used.

Resistance. The basis for guideline development was to recommend an effective antimicrobial with the most narrow spectrum of activity. Alternative antimicrobials were included on the basis of documented efficacy. Individual health systems must take into consideration specific resistance patterns at their practice site when adopting these recommendations.

When considering the use of antimicrobials for prophylaxis, one must also consider the risks of contributing to the development of antimicrobial resistance. In numerous studies of prophylaxis, both surgical^{5,6} and nonsurgical,^{7–16} attempts have been made to evaluate the impact of antimicrobial prophylaxis on the development of resistance. Numerous studies^{5,7–13} demonstrated an increase in resistance, yet other studies^{6,14–16} failed to demonstrate the emergence of resistance. Most of the studies demonstrating the development of resistance involved the use of broad-spectrum antimicrobials.^{5,7–13} Thus, current recommended practice is to use narrow-spectrum antimicrobials for the shortest duration to reduce the development of antimicrobial resistance.

The frequency with which methicillin-resistant staphylococci have been recovered from various infection sites has increased steadily throughout the United States.^{17–19} The frequency of methicillin resistance among staphylococcal strains rose from 2.4% in 1975 to 29% in 1991.¹⁹ CDC's National Nosocomial Infections Surveillance identified a rapid increase in vancomycin-resistant enterococci (VRE) from 0.3% in 1989 to 7.9% in 1993. The rate of high-level enterococcal resistance to penicillin and aminoglycosides increased simultaneously. The use of vancomycin has been reported consistently as a risk factor for infection and colonization with VRE and may increase the possibility of the emergence of vancomycin-resistant *S. aureus* or vancomycin-resistant *Staphylococcus epidermidis*.²⁰ In response, the Hospital Infection Control Practices Advisory Committee (HICPAC), with the support of other major organizations, developed control measures for preventing and controlling vancomycin resistance.²¹ The ASHP guidelines are consistent with the HICPAC recommendations. The following situations are appropriate or acceptable for use of vancomycin: prophylaxis of endocarditis (as recommended by AHA) before certain procedures and for major surgical procedures involving implantation of prosthetic materials or devices (e.g., cardiac and vascular procedures, total hip replacement) at institutions with a high rate of infections due to MRSA or methicillin-resistant *S. epidermidis*. Use of vancomycin for routine surgical prophylaxis should be discouraged (other than in a patient with life-threatening allergy to β -lactam antimicrobials).

Cost. Pharmacoeconomic studies have been lacking or inadequate with regard to the prophylactic use of antimicrobials; therefore, a cost-minimization approach was employed in developing these guidelines. When antimicrobials have been shown to be equally efficacious and safe, the recommendation is based on the least expensive agent (on the basis of average wholesale price). The other antimicrobials are considered to be alternative agents. The recommendation of an antimicrobial is determined primarily by efficacy and secondarily by cost. Because of variations in cost from one health system to another, health systems must tailor the choice of antimicrobials to their individual acquisition costs.

Endocarditis

Background. The incidence of infective endocarditis is difficult to estimate because of the difficulty of accurate diagnosis and the variability in reporting criteria. However, estimates have ranged from one to six cases per 100,000 people annually.^{22,23} Infective endocarditis continues to cause serious morbidity and mortality despite treatment advances.²⁴⁻²⁷ A study of 300 episodes of endocarditis occurring in 287 patients demonstrated that complications are common.²⁶ Complications included cardiac, neurologic, septic, and renal complications; extracranial systemic arterial embolism; septic pulmonary embolism; and complications related to surgical treatment. A cohort study with a 15-year follow-up involving 112 patients addicted to nonintravenous drugs demonstrated survival rates of 90% at 2 years, 88% at 5 years, 81% at 10 years, and 61% at 15 years.²⁷

Several guidelines for prophylaxis before medical and dental procedures are available.^{23,28-33} The rationale for prophylactic therapy is that, if the appropriate antimicrobial is present at the time of bacteremia, organisms are unable to colonize to the tissue in sufficient numbers to cause endocarditis. The various guidelines attempt to identify patient groups and procedures associated with a higher risk of infective endocarditis. AHA's most recent recommendations contain the following changes: a single dose of oral amoxicillin with no follow-up dose, a lower amoxicillin dose, and cephalexin, cefodoxil, azithromycin, and clarithromycin as alternatives to erythromycin for penicillin-allergic patients.²⁹ Although erythromycin remains an appropriate choice for prophylaxis, the committee did not specifically recommend it because of the GI adverse effects and the complicated pharmacokinetics of the various formulations compared with the newer agents in this class.

The most common causative organisms identified in patients with endocarditis are viridans streptococci and are known to cause bacteremia after dental or respiratory tract procedures.^{24,26,29,34,35} Viridans streptococci that have been isolated in endocarditis include *S. gordonii*, *S. sanguis*, *S. mitis*, *S. oralis*, *S. adjacens*, *S. defectivus*, *S. mutans*, and *S. sobrinus*.³⁶ Other organisms identified include *S. aureus*,^{24,29,34,37} *S. epidermidis*,^{32,37} enterococci,^{24,29,34} and, less commonly, gram-negative bacteria and fungi.^{24,34} Reports of staphylococcal endocarditis are notably higher among patients undergoing valvular surgery.^{34,37} Enterococci are most commonly implicated after high-risk GU and GI procedures.²⁹

The costs and benefits of prophylaxis have been analyzed for at-risk patients undergoing procedures that produce bacteremia as well as for some subgroups of patients, notably those with mitral valve prolapse.³⁸ The cost of treating a patient with endocarditis has been estimated to be \$46,000. For oral erythromycin and amoxicillin prophylaxis regimens, the estimated net cost was about \$0.75 and \$1.50, respectively, per dental procedure, compared with approximately \$12,000 and \$19,000 to treat each case of infective endocarditis prevented.³⁸ The cost-benefit analysis clearly favors prophylaxis.

Persons at Risk. Animal data and the results of in vitro studies support the concept that the development of infective endocarditis involves deposition of platelets and fibrin on an altered endocardial surface followed by bacterial colonization of these sites.³⁴ Persons at highest risk are those who

have prosthetic cardiac valves, including bioprosthetic and homograft valves; previous bacterial endocarditis; complex cyanotic congenital heart disease (e.g., single ventricle states, transposition of the great arteries, tetralogy of Fallot); and surgically constructed systemic pulmonary shunts or conduits. Persons at moderate risk are those who have congenital cardiac malformations, including patent ductus arteriosus, ventricular septal defect, primum atrial septal defect, coarctation of the aorta, and bicuspid aortic valve; acquired valvar dysfunction (e.g., rheumatic heart disease); hypertrophic cardiomyopathy; and mitral valve prolapse with valvar regurgitation or thickened leaflets, including myxomatous mitral valve degeneration with regurgitation.²⁹

Special considerations are involved in prescribing prophylaxis for bacterial endocarditis in patients with a history of rheumatic fever. These patients often receive secondary antimicrobial prophylaxis to prevent colonization or infection of the upper respiratory tract by group A streptococci and subsequent recurrent attacks of rheumatic fever. The secondary prophylactic therapy often continues into adulthood and may have to be continued for life in patients with a history of rheumatic carditis.²⁹

Efficacy. There have been no randomized or placebo-controlled prospective clinical trials in humans to evaluate the efficacy of endocarditis prophylaxis before dental or medical procedures. Available data are from retrospective case-control studies. One study demonstrated that antimicrobial prophylaxis given before dental procedures was protective in 91% of patients with cardiac lesions.³⁹ In contrast, a case-control study of 438 patients who developed endocarditis after a medical or dental procedure demonstrated that only about 6% of endocarditis cases were preventable.⁴⁰ A retrospective analysis of a national registry identified cases of apparent failure of endocarditis prophylaxis.⁴¹ Although the results call into question the effectiveness of antimicrobial regimens for endocarditis prophylaxis, care must be taken in interpreting case registry data, and it should be noted that only 12% of patients had received a regimen that followed the AHA guidelines at the time. Given the rarity of endocarditis, it would take an estimated 6000 patients with preexisting valvular heart disease who were undergoing dental procedures to show a significant benefit of prophylactic antimicrobials.²³ Because endocarditis prophylaxis is currently commonplace, it is unlikely that such a trial will be done.

The evidence supporting the use of prophylactic antimicrobials for high-risk patients with cardiac lesions before medical or dental procedures that produce bacteremia is incomplete but suggests that the benefits of prophylaxis against endocarditis outweigh the risks and costs for these patients. The choice of antimicrobials recommended by the AHA guidelines for endocarditis prophylaxis is based on the organisms that most frequently produce infective endocarditis and on the types of bacteremia produced by specific procedures.²⁹ AHA also used relevant literature on procedure-related endocarditis, including the results of animal experiments of endocarditis and retrospective analyses of human endocarditis cases.

Although there are no supporting data, ciprofloxacin has been recommended for antimicrobial prophylaxis in patients undergoing endoscopic retrograde cholangiopancreatography (ERCP) by a working party for the British Society of Gastroenterology Endoscopy Commit-

tee.³³ For this procedure, the choice of antimicrobial is directed at the pathogens most likely to cause gram-negative sepsis after ERCP rather than at enterococci, the organisms most commonly associated with endocarditis resulting from GI procedures. Most panel members considered ciprofloxacin or any fluoroquinolone to be an acceptable alternative agent for patients undergoing ERCP. However, a minority of panel members believed that fluoroquinolones, in general, should be avoided because of classwide resistance.

The development of resistant organisms is a concern associated with the use of antimicrobial prophylaxis against bacterial endocarditis. A prospective, uncontrolled study demonstrated resistant streptococci in the mouths of 8 out of 20 healthy adult volunteers administered oral penicillin V.⁴² The relevance of these findings with respect to endocarditis prophylaxis is unclear because the number of resistant strains was low relative to the number of total oral streptococci.

Pediatric Efficacy. No well-controlled studies have evaluated the effect of prophylaxis against bacterial endocarditis in pediatric patients. The AHA guidelines provide pediatric dosage recommendations.²⁹

Recommendation. The choice of antimicrobials for bacterial endocarditis prophylaxis is based on the procedure and the patient's level of risk for endocarditis (Table 1). Dental procedures for which prophylaxis is recommended include dental extractions, periodontal procedures (including surgery, scaling and root planing, probing, and recall maintenance), dental implant placement and reimplantation of avulsed teeth, endodontic (root canal) instrumentation or surgery only beyond the apex, subgingival placement of antimicrobial fibers or strips, initial placement of orthodontic bands but not brackets, intraligamentary local anesthetic injections, and prophylactic cleaning of teeth or implants when bleeding is anticipated. Prophylaxis is optional when there may be substantial bleeding, such as with operative and prosthodontic restorative dentistry, including restoration of decayed teeth (filling cavities) and replacement of missing teeth. Respiratory tract procedures for which prophylaxis is warranted include tonsillectomy and adenoidectomy, surgical operations that involve respiratory mucosa, and bronchoscopy with a rigid bronchoscope. Prophylaxis is optional for high-risk patients undergoing bronchoscopy with a flexible bronchoscope, with or without biopsy. Esophageal procedures include sclerotherapy for esophageal varices and esophageal stricture dilation. GI procedures include endoscopic retrograde cholangiography with biliary obstruction, biliary tract surgery, and surgical operations that involve intestinal mucosa. Prophylaxis is optional for high-risk patients undergoing transesophageal echocardiography and endoscopy with or without GI biopsy. GU tract procedures include prostatic surgery, cystoscopy, and urethral dilation. Prophylaxis is optional for high-risk patients undergoing vaginal hysterectomy and vaginal delivery. A list of related procedures, such as endotracheal intubation, for which endocarditis prophylaxis is not recommended because of the lesser risk of associated bacteremia can be found in the AHA guidelines. Patients who take an oral penicillin for secondary prophylaxis are often colonized by penicillin-, amoxicillin-, or ampicillin-resistant viridans streptococci. These patients should receive clindamycin, azithromycin, or clarithromycin instead of penicillin, amoxicillin, or ampicillin.²⁹

Dental, respiratory tract, and esophageal procedures in patients at moderate or high risk. The recommended regimen for moderate- or high-risk patients undergoing dental, respiratory tract, or esophageal procedures is amoxicillin 2 g orally one hour before the procedure. For patients unable to take oral medications, the alternative is ampicillin 2 g (as the sodium) i.v. or i.m. within 30 minutes of the procedure. For patients allergic to penicillin, the alternative is clindamycin 600 mg (as the hydrochloride) orally one hour before the procedure, cephalexin or cefadroxil 2 g orally one hour before the procedure, or azithromycin or clarithromycin 500 mg orally one hour before the procedure. An acceptable alternative is erythromycin 800 mg (as the ethylsuccinate) or 1 g (as the stearate) orally two hours before the procedure and then half the dose six hours after the initial dose. For penicillin-allergic patients and patients unable to take oral medications, the alternative is clindamycin 600 mg (as the phosphate) i.v. within 30 minutes before the procedure or cefazolin 1 g (as the sodium) i.v. or i.m. within 30 minutes of the procedure.

GI and GU procedures for patients at moderate risk. For moderate-risk patients undergoing GI or GU procedures, the recommended regimen is amoxicillin 2 g orally one hour before the procedure or ampicillin 2 g (as the sodium) i.v. or i.m. within 30 minutes of the start of the procedure. For patients allergic to ampicillin or amoxicillin, the alternative is vancomycin 1 g (as the hydrochloride) i.v. over one to two hours (complete infusion within 30 minutes of the start of the procedure). For ERCP procedures, a fluoroquinolone such as ciprofloxacin given at a dose of 750 mg (as the base or hydrochloride) orally 60 to 90 minutes before the procedure is considered by some to be an acceptable alternative regimen.

GI and GU procedures for patients at high risk. The recommended regimen for high-risk patients undergoing GI or GU procedures is ampicillin 2 g (as the sodium) i.v. or i.m. plus gentamicin 1.5 mg/kg (as the sulfate; not to exceed 120 mg) i.v. or i.m. within 30 minutes of the start of the procedure followed by ampicillin 1 g i.v. or i.m. or amoxicillin 1 g orally six hours later. For patients allergic to ampicillin or amoxicillin, the alternative is vancomycin 1 g (as the hydrochloride) i.v. over one to two hours (complete infusion within 30 minutes of the start of the procedure) plus gentamicin 1.5 mg/kg (not to exceed 120 mg) i.v. or i.m. (complete injection within 30 minutes of the start of the procedure). For patients undergoing an ERCP procedure, ciprofloxacin 750 mg (as the base or hydrochloride) orally (any fluoroquinolone may be appropriate) given 60 to 90 minutes before the procedure may be considered an acceptable alternative regimen. (Strength of evidence for prophylaxis = B)

Pediatric Dosage. The choice of antimicrobials for endocarditis prophylaxis in pediatric patients is based on the procedure and the patient's level of risk for endocarditis. Readers are referred to the adult recommendations for the choice of antimicrobials. The equivalent pediatric initial doses are oral amoxicillin 50 mg/kg, oral clindamycin 20 mg/kg (as the hydrochloride), ampicillin 50 mg/kg (as the sodium) i.v. or i.m., clindamycin 20 mg/kg (as the phosphate) i.v., gentamicin 1.5 mg/kg (as the sulfate) i.v., and vancomycin 20 mg/kg (as the hydrochloride) i.v. The total pediatric dose should not exceed the total adult dose.

Meningitis After Nonpenetrating Head Trauma Associated with Basilar Skull Fracture

Background. The reported frequency of acute intracranial infection after basilar skull fractures is highly variable and ranges from 0% to 50%.⁴³⁻⁴⁵ No prospective study involving patients with basilar skull fractures has compared the development of meningitis in patients with documented cerebrospinal fluid (CSF) leakage with development in patients without clinically detectable CSF leakage. No prospective study has investigated the time course for the development of meningitis after a basilar skull fracture. Although most central nervous system (CNS) infections are reported to develop within days to weeks after nonpenetrating head trauma, meningitis has been reported to occur months to years later.⁴⁶

Several organisms have been isolated from the CSF of patients developing meningitis after basilar skull fractures. These include both gram-positive organisms (*Streptococcus* and *Staphylococcus*) and gram-negative organisms (*Escherichia coli*, *Serratia*, *Haemophilus*, *Klebsiella*, and *Acinetobacter*).^{43,46-48} The most common organisms are *Streptococcus pneumoniae*, group A β -hemolytic streptococci, and *H. influenzae*.⁴⁹

Persons at Risk. Basilar skull fractures after nonpenetrating head trauma are often, but not necessarily, associated with an interruption of the meninges. Meningeal tears, occurring in proximity to the nasopharynx, nasal or mastoid sinuses, or the external auditory canal, predispose patients with basilar skull fractures to meningitis. The direct spread of pathogenic organisms colonizing these contiguous-air-space areas is believed to be the cause of subsequent meningeal infection.

Efficacy. No prospective, randomized, double-blind, placebo-controlled trials have evaluated the potential benefits and risks of prophylactic antimicrobial administration after the diagnosis of basilar skull fracture. Only two reported studies have used prospective data collection in investigating this issue.^{50,51} No recommendations could be made because these studies contained numerous flaws.

Most retrospective case series involving adults with basilar skull fractures have not supported the use of prophylactic antimicrobials.^{47,48,52} Retrospective case series in which it was claimed that prophylactic antimicrobials were associated with a lower frequency of meningitis have been flawed by the nature of retrospective data collection, a small sample size, a lack of standardized antimicrobial regimens, and failure to account for confounding variables such as neurosurgical intervention and injury severity.⁵³ In contrast, a meta-analysis demonstrated a significantly lower frequency of meningitis (2.5% versus 10%) when prophylactic antimicrobials were administered to patients with CSF leakage.⁵⁴ Prophylactic antimicrobials may have a role in patients with CSF leakage. However, the meta-analysis, because of its limitations (including an inadequate amount of specific details on the choice, dosage, and duration of antimicrobial therapy; on the duration of CSF leakage; and on the latency of the meningitis), provides inadequate data for a specific recommendation.

Resistance. Retrospective case series in which it was claimed that prophylactic antimicrobials were responsible for the selection of more invasive, pathogenic, and antimicrobial-

resistant organisms have been less numerous but equally as flawed as studies in which there was an alleged benefit from prophylactic antimicrobial administration.

Pediatric Efficacy. No well-controlled studies have evaluated the effect of prophylaxis for pediatric patients with a basilar skull fracture after nonpenetrating head trauma, either with or without CSF leakage. Retrospective case series involving children with basilar skull fractures have not supported the use of prophylactic antimicrobials.^{47,48,55}

Recommendation. Prophylactic administration of antimicrobials to patients with a basilar skull fracture after nonpenetrating head trauma, either with or without CSF leakage, is not recommended (Table 1). (Strength of evidence against prophylaxis = C)

Pediatric Dosage. Prophylaxis for pediatric patients with a basilar skull fracture after nonpenetrating head trauma, either with or without CSF leakage, is not recommended.

Nosocomial Pneumonia in Patients Receiving Mechanical Ventilation

Background. The frequency of nosocomial pneumonia in the medical, surgical, and cardiothoracic intensive care unit (ICU) ranges from 10% to 65%, with case mortality rates of 13% to 55%.⁵⁶ CDC recently developed comprehensive guidelines for the prevention of nosocomial pneumonia.⁵⁷

Selective decontamination of the GI tract has been widely used in Europe as a prophylactic regimen for ventilator-associated nosocomial pneumonia. These regimens are intended to reduce the rate of respiratory tract colonization, reduce the rate of nosocomial infections, and therefore reduce patient mortality. The most common regimens have included two components: (1) administration of a combination of oral nonabsorbable antimicrobials, such as aminoglycosides, colistin, and amphotericin B, to prevent GI microorganisms, and (2) application of a paste containing the same agents to the oral mucosa to prevent upper-respiratory-tract colonization. Vancomycin has been included in some regimens in an effort to prevent *S. aureus* infections. In addition, some investigators have included a brief course of an i.v. antimicrobial to treat an "incubating" pneumonia that may have been acquired at the time of admission.⁵⁸⁻⁶⁴

The most frequently isolated pathogens include gram-negative bacilli (most commonly *Pseudomonas aeruginosa* and Enterobacteriaceae), *S. aureus*, and coagulase-negative staphylococci. Although *Candida* is frequently isolated, it is a rare cause of pneumonia.^{60,63,65}

Proper pharmaco-economic evaluations of selective decontamination have not been conducted. A few studies have calculated the relative costs (primarily drug acquisition costs) of selective decontamination compared with placebo. In one study, selective decontamination was associated with lower overall antimicrobial and hospitalization costs.⁶⁶ In contrast, the cost of selective decontamination results in a higher total cost of ICU care (antimicrobials, microbiological surveillance, and nursing time) compared with the cost of placebo⁶³ and a higher cost of antimicrobials (both topical and systemic) compared with placebo.⁶⁷ A recent analysis showed that, to prevent one case of nosocomial pneumonia, 6 patients would have to be treated with selective decontamination and that, to prevent one death, 23 patients would have to be treated.⁵⁷

Persons at Risk. Patients requiring prolonged mechanical ventilation are at greatest risk for nosocomial pneumonia. Oropharyngeal and gastric colonization by pathogenic organisms with subsequent aspiration is a major mechanism of ventilator-associated nosocomial pneumonia.⁶⁰ Other risk factors for nosocomial pneumonia include advanced age, organ system failure, prior administration of antimicrobials, supine head position during mechanical ventilation, longer ICU stay, and diagnosis of trauma.^{56,65} Concomitant use of a histamine H₂-receptor antagonist (ranitidine or cimetidine) has been identified as a risk factor for nosocomial pneumonia in some,⁶⁸⁻⁷⁰ but not all,⁷¹⁻⁷⁶ studies.

Efficacy. Selective decontamination has been the subject of investigation for more than 20 years and is practiced widely in Europe. However, most of the early studies were either not randomized^{77,78} or not placebo controlled.^{58,59,79-81} The use of selective decontamination has not been studied in the United States, primarily because of a widespread concern about the possibility of overgrowth of resistant organisms. Results of well-controlled trials indicate that, although selective decontamination is associated with a lower rate of bacterial colonization and nosocomial pneumonia, there is no significant benefit in terms of ICU stay, hospital stay, or mortality.

For the development of these guidelines, only randomized, double-blind, placebo-controlled trials with a clearly stated definition of pneumonia were evaluated.^{60,63,64,66,67,82-84} In these studies, the use of selective decontamination was very effective in reducing respiratory tract colonization of bacteria, particularly gram-negative bacilli and *Candida* species. In three studies, there was a significantly lower frequency of pneumonia among patients receiving selective decontamination than among placebo recipients.^{64,83,84} The frequency of pneumonia ranged from 15% to 28% among patients receiving selective decontamination and from 33% to 78% among patients receiving placebo. With one exception,⁶⁴ however, there was no difference in mortality between treated and placebo groups. In addition, selective decontamination had no effect on the duration of ICU or hospital stay.^{60,63,64,67,82,83} A meta-analysis supported these conclusions.⁸⁵ It showed that nosocomial pneumonia was significantly lower among patients receiving selective decontamination than control patients; however, there was no significant difference between groups in mortality rate.

Resistance. The development of resistant organisms is the greatest concern associated with the use of selective decontamination and may explain why reducing the rate of pneumonia is not associated with lower mortality. Two long-term studies showed that, although the rate of colonization with gram-negative bacilli was lower, the rate of gram-positive bacilli colonization was higher.^{61,86} A trend toward a higher rate of staphylococcal pneumonia among patients receiving selective decontamination has been demonstrated.⁶⁷ The addition of vancomycin to the antimicrobial regimen in order to decrease the rate of *S. aureus* colonization was not consistently associated with a reversal of this trend.⁸³ In addition, selective decontamination regimens do not cover *Enterococcus faecalis*, and five cases of *E. faecalis* colonization and endocarditis have been reported in patients receiving these regimens.⁶² Selective decontamination was also associated with significantly higher resistance to cefotaxime and tobramycin.⁶⁴ However, the long-term use of selective decontamination has also been reported to have no effect on antimicrobial resistance or nosocomial pathogens.⁸⁷

Pediatric Efficacy. No well-controlled studies have yet evaluated the effect of prophylaxis for mechanically ventilated pediatric patients.

CDC recently developed comprehensive guidelines for the prevention of nosocomial pneumonia.⁵⁷ CDC views selective decontamination for mechanically ventilated patients as an unresolved issue and therefore has no recommendations for or against the use of selective decontamination.

Recommendation. Because there is no significant benefit in terms of ICU stay, hospital stay, or mortality, the routine use of selective decontamination in mechanically ventilated patients cannot be recommended (Table 1). (Strength of evidence against prophylaxis = A)

Pediatric Dosage. Selective decontamination is not recommended in mechanically ventilated pediatric patients.

Influenza A

Background. Influenza A infection is associated with fever, myalgia, sore throat, nonproductive cough, and secondary bacterial pneumonia and may result in death. The illness increases health care use secondary to increases in hospital admissions and visits to physicians' offices, clinics, and emergency rooms. More than 20,000 influenza-associated deaths occurred during each of nine different U.S. epidemics from 1972-73 to 1990-92, and more than 40,000 influenza-associated deaths occurred during each of four of those epidemics.⁸⁸

Persons at Risk. Groups at high risk for influenza-related complications include (1) persons 65 years of age and older, (2) residents of nursing homes and other chronic care facilities, (3) adults and children with chronic disorders of the pulmonary or cardiovascular system, including children with asthma, (4) adults and children who have required regular medical follow-up or hospitalization during the preceding year because of chronic metabolic diseases (including diabetes mellitus), renal dysfunction, hemoglobinopathy, or immunosuppression (including immunosuppression caused by medications or HIV infection) and who are expected to have inadequate antibody response to the vaccine, (5) children and teenagers (six months to 18 years of age) who are receiving long-term aspirin therapy and who therefore might be at risk for developing Reye syndrome after influenza, and (6) women who will be in the second or third trimester of pregnancy during the influenza season.⁸⁹

Groups that can transmit influenza to persons at high risk include (1) physicians, nurses, and other personnel in hospital or outpatient health care settings, (2) employees of nursing homes or chronic care facilities who have contact with patients or residents, (3) providers of home care to persons at high risk (e.g., visiting nurses, volunteers), and (4) household members (including children) of persons in high-risk groups.⁸⁹

Efficacy. Amantadine and rimantadine were both approved by FDA for prophylactic and therapeutic use against influenza A. Double-blind, placebo-controlled, clinical trials have demonstrated that the prophylactic effectiveness of amantadine and rimantadine is similar.⁹⁰⁻⁹⁵ Amantadine and rimantadine were highly effective in preventing influenza-like illness; the rate of illness was 78% and 65% lower, respectively, compared with placebo.⁹⁴ The efficacy rates

Table 1.
Prevention of Infection in Specialized Settings^a

Infection and Setting ^b	Eligible Patients ^c	Recommended Regimen ^d	Alternative Regimens ^{d,e}	Strength of Evidence ^f
Bacterial endocarditis Dental, respiratory tract, or esophageal procedure	Adult; moderate or high risk ^g	Amoxicillin 2 g p.o. 1 hr before procedure or ampicillin 2 g i.v. or i.m. 30 min before procedure ^h	Clindamycin 600 mg, cephalexin 2 g, cefadroxil 2 g, azithromycin 500 mg, or clarithromycin 500 mg p.o. 1 hr before procedure; erythromycin ethylsuccinate 800 mg or erythromycin stearate 1 g p.o. 2 hr before procedure, then half initial dose p.o. 6 hr after initial dose; or clindamycin 600 mg i.v. or cefazolin 1 g i.v. or i.m. 30 min before procedure	B
	Pediatric; moderate or high risk ^g	Amoxicillin 50 mg/kg p.o. 1 hr before procedure or ampicillin 50 mg/kg i.v. or i.m. 30 min before procedure ^h	Clindamycin 20 mg/kg, cephalexin 50 mg/kg, cefadroxil 50 mg/kg, azithromycin 15 mg/kg, or clarithromycin 15 mg/kg 1 hr before procedure; erythromycin ethylsuccinate or stearate 20 mg/kg p.o. 2 hr before procedure, then 10 mg/kg p.o. 6 hr after initial dose; or clindamycin 20 mg/kg i.v. or cefazolin 25 mg/kg i.m. or i.v. 30 min before procedure	NA
Gastrointestinal or genitourinary procedure	Adult; moderate risk	Amoxicillin 2 g p.o. 1 hr before procedure or ampicillin 2 g i.v. or i.m. 30 min before procedure	Vancomycin 1 g i.v. over 1–2 hr, completing infusion within 30 min of starting procedure; for ERCP, ciprofloxacin 750 mg p.o. 60–90 min before procedure ⁱ	B
	Adult; high risk	Ampicillin 2 g i.v. or i.m. plus gentamicin 1.5 mg/kg (maximum 120 mg) i.v. or i.m. 30 min before procedure, then ampicillin 1 g i.v. or i.m. or amoxicillin 1 g p.o. 6 hr later ^h	Vancomycin 1 g i.v. over 1–2 hr plus gentamicin 1.5 mg/kg (maximum 120 mg) i.v. or i.m., completing both i.v. infusions within 30 min of starting procedure; for ERCP, ciprofloxacin 750 mg p.o. 60–90 min before procedure ⁱ	B
	Pediatric; moderate risk	Amoxicillin 50 mg/kg p.o. 1 hr before procedure or ampicillin 50 mg/kg i.v. or i.m. 30 min before procedure	Vancomycin 20 mg/kg i.v. over 1–2 hr, completing infusion within 30 min of starting procedure	NA
	Pediatric; high risk	Ampicillin 50 mg/kg i.v. or i.m. (maximum 2 g) plus gentamicin 1.5 mg/kg (maximum 120 mg) i.v. or i.m. 30 min before procedure, then ampicillin 25 mg/kg i.v. or i.m. or amoxicillin 25 mg/kg p.o. 6 hr later	Vancomycin 20 mg/kg i.v. over 1–2 hr plus gentamicin 1.5 mg/kg (maximum 120 mg) i.v. or i.m., completing both infusions within 30 min of starting procedure	NA

Continued on next page

for prevention of laboratory-documented influenza were 91% for amantadine and 85% for rimantadine.⁹⁴

Amantadine and rimantadine are not active against influenza B, which is responsible for approximately 20% of all influenza epidemics. In a given year, influenza B may be the only virus circulating.⁹⁶ Rimantadine has a lower frequency of CNS adverse effects, including nervousness, anxiety, difficulty concentrating, and lightheadedness.⁸⁹

Resistance. In a 10-year study of one community, the investigators failed to detect naturally occurring drug-resistant strains of influenza A virus in untreated patients.⁹⁷

However, rimantadine-resistant influenza A virus isolates have been recovered from rimantadine-treated index patients, and the resistance can be transmitted and cause illness in other family members taking rimantadine for postexposure prophylaxis.⁹⁸ Amantadine-resistant influenza A was reported in a nursing facility where amantadine-resistant virus was shed by patients being treated for influenza with amantadine and caused illness in patients receiving the drug prophylactically.⁹⁹

Pediatric Efficacy. Double-blind, placebo-controlled clinical trials in pediatric patients (ages 1–18 years) have demon-

Table 1 (continued)

Infection and Setting ^b	Eligible Patients ^c	Recommended Regimen ^d	Alternative Regimens ^{d,e}	Strength of Evidence ^f
Meningitis Nonpenetrating head trauma	Adult; basilar skull fracture	Not recommended	None	C
	Pediatric; basilar fracture	Not recommended	None	NA
Nosocomial pneumonia Intensive care unit	Adult; mechanical ventilation	Not recommended	None	A
	Pediatric; mechanical ventilation	Not recommended	None	NA

^aAdult recommendations adapted from American Heart Association (AHA) recommendations (reference 29).

^bDental procedures include extractions, periodontal procedures (including surgery, scaling and root planing, probing, and recall maintenance), dental implant placement and reimplantation of avulsed teeth, endodontic (root canal) instrumentation or surgery only beyond the apex, subgingival placement of antimicrobial fibers or strips, initial placement of orthodontic bands but not brackets, intraligamentary local anesthetic injections, and prophylactic cleaning of teeth or implants when bleeding is anticipated. Prophylaxis is optional for procedures in which there may be significant bleeding, such as operative and prosthodontic restorative dentistry, including restoration of decayed teeth (filling cavities), and replacement of missing teeth. Respiratory tract procedures include tonsillectomy or adenoidectomy, surgical operations that involve respiratory mucosa, and bronchoscopy with a rigid bronchoscope. Prophylaxis is optional for high-risk patients undergoing bronchoscopy with a flexible bronchoscope, with or without biopsy. Esophageal procedures include sclerotherapy for esophageal varices and esophageal stricture dilation. Gastrointestinal tract procedures include endoscopic retrograde cholangiography with biliary obstruction, biliary tract surgery, and surgical operations that involve intestinal mucosa. Prophylaxis is optional for high-risk patients undergoing transesophageal echocardiography and endoscopy with or without gastrointestinal biopsy. Genitourinary tract procedures include prostatic surgery, cystoscopy, and urethral dilation. Prophylaxis is optional for high-risk patients undergoing vaginal hysterectomy or vaginal delivery.

^cModerate-risk patients include those with most congenital cardiac malformations, including the uncorrected conditions of patent ductus arteriosus, ventricular septal defect, primum atrial septal defect, coarctation of the aorta, and bicuspid aortic valve; acquired valvar dysfunction (e.g., rheumatic heart disease); hypertrophic cardiomyopathy; and mitral valve prolapse with valvar regurgitation or thickened leaflets (including myxomatous mitral valve degeneration with regurgitation). High-risk patients include those with prosthetic cardiac valves, including bioprosthetic and homograft valves; previous history of bacterial endocarditis; complex cyanotic congenital heart disease (e.g., single ventricle states, transposition of the great arteries, tetralogy of Fallot); and surgically constructed systemic-pulmonary shunts or conduits.

^dWhen oral and parenteral regimens are indicated, the oral is preferred; the parenteral is to be used if the patient cannot take oral medication.

^eFor patients allergic to penicillin. Cephalosporins should not be used in patients with immediate-type hypersensitivity reaction (urticaria, angioedema, or anaphylaxis) to penicillins.

^fStrength of evidence that supports the use or nonuse of prophylaxis is classified as A (levels I–III), B (levels IV–VI), or C (level VII). Level I evidence is from large, well-conducted randomized, controlled clinical trials. Level II evidence is from small, well-conducted randomized, controlled clinical trials. Level III evidence is from well-conducted cohort studies. Level IV evidence is from well-conducted case-control studies. Level V evidence is from uncontrolled studies that were not well conducted. Level VI evidence is conflicting evidence that tends to favor the recommendation. Level VII evidence is expert opinion. Strength-of-evidence classification not applied (NA) to pediatric recommendations.

^gAHA recommends the same prophylactic regimen for dental, respiratory tract, and esophageal procedures in high- and moderate-risk patients.

^hPatients who take an oral penicillin for secondary prophylaxis are often colonized by penicillin- or ampicillin-resistant viridans streptococci. These patients should receive clindamycin, azithromycin, or clarithromycin instead of penicillin, amoxicillin, or ampicillin.

ⁱAny fluoroquinolone may be appropriate for patients undergoing endoscopic retrograde cholangiopancreatography (ERCP).

stated that prophylactic rimantadine is efficacious; the infection rate was 30% in the placebo group and less than 10% in the rimantadine group.^{100,101} Infection was defined by a positive viral throat culture or a fourfold increase in antibody titer. A double-blind, placebo-controlled trial in pediatric patients (average age of eight years) demonstrated that prophylactic amantadine is efficacious; the infection rate was 30% in the placebo group and 10% in the amantadine group.¹⁰² Infection was defined by a temperature of 101 °F or more with a fourfold or more increase in titer of complement fixation plus hemagglutination inhibition.

Recommendation. Chemoprophylaxis is not a substitute for vaccination. Practitioners should refer to CDC annually for specific vaccine recommendations.

CDC recommends chemoprophylaxis with amantadine or rimantadine against influenza A in persons at risk (see above) for developing complications under certain circumstances: (1) persons at high risk who were vaccinated after influenza A activity began, because the development of antibodies can take as long as two weeks, (2) persons providing care to those at high risk who are not vaccinated; prophylaxis should be considered for all employees, regardless of their vaccination status, if the outbreak is caused by a variant strain of influenza A that might not be controlled by the vaccine, (3) persons who have immune deficiency and who are expected to have an inadequate antibody response to influenza vaccine, (4) per-

sons for whom influenza vaccine is contraindicated, including persons who have severe anaphylactic hypersensitivity to egg protein or other vaccine components, and (5) other persons who wish to avoid influenza A illness.

Factors that should be considered before initiation of chemoprophylaxis are cost, adherence, and potential adverse effects.⁸⁹ No well-controlled studies of pregnant women have been conducted, and the drug should be used during pregnancy only when the potential benefits outweigh the possible risk to the fetus.

On the basis of cost minimization, the regimen of choice is usually amantadine hydrochloride 100 mg orally twice daily (Table 2). An alternative regimen is rimantadine hydrochloride 100 mg orally twice daily for persons who cannot tolerate the CNS adverse effects of amantadine. Prophylaxis should be continued for 10 days after exposure. When an antiviral agent is used in conjunction with the vaccine, prophylaxis should be continued for two weeks after administration of the vaccine. If the vaccine is unavailable or contraindicated, prophylaxis should be continued for the duration of influenza A activity in the community. (Strength of evidence for prophylaxis = A)

Pediatric Dosage. Amantadine is the first drug of choice for influenza A prophylaxis; rimantadine is an alternative. Readers are referred to the adult recommendations for the indications to use chemoprophylaxis.

The dosage of amantadine hydrochloride in children of ages one to eight years and in older children who weigh less than 40 kg is 5–9 mg/kg/day orally in two divided doses (up to 200 mg daily).³ For children 9 to 12 years of age who weigh more than 40 kg, the dosage of amantadine hydrochloride is 100 mg orally twice daily. The dosage of rimantadine hydrochloride in children less than 10 years of age is 5 mg/kg orally once daily (up to 150 mg daily). For children older than 10 years, the dosage of rimantadine hydrochloride is 100 mg orally twice daily. Prophylaxis should be continued for 10 days after exposure to influenza A. When an antiviral agent is used in conjunction with the vaccine, prophylaxis should be continued for two weeks after the last dose of vaccine (one dose is recommended for children older than nine years; two doses of vaccine are required for children up to nine years of age who have not been previously vaccinated). If the vaccine is unavailable or contraindicated, prophylaxis should be continued for the duration of influenza A activity in the community.

Malaria

Background. Malaria is caused by one or more of four parasites from the genus *Plasmodium*: *P. falciparum*, *P. vivax*, *P. ovale*, and *P. malariae*. *P. falciparum* infection is the most dangerous and may produce severe metabolic effects and microvascular disease. Microvascular disease can affect most organ systems, including the kidneys, the lungs, the GI system, and the CNS. *P. falciparum* infection can result in death. *P. vivax* and *P. ovale* do not cause microvascular complications and have less severe sequelae. *P. malariae* infection may produce an immune complex (parasite antigens, host antibodies, and complement) glomerulonephritis, which usually occurs three to six months after the malaria-transmission season.¹⁰³

Persons at Risk. Malaria is so common that a person who has traveled in a malarious area for two months or longer should be considered to have malaria until proven otherwise.¹⁰⁴ The frequency of infection in high-risk areas varies from 20%¹⁰⁵ to almost 100%.¹⁰⁶ Persons who previously lived in an endemic area, moved away, and return to the area should also be considered at risk for developing malaria.

Efficacy. Various drug regimens and combinations have been used to prevent malaria infection. Chloroquine is the drug of choice for people traveling to regions where resistance has not developed. In chloroquine-resistant areas, mefloquine has been shown to be effective for malaria prophylaxis. In a large-scale study, five different treatment groups, including chloroquine and placebo, were compared. Malaria occurred less frequently in the groups taking mefloquine and a fixed combination of mefloquine plus sulfadoxine plus pyrimethamine, although the difference between these groups and the groups taking chloroquine or placebo was not significant.¹⁰⁷

A study comparing mefloquine, chloroquine plus pyrimethamine plus sulfadoxine, and chloroquine alone in 334 patients showed that the *P. falciparum*-associated malaria infection rate was 79% lower in the mefloquine group than the chloroquine control group, which had a 69% infection rate.¹⁰⁸ Chloroquine plus pyrimethamine plus sulfadoxine was associated with an infection rate that was only 18% lower than that in the chloroquine control group. In a randomized, double-blind, placebo-controlled study of 567

men in Nigeria, the following regimens were compared: mefloquine, mefloquine plus sulfadoxine and pyrimethamine, pyrimethamine plus sulfadoxine, chloroquine, and placebo.¹⁰⁵ This study did not demonstrate a significant difference in prevention of new parasitemias between groups. However, during the treatment phase of the study, three patients developed symptomatic *P. falciparum* infection in the placebo group, compared with no patients in the treatment groups. In the posttherapy follow-up segment of the study, four more placebo patients and one patient in the group receiving mefloquine plus sulfadoxine and pyrimethamine (33 days after the last dose) developed symptomatic malaria. The infection rate was probably not high enough to enable a significant difference between groups to be detected. A study of 609 adult military personnel demonstrated that a 100-mg daily dose of doxycycline was 64% more efficacious in preventing malaria than a combination of pyrimethamine and dapsone.¹⁰⁶ Two studies, one comparing primaquine plus chloroquine with chloroquine alone¹⁰⁹ and the second comparing primaquine with chloroquine, demonstrated the efficacy of primaquine for malaria prophylaxis.¹¹⁰

Resistance. Malaria resistant to chloroquine is common. Malarious areas that do not have chloroquine-resistant *P. falciparum* are Central America and the Caribbean. Resistance is uncommon in the Middle East. Malarious areas where chloroquine-resistant malaria is common include Southeast Asia, sub-Saharan Africa, and northern South America.¹¹¹

Pediatric Efficacy. A randomized study demonstrated that mefloquine hydrochloride 125 mg weekly was equally effective as primaquine and doxycycline in preventing symptomatic and asymptomatic malaria infections in children of ages 9–14 years.¹¹² Despite the fact that mefloquine's efficacy is comparable to that of primaquine and doxycycline, CDC recommends that mefloquine be reserved for chloroquine-resistant areas.

Recommendation. Nonantimicrobial measures. Implementing measures to reduce the risk of mosquito bites is the nonantimicrobial approach to preventing malaria. Travelers should remain in well-screened areas, use mosquito nets, and wear clothing that covers their entire body. Insect repellents should be used on exposed areas of skin. The most effective mosquito repellent is *N,N*-diethyl metatoluamide (DEET). DEET-containing repellents should be used according to directions and should be used sparingly on children. Adults should use 30–35% DEET on exposed skin; pediatric preparations containing 6–10% DEET are also available.¹¹¹ For current travel recommendations, contact the CDC travel hotline at (888) 232-3299 or (888) 232-3228 or see <http://www.cdc.gov> (select Travelers' Health).

Areas of chloroquine susceptibility. Chloroquine alone is recommended for malaria prophylaxis in areas of chloroquine susceptibility (Table 2). The adult dosage is chloroquine phosphate 500 mg (300 mg base) once a week initiated one week before entry into the malarious area and continuing for four weeks after departure from the area.¹¹¹

Areas of chloroquine resistance. Mefloquine is recommended for malaria prophylaxis in areas of chloroquine resistance. The adult dosage is mefloquine hydrochloride 250 mg (228 mg base) once weekly beginning one week before travel and

continued for four weeks after the person leaves the malarious area. Mefloquine should not be used by travelers with a history of epilepsy, psychiatric disorders, or a known hypersensitivity to mefloquine. An alternative is doxycycline 100 mg (as the calcium, hyclate, or monohydrate) daily beginning one day before travel and continued for four weeks after the person leaves the area. Doxycycline should not be used by pregnant women.¹¹¹ Another alternative is chloroquine phosphate (same dosage as previously described) with or without chloroguanide hydrochloride (proguanil) 200 mg/day during exposure and for four weeks after last exposure plus combination tablets of pyrimethamine (25 mg/tablet) and sulfadoxine (500 mg/tablet) as presumptive treatment—three tablets for febrile illness when medical care is not immediately available.¹¹³ (Strength of evidence for prophylaxis = B)

Pediatric Dosage. Areas of chloroquine susceptibility. Chloroquine is recommended for malaria prophylaxis in children in areas of chloroquine susceptibility. The pediatric dosage is chloroquine phosphate 8.3 mg/kg (5 mg/kg base) orally once a week. The maximum weekly dose is 498 mg of chloroquine phosphate (300 mg base).

Areas of chloroquine resistance. Mefloquine hydrochloride is the drug of choice for malaria prophylaxis in children in areas of chloroquine resistance. The pediatric dosage is mefloquine hydrochloride 5 mg/kg (4.6 mg/kg base) weekly for children weighing less than 15 kg, one quarter of a 250-mg mefloquine hydrochloride tablet per week for children weighing 15–19 kg, half a tablet per week for children weighing 20–30 kg, three quarters of a tablet per week for children weighing 31–45 kg, and one tablet weekly for children weighing more than 45 kg.^{111,112} An alternative is doxycycline 2 mg/kg/day (as the calcium, hyclate, or monohydrate) (maximum daily dose, 100 mg/day) for children older than eight years. Doxycycline should not be used in children less than eight years of age. Another suggested alternative is chloroquine phosphate (same dosage as previously described), with or without chloroguanide hydrochloride 50 mg/day for children younger than 2 years, 100 mg/day for ages 2–6 years, 150 mg/day for ages 7–10 years, or 200 mg/day for children older than 10 years plus combination pyrimethamine (25 mg/tablet) and sulfadoxine (500 mg/tablet) for presumptive treatment (one quarter of a tablet for children younger than 1 year, half a tablet for 1–3 years, one tablet for 4–8 years, two tablets for 9–14 years, and three tablets for children older than 14 years).¹¹³

Traveler's Diarrhea

Background. Traveler's diarrhea is a common affliction among people traveling from industrialized countries to developing countries. Traveler's diarrhea frequently starts during the first week of travel, and the risk of diarrhea persists with prolonged stays in endemic areas.¹¹⁴ The syndrome is characterized by a twofold increase in the frequency of unformed bowel movements, often accompanied by such symptoms as abdominal cramping, nausea, fever, chills, urgency, and malaise. Symptoms are usually self-limiting and resolve within three to four days; 60% of persons affected recover within the first 48 hours. For some, the duration of symptoms may be as long as one week or even longer than three months (1% of travelers per year of stay).¹¹⁵ Complications from traveler's diarrhea are rare.

The most common bacterial pathogens associated with traveler's diarrhea are *E. coli*, *Shigella*, *Salmonella*, *Campylobacter jejuni*, *Vibrio parahaemolyticus*, *Vibrio cholerae*, and *Vibrio fluvialis*. Although far less common, diarrhea may be due to protozoa (*Entamoeba histolytica*, *Giardia lamblia*, or *Cryptosporidium*). Viruses such as rotaviruses, Norwalk virus, and adenoviruses have also been implicated in traveler's diarrhea.¹¹⁶

Persons at Risk. Risk factors for traveler's diarrhea include young age, inexperience in traveling to an endemic area, high socioeconomic status, and prolonged stay. The illness is believed to result from the ingestion of fecally contaminated food or water. Foods associated with increased risk include salads, uncooked fruits and vegetables, unpasteurized dairy products, and raw meat and shellfish.¹¹⁷

Travel to some less-developed countries is associated with a high frequency of diarrhea. Travelers to such countries would appear to benefit most from antimicrobial prophylaxis. The frequency of traveler's diarrhea is highest among persons traveling to Latin America (mean, 53%; range, 21–100%), Africa (mean, 54%; range, 36–62%), the Middle East (percentage not available), and Asia (mean, 54%; range, 21–57%) and lowest among persons traveling to industrialized countries.¹¹⁵

Efficacy. Various antimicrobials, including trimethoprim-sulfamethoxazole,¹¹⁸ doxycycline,¹¹⁹ trimethoprim,^{118,120} ciprofloxacin,¹²¹⁻¹²³ and norfloxacin,^{124,125} have been shown to decrease the frequency of diarrhea in persons traveling for short periods (less than three weeks). Bismuth subsalicylate reduced the frequency and severity of traveler's diarrhea by up to 65% among college students traveling to Mexico.¹²⁶ The benefit of prophylaxis lasts only as long as the antimicrobial is taken.¹²⁰ In a contrasting study, doxycycline was not shown to be significantly more protective than placebo.¹²⁷ Despite the demonstrable efficacy of prophylaxis, CDC does not recommend prophylaxis for traveler's diarrhea because, even if untreated, the condition is most often mild and transient.¹¹⁷ Furthermore, antimicrobial therapy places otherwise healthy people at unnecessary risk of toxicity and superinfection and encourages the emergence of resistant organisms.

Pediatric Efficacy. No well-controlled studies have yet evaluated the effect of prophylaxis of traveler's diarrhea in children.

Recommendation. Prophylaxis of traveler's diarrhea is not recommended. Traveler's diarrhea, even when untreated, is most often mild and transient. The antimicrobials used as prophylaxis against traveler's diarrhea place the otherwise healthy person at unnecessary risk of toxicity and superinfection and encourage the emergence of resistant organisms. A National Institutes of Health consensus panel recommended that travelers who are otherwise healthy not take antimicrobials for the prevention of traveler's diarrhea.¹¹⁶ In addition, CDC does not recommend antimicrobial prophylaxis, focusing instead on prevention of traveler's diarrhea through dietary control (Table 2). Consumption of boiled, bottled, or chemically disinfected water and avoidance of uncooked fruits and vegetables, unpasteurized dairy products, and raw meat or shellfish are the safest methods for avoiding traveler's diarrhea.¹¹⁷ Immunocompromised patients may be viable candidates for prophylaxis (trimethoprim-

sulfamethoxazole, bismuth subsalicylate, and ciprofloxacin are all effective), but no studies in this population are available. (Strength of evidence against prophylaxis = C)

Pediatric Dosage. Prophylaxis of traveler's diarrhea is not recommended for children.

Tuberculosis

Background. Before the 1990s, the incidence of TB had been declining in the United States. In the early 1990s there was a 9% increase in the reported TB cases (25,000 cases reported in 1990).¹²⁸ Much of this increase is attributable to the spread of HIV infection and the increase in immigrants with TB.¹²⁹ Between 1993 and 1996 the number of cases reported decreased, with 21,000 reported in 1996.¹²⁸

Most new cases of TB in the United States occur in patients in whom the primary infection with *Mycobacterium tuberculosis* occurred at an earlier date. Prevention of TB reactivation is the basis for selective periodic screening of patients at risk for exposure to *M. tuberculosis* and the use of antimicrobial preventive therapy in selected patients with positive skin-test results.

Persons at Risk. The Advisory Council for the Elimination of Tuberculosis (ACET) recommends that the following persons should be screened for TB¹³⁰:

1. Close contacts (i.e., persons sharing the same household or other enclosed environments) of a person known or suspected to have TB.
2. Persons infected with HIV.
3. Persons who inject illicit drugs or other locally identified high-risk substance users (i.e., crack cocaine users).
4. Persons with one of the following medical conditions: diabetes mellitus, conditions requiring prolonged high-dose corticosteroid therapy and other immunosuppressive therapy, chronic renal failure, some hematologic disorders, other specific malignancies, $\geq 10\%$ below ideal body weight, silicosis, gastrectomy, jejunoileal bypass, and abnormal chest radiograph showing fibrotic lesions consistent with old, healed TB.
5. Residents and employees of high-risk congregate settings.
6. Health care workers who serve high-risk clients.
7. Foreign-born persons, including children, recently arrived from countries that have a high incidence or prevalence of TB.
8. Some medically underserved, low-income populations.
9. High-risk racial or ethnic minority populations, as defined locally.
10. Infants, children, and adolescents exposed to adults in high-risk categories.

Efficacy. Isoniazid is the only drug with proven efficacy in the prophylaxis of TB. Prophylaxis can reduce the risk of TB by more than 90% in infected persons who adhere to therapy.¹³¹ The efficacy of isoniazid preventive therapy in HIV-infected persons has been investigated only in small trials; however, the drug appears to confer protection.¹²⁹

Resistance. Outbreaks of multidrug-resistant TB (defined as infection with a strain of *M. tuberculosis* resistant to both

isoniazid and rifampin) have added to the concern about the re-emergence of TB.^{129,132} TB caused by multidrug-resistant organisms may be associated with a very high mortality rate (72–89%).¹²⁹ The most important factors that contribute to the emergence of drug resistance are (1) the use of antituberculosis medications in uncontrolled nonprescription preparations available in many foreign countries, (2) poor adherence, and (3) improper therapy, usually the failure to employ adequate antituberculosis therapy at the beginning of treatment.¹³¹ The level of patient adherence is inversely correlated with the duration of therapy. More than one year of therapy provides the maximum benefit, whereas six months confers a lesser benefit but is associated with higher adherence.¹³³ Because poor adherence contributes to resistance, the recommended duration of prophylaxis is six months.¹³⁰ Improving patient adherence is an important strategy for reducing the occurrence of multidrug-resistant TB and has been previously addressed by ASHP.¹³⁴

Pediatric Efficacy. No well-controlled studies have yet evaluated the effect of prophylaxis for TB in children. Pediatric recommendations are provided by CDC.^{113,130,135-137}

Recommendation. Official recommendations for the prevention of TB have been published by ACET.^{130,135,138} The recommendation to start preventive therapy is based on risk factors and skin-test results (Table 2). Preventive therapy is indicated for the following skin-test results and risk factors:

1. In persons of any age with an induration of ≥ 5 mm who have had recent close contact with persons who have active TB, who have HIV infection or risk factors for HIV infection but unknown HIV status, or who have fibrotic chest radiographs consistent with healed TB.
2. In persons of any age with an induration of ≥ 10 mm who are intravenous drug users known to be HIV seronegative and who have other medical conditions (see risk factors).
3. In persons with an induration of ≥ 10 mm who are residents or employees of high-risk congregate settings (prisons and jails, nursing homes and other long-term-care facilities for the elderly, health care facilities, mental institutions, and homeless shelters), foreign-born persons recently arrived (i.e., within the past five years) from countries with a high prevalence or incidence of TB, some medically underserved, low-income populations (i.e., migrant farm workers, homeless persons), high-risk racial or ethnic minority populations (as defined locally), or infants, children, and adolescents exposed to adults in high-risk categories.
4. In persons less than 35 years of age with an induration of ≥ 10 mm or in persons 35 years of age or older with an induration of ≥ 15 mm who are recent converters (within the past two years).
5. In persons with an induration of ≥ 15 mm who do not meet any of the previous criteria.^{130,135}

The recommended dosage of isoniazid is 300 mg orally daily for six months. An alternative dosage is 15 mg/kg (up to 900 mg) twice weekly for patients who must have therapy directly observed. In patients with immunosuppression or with radiographic abnormalities suggestive of "old" TB, the recommended duration of prophylaxis is 12 months. In patients who cannot take isoniazid because of adverse effects, oral rifampin 600 mg every day with or without

Table 2.
Prevention of Infection in Anticipation of or after Defined Exposure^a

Infection and Setting	Eligible Patients	Recommended Regimen	Alternative Regimens	Strength of Evidence ^b	
Influenza A ^c	Adult high-risk patients ^d and groups that can transmit infection to high-risk patients ^e	Amantadine 100 mg p.o. b.i.d. before and throughout epidemic period ^f	Rimantadine 100 mg p.o. b.i.d. in patients unable to tolerate central nervous system effects of amantadine	A	
	Pediatric high-risk patients ^d and groups that can transmit infection to high-risk patients ^e	Amantadine 5–9 mg/kg/day (maximum 200 mg/day) p.o. in 2 divided doses if 1–8 yr old and <40 kg; amantadine 100 mg p.o. b.i.d. if 9–12 yr old or >40 kg ^f ; use before and throughout epidemic period	Rimantadine 5 mg/kg (maximum 150 mg/day) p.o. daily if <10 yr old; rimantadine 100 mg p.o. b.i.d. if >10 yr old	NA	
Malaria	Travel in areas of chloroquine susceptibility	Adult travelers to countries endemic for malaria	None	B	
		Pediatric travelers to countries endemic for malaria	None	NA	
	Travel in areas of chloroquine resistance	Adult travelers to countries endemic for malaria	Mefloquine hydrochloride 250 mg p.o. weekly starting 1 wk before travel, continue 4 wk after leaving area	Doxycycline 100 mg p.o. daily starting 1 day before travel, continue 4 wk after leaving area; or chloroquine (same adult dosage and duration as above) with or without chloroguanide 200 mg/day p.o. during exposure and for 4 wk after last exposure plus pyrimethamine–sulfadoxine 3 tablets p.o. as presumptive treatment for febrile illness when medical care not immediately available (pyrimethamine 25 mg and sulfadoxine 500 mg per tablet)	B
	Pediatric travelers to countries endemic for malaria	Mefloquine hydrochloride 5 mg/kg p.o. weekly if <15 kg, 0.25 tablet weekly if 15–19 kg, 0.5 tablet weekly if 20–30 kg, 0.75 tablet weekly if 31–45 kg, 1 tablet weekly if >45 kg (1 tablet = 250 mg mefloquine hydrochloride)	Doxycycline 2 mg/kg/day (maximum 100 mg/day) p.o. if >8 yr old (not to be used in younger children); or chloroquine (same pediatric dosage and duration as above) with or without chloroguanide 50 mg/day p.o. if <2 yr old, 100 mg/day if 2–6 yr old, 150 mg/day if 7–10 yr old, 200 mg/day if >10 yr old plus pyrimethamine–sulfadoxine 0.25 tablet p.o. if <1 yr old, 0.5 tablet if 1–3 yr old, 1 tablet if 4–8 yr old, 2 tablets if 9–14 yr old, 3 tablets if >14 yr old as presumptive treatment for febrile illness when medical care not immediately available (pyrimethamine 25 mg and sulfadoxine 500 mg per tablet)	NA	
Traveler's diarrhea	Travel to underdeveloped countries	None (adult and pediatric)	Not recommended	None	C

Continued on next page

Table 2 (continued)

Infection and Setting	Eligible Patients	Recommended Regimen	Alternative Regimens	Strength of Evidence ^b
Tuberculosis ^h PPD induration ≥ 5 mm	Adults with recent close contact with person with active TB; HIV infected or with risk factors for HIV, fibrotic chest radiographs consistent with healed TB	Isoniazid 300 mg p.o. a daily for 6 mo; 12 mo if HIV infected or with radiographic evidence of old TB	Isoniazid 15 mg/kg (maximum 900 mg) p.o. twice weekly in directly observed therapy; if unable to take isoniazid, rifampin 600 mg p.o. daily with or without ethambutol 15 mg/kg/day p.o.; if exposed to multidrug-resistant TB and with high likelihood of infection, pyrazinamide 25 mg/kg/day p.o. with ethambutol 15 mg/kg/day p.o. or with a fluoroquinolone (ofloxacin 400 mg or ciprofloxacin 750 mg p.o. b.i.d.). Pyridoxine 50 mg p.o. daily generally not necessary ^j	A
	Children with same eligibility as nonpediatric patients with induration ≥ 5 mm	Isoniazid 10 mg/kg/day (maximum 300 mg/day) p.o. for 6 mo	If unable to take isoniazid, rifampin 10–20 mg/kg/day (maximum 600 mg/day) p.o. as single daily dose; if exposed to multidrug-resistant TB and with high likelihood of infection, pyrazinamide 20–40 mg/kg/day (maximum 2 g/day) p.o. in divided doses (every 12–24 hr) plus ethambutol 15–25 mg/kg/day (maximum 2.5 g/day) p.o. ^l Pyridoxine prophylaxis 1–2 mg/kg/day p.o. generally not necessary ^j	NA
PPD induration ≥ 10 mm	Adult i.v. drug users known to be HIV seronegative; adults with certain conditions ^k Adult residents and employees of high-risk congregate settings; ^l foreign-born persons recently arrived from country with high prevalence or incidence of TB; some medically underserved, low-income populations; high-risk racial or ethnic minorities	Adult isoniazid as above	Adult isoniazid alternatives as above	A

Continued on next page

ethambutol hydrochloride 15 mg/kg/day may be used. In patients infected with an isoniazid-resistant organism, rifampin with or without isoniazid or ethambutol has been recommended. Prophylaxis with pyridoxine hydrochloride 50 mg daily to prevent peripheral neuritis or convulsions due to isoniazid is generally not necessary, except for persons with conditions in which neuropathy is common (diabetes, uremia, alcoholism, malnutrition), pregnant women, and persons with a seizure disorder. For persons exposed to multidrug-resistant TB and with a high likelihood of being infected (with an induration of >5 mm, anergic, or with HIV infection), oral pyrazinamide 25 mg/kg/day and oral ethambutol hydrochloride 15 mg/kg/day or pyrazinamide and a fluoroquinolone (ciprofloxacin 750 mg twice a day or ofloxacin 400 mg twice a day) for 12 months are recommended. (Strength of evidence for prophylaxis = A)

Pediatric Dosage. The recommendation for TB prophylaxis in children is isoniazid 10 mg/kg/day (maximum daily dose, 300 mg) administered as a single daily dose for six months. For children unable to take isoniazid, rifampin 10–20 mg/

kg/day (maximum daily dose, 600 mg) in a single daily dose is recommended. Prophylaxis with pyridoxine hydrochloride 1–2 mg/kg/day to prevent peripheral neuritis or convulsions due to isoniazid is generally not necessary, except for persons with conditions in which neuropathy is common (diabetes, uremia, malnutrition), children or adolescents on meat- or milk-deficient diets, breast-feeding infants, and children with a seizure disorder. For children exposed to multidrug-resistant TB and with a high likelihood of being infected, pyrazinamide 20–40 mg/kg/day with doses given every 12–24 hours (maximum daily dose, 2 g) and ethambutol hydrochloride 15–25 mg/kg/day (maximum daily dose, 2.5 g) should be used. Ethambutol is generally not recommended for children whose visual acuity cannot be monitored. However, ethambutol should be considered for all children with organisms resistant to other drugs when susceptibility to ethambutol has been demonstrated or is likely.

Occupational Exposure to HIV

Persons at Risk. The risk of HIV seroconversion through

Table 2 (continued)

Infection and Setting	Eligible Patients	Recommended Regimen	Alternative Regimens	Strength of Evidence ^b
PPD induration ≥ 10 mm and patient <35 yr old	Adult converter within last 2 yr	Adult isoniazid as above	Adult isoniazid alternatives as above	A
PPD induration ≥ 10 mm	Children with the same eligibility as adults with induration ≥10 mm; exposure to high-risk categories	Pediatric isoniazid as above	Pediatric isoniazid alternatives as above	NA
PPD induration ≥ 15 mm and patient ≥35 yr old	Adult converter within last 2 yr	Adult isoniazid as above	Adult isoniazid alternatives as above	A
PPD induration ≥ 15 mm	Adults with none of above adult eligibility criteria	Adult isoniazid as above	Adult isoniazid alternatives as above	A
PPD induration ≥15 mm	Children with none of above pediatric eligibility criteria	Pediatric isoniazid as above	Pediatric isoniazid alternatives as above	NA

^aPPD = purified protein derivative (tuberculin skin test), TB = tuberculosis.

^bStrength of evidence that supports the use or nonuse of prophylaxis is classified as A (levels I–III), B (levels IV–VI), or C (level VII). Level I evidence is from large, well-conducted randomized, controlled clinical trials. Level II evidence is from small, well-conducted randomized, controlled clinical trials. Level III evidence is from well-conducted cohort studies. Level IV evidence is from well-conducted case–control studies. Level V evidence is from uncontrolled studies that were not well conducted. Level VI evidence is conflicting evidence that tends to favor the recommendation. Level VII evidence is expert opinion. Strength-of-evidence classification not applied (NA) to pediatric recommendations.

^cProphylaxis is recommended for the following: (1) Persons at high risk vaccinated after influenza A activity has begun. The development of antibodies can take as long as two weeks. Children who receive influenza vaccine for the first time can require as long as six weeks of prophylaxis (i.e., prophylaxis for two weeks after the second dose of vaccine has been received). (2) Persons providing care to those at high risk who are not vaccinated. Prophylaxis should be considered for all employees, regardless of their vaccination status, if the outbreak is caused by a variant strain of influenza A that might not be controlled by the vaccine. (3) Persons who have immune deficiency who are expected to have an inadequate antibody response to influenza vaccine. (4) Persons for whom influenza vaccine is contraindicated, including persons who have severe anaphylactic hypersensitivity to egg protein or other vaccine components. (5) Other persons who wish to avoid influenza A illness.

^dGroups at high risk for influenza-related complications include (1) persons at least 65 years old, (2) residents of nursing homes and other chronic care facilities, (3) adults and children with chronic disorders of the pulmonary or cardiovascular systems, including children with asthma, (4) adults and children who have required regular medical follow-up or hospitalization during the preceding year because of chronic metabolic diseases (including diabetes mellitus), renal dysfunction, hemoglobinopathies, or immunosuppression, (5) children and teenagers (six months–18 years old) who are receiving long-term aspirin therapy and therefore might be at risk for developing Reye syndrome after influenza, and (6) women who will be in the second or third trimester of pregnancy during the influenza season. No well-controlled studies have been conducted in pregnant women, and chemoprophylaxis should be used during pregnancy only when the potential benefits outweigh the possible risk to the fetus.

^eGroups that can transmit influenza to persons at high risk include (1) physicians, nurses, and other health care personnel, (2) employees of nursing homes and chronic care facilities who have contact with patients or residents, (3) providers of home care to persons at high risk (e.g., visiting nurses, volunteers), and (4) household members (including children) of persons in high-risk groups.

^fContinue for 10 days after exposure. When used in conjunction with vaccine, continue for two weeks after vaccine (after the second of two vaccine doses required in children younger than nine years who have not previously been vaccinated). If vaccine is unavailable or contraindicated, continue for the duration of influenza activity in the community.

^gHousehold members of persons in high-risk groups.

^hAdapted from recommendations of the Centers for Disease Control and Prevention (reference 130).

ⁱEthambutol is generally not recommended for children whose visual acuity cannot be monitored. However, ethambutol should be considered for all children with organisms resistant to other drugs when susceptibility to ethambutol has been demonstrated or is likely.

^jPyridoxine prophylaxis to prevent isoniazid-associated peripheral neuritis or convulsions is generally not necessary, except in persons with conditions in which neuropathy is common (diabetes, uremia, alcoholism, malnutrition), pregnant women, children or adolescents on meat- or milk-deficient diets, breast-feeding infants, and persons with a seizure disorder.

^kCertain conditions include HIV infection, diabetes mellitus, conditions requiring prolonged high-dose corticosteroid therapy and other immunosuppressive therapy (including bone marrow and organ transplantation), chronic renal failure, some hematologic disorders (e.g., leukemias, lymphomas), other specific malignancies (e.g., carcinoma of the head and neck), ≥10% below ideal weight, silicosis, gastrectomy, and jejunoileal bypass.

^lCorrectional institutions, nursing homes, mental institutions, other long-term residential facilities, and shelters for the homeless.

occupational exposure in health care workers is approximately 0.3% from a percutaneous injury from a needle or other device.^{139,140} The risk after mucous membrane or skin exposure to HIV-infected blood is approximately 0.1% or <0.1%, respectively.¹⁴¹ Variables related to the risk of HIV transmission include volume of blood involved in the exposure, stage of HIV disease, and plasma HIV RNA level in the source patient as well as site and mechanism of exposure.^{142,143} In a case–control study involving 33 case patients from France, Italy, the United Kingdom, and the United States, the risk of HIV seroconversion was higher when exposure was associated with a deep injury, visible blood on the device involved, a device previously placed in a source patient's vein or artery, or exposure to a terminally ill AIDS

patient.¹⁴⁴ The risk of HIV seroconversion was lower with postexposure use of zidovudine.

Efficacy. Animal data on zidovudine have been inconclusive, and human experience has been limited.^{144–150} Evaluation of zidovudine in humans is difficult because the low occurrence of HIV seroconversion after occupational exposure necessitates a very large sample to demonstrate a prophylactic effect.

In a case–control study involving national surveillance from the United States, France, Italy, and the United Kingdom, zidovudine prophylaxis was associated with an almost 80% lower risk of HIV seroconversion after percutaneous exposure to HIV-infected blood.¹⁴⁴ Caution should be

used in interpreting these results because of retrospective data collection, use of cases and controls, differing sources of cases and controls, and reporting or ascertainment bias.

Because well-controlled trials of chemoprophylaxis after occupational exposure have not been conducted, recommendations must be extrapolated from trials in patients with HIV infection. Single- and combination-drug therapies have been studied for treatment in HIV-infected patients. Although there are no data showing that monotherapy is more efficacious than combination therapy in postexposure prophylaxis, combination therapy has demonstrated greater efficacy than monotherapy in HIV-infected patients¹⁵¹⁻¹⁵⁴ and is the standard of care for the treatment of these patients.¹⁵⁵ The combination of zidovudine and didanosine, zidovudine plus zalcitabine, or didanosine alone slows the progression of HIV disease and is superior to treatment with zidovudine alone.¹⁵¹ The combination of indinavir, zidovudine, and lamivudine demonstrated undetectable viral RNA levels at week 24 in 22 of 24 patients. In contrast, only 9 of 24 patients treated with indinavir alone and 0 of 24 patients treated with zidovudine and lamivudine had undetectable levels.¹⁵³

For HIV prophylaxis after occupational exposure, CDC recommends the combination of zidovudine, lamivudine, and indinavir or nelfinavir in persons at highest risk for seroconversion.^{156,157} Zidovudine and lamivudine may be better tolerated and appear to have comparable antiretroviral potency, although there are no comparative markers and the potency is based on surrogate markers (HIV RNA levels and CD4+ lymphocyte counts).¹⁵⁸ Indinavir may be better tolerated than the other protease inhibitors. The addition of indinavir to the zidovudine and lamivudine combination enhances the antiretroviral potency.¹⁵³ However, there are no clinical data showing that three antiviral agents are more efficacious than two in postexposure prophylaxis.

Changes in drug protocols may be appropriate on the basis of factors such as antiretroviral drug resistance profile of HIV from the source patient as well as medical conditions, concurrent drug therapy, drug toxicity in the exposed worker, and patient adherence. A variable to consider when choosing antiretroviral agents is the antiretroviral therapy of the source patient. Some experts give the health care worker at least two antiretrovirals that the source patient is not taking because of the concern about resistance. Although not included in the CDC recommendations, alternative regimens have consisted of stavudine plus lamivudine and stavudine plus didanosine. Alternative regimens may be required in certain situations, such as the source person's virus being resistant to the standard regimen.¹⁵⁷ An alternative to indinavir is nelfinavir. Because most occupational exposures to HIV do not result in seropositivity, potential toxicity should be considered when postexposure prophylaxis is prescribed. One third of health care workers in two surveillance studies prematurely discontinued zidovudine because of adverse effects.^{139,149} Another concern is adherence to the drug regimen. Despite a lack of efficacy data, some experts choose a combination product containing zidovudine and lamivudine for better adherence.

Resistance. There are no data available on the resistance rates with prophylactic antivirals in the setting of occupational exposure; however, development of resistance is common when antivirals are used to treat HIV-infected persons.¹⁵⁵

Pediatric Efficacy. Not applicable.

Recommendation. The best means of preventing HIV

seroconversion from occupational exposure is to reduce the likelihood of exposure through the use of standard precautions during procedures and in the handling of blood and other body fluids. In the case of occupational exposure, current guidelines have been proposed by USPHS^{156,157} and supported by an international panel.^{155,158} The recommendations are provisional because of limited data on efficacy and toxicity of postexposure prophylaxis and risk for HIV seroconversion after different types of exposure. The recommended dosages are zidovudine 300 mg orally twice daily or 200 mg three times a day, lamivudine 150 mg orally twice a day, and indinavir 800 mg (as the sulfate) orally three times a day or nelfinavir 750 mg (as the mesylate) orally three times a day (Table 3). Prophylaxis is continued for four weeks.

Alternative regimens with other nucleoside reverse-transcriptase inhibitors, protease inhibitors, or nonnucleoside reverse-transcriptase inhibitors may be required. Postexposure prophylaxis should be initiated promptly, preferably within one to two hours after HIV exposure. Although animal studies suggest that postexposure prophylaxis is not effective when started later than 24–36 hours after exposure,^{141,159} the interval after which there is no benefit from postexposure prophylaxis for humans is undefined. CDC recommends prophylaxis for all high-risk exposures. CDC does not recommend prophylaxis for lower-risk exposures, with the provision that these exposed health care workers be offered the option of receiving prophylaxis. Specific considerations by route of exposure follow.

Percutaneous exposure to blood. When a large volume of blood (e.g., in the case of deep injury with a large-diameter hollow needle that was previously in the source patient's vein or artery, especially involving an injection of the source patient's blood) or blood containing a high HIV titer (e.g., if the source patient has acute retroviral illness or end-stage AIDS, in which case viral load measurement may be considered but has not been evaluated in relation to prophylaxis) or both are involved, zidovudine plus lamivudine plus indinavir should be recommended. (These situations are regarded as presenting the highest or increased risk.)

When neither a large volume of blood nor blood with a high titer of HIV (e.g., a solid suture-needle injury from a source patient with asymptomatic HIV infection) is involved, prophylaxis is not recommended. The exposed worker may be offered zidovudine plus lamivudine. (This scenario is regarded as presenting no increased risk.)

Percutaneous exposure to fluid containing visible blood or tissue. When fluid (including semen, vaginal secretions, and cerebrospinal, synovial, pleural, peritoneal, pericardial, and amniotic fluids) is involved, prophylaxis is not recommended. The exposed worker may be offered zidovudine plus lamivudine.

Percutaneous exposure to other fluid. When other fluid (e.g., urine) is involved, prophylaxis is not recommended and should not be offered.

Mucous membrane exposure and skin exposure. Regarding skin, risk is increased for exposures involving a high titer of HIV, prolonged contact, an extensive area, or an area in which skin integrity is visibly compromised. For skin exposures without increased risk, the risk of drug toxicity outweighs the benefit of postexposure prophylaxis. When blood

or skin exposure is involved, prophylaxis is not recommended. The exposed worker may be offered zidovudine plus lamivudine. Addition of indinavir is optional (associated with an increased risk of toxicity).

When fluid containing visible blood, other fluid (including semen, vaginal secretions, and cerebrospinal, synovial, pleural, peritoneal, pericardial, and amniotic fluids), or tissue is involved, prophylaxis is not recommended. The exposed worker may be offered zidovudine plus lamivudine.

When other fluid (e.g., urine) is involved, prophylaxis is not recommended and should not be offered. (Strength of evidence for prophylaxis = C)

Pediatric Dosage. Not applicable.

Resources. The following resources may be useful in the event of occupational exposure to HIV: CDC's home page (<http://www.cdc.gov>), the Epidemiology and Prevention Center at the University of California, San Francisco (<http://epi-center.ucsf.edu>), and a 24-hour hotline on caring for occupational exposure (888-448-4911). Health care professionals are encouraged to register pregnant women receiving antiretrovirals with the antiretroviral pregnancy registry (800-258-4263) and to register health care professionals receiving prophylaxis with the HIV postexposure prophylaxis registry (888-737-4448).

Perinatally Acquired HIV Infection

Background. Maternal–infant transmission of HIV is the primary means by which young children become infected. Approximately 7000 infants are born to HIV-infected women each year in the United States; 1000–2000 of these children will be infected with HIV.¹⁶⁰ It has been demonstrated that the maternal–infant transmission rate is 15–40%.¹⁶¹⁻¹⁶³

Persons at Risk. All infants born to HIV-infected women are considered at high risk for HIV infection. Infection may occur in utero, during labor and delivery, or by breastfeeding.¹⁶⁴ The presence of ruptured maternal membranes for more than four hours before delivery has been shown to nearly double the risk of maternal–infant transmission.¹⁶⁵ Transmission risk may be increased in women with low CD4+ lymphocyte counts or AIDS,^{165,166} but this has not been consistently reported. Two recent studies have demonstrated that the risk of transmission is significantly associated with maternal viral load at the time of study entry or delivery.^{167,168} Although the two studies did not stratify plasma HIV RNA levels versus transmission rates in the same way, it is clear that the risk of transmission increases significantly as viral load increases. In one study the transmission rate was 0% among 63 women with <20,000 RNA copies per mL of plasma compared with 100% transmission among 13 women with >80,000 RNA copies per mL of plasma.¹⁶⁷ Maternal HIV RNA levels are thus highly predictive of perinatal transmission risk. However, even low-level maternal viremia may be associated with a significant risk of perinatal transmission, while high maternal viral loads do not result in perinatal transmission to all infants. It is currently unclear whether routine maternal HIV viral load measurements will be useful because of the poor predictive value of maternal viral load for perinatal transmission risk.¹⁶⁹

Efficacy. CDC issued official recommendations for prophylaxis of maternal–infant transmission of HIV in 1994 based

solely on the results of the AIDS Clinical Trials Group Protocol 076 (ACTG 076). ACTG 076 demonstrated that the relative risk of maternal–infant transmission was 67.5% lower with zidovudine than with placebo (8.3% and 25.5%, respectively).¹⁶³ Subsequent studies have similarly demonstrated differences in transmission between no prophylaxis (19–29%) and zidovudine monotherapy (3–14%).^{166,170-172}

Although ACTG 076 specifically studied women with CD4+ lymphocyte counts of >200 cells/mL, subsequent studies have found that benefits of prophylaxis can be demonstrated regardless of CD4+ lymphocyte count or plasma HIV RNA levels.^{162,166-168,170} There is also no apparent association between efficacy of prophylaxis and clinical stage of disease.

Studies addressing the use of nonzidovudine monotherapy or combination therapy with agents from one or more antiretroviral drug classes have not yet been completed. However, CDC recommends an initial triple-drug regimen consisting of two nucleoside-analogue reverse-transcriptase inhibitors and a protease inhibitor for the treatment of HIV infection. The recommended triple-drug regimen has potential additional efficacy in the prevention of maternal–infant transmission of HIV.¹⁵⁵ Studies are currently being conducted to evaluate the safety and efficacy of multiple-drug regimens for prevention of vertical transmission.

The CDC recommendations call for prophylaxis of HIV-infected pregnant women to begin at 14–34 weeks of gestation. Because zidovudine has been shown to be mutagenic in a mammalian in vitro cell-transformation assay and because it was associated with embryotoxic effects and fetal resorptions in animal studies, antiretroviral drug use during the first trimester of pregnancy is not recommended. However, observational studies have demonstrated no apparent association of fetal abnormalities with zidovudine use throughout pregnancy.^{170,173,174} The frequency of congenital malformations in ACTG 076 or subsequent studies was not increased.¹⁶³ Studies in rodents have raised hypothetical concerns about the possible transplacental carcinogenicity of zidovudine. However, a panel of experts convened by NIH recently concluded that the proven benefits of zidovudine in reducing the risk of perinatal transmission outweigh these hypothetical concerns. Thus zidovudine continues to be used as standard therapy according to recommended protocols during weeks 14–34 of pregnancy.¹⁶⁹ Prophylaxis regimens are also associated with minimal maternal toxicity and appear to be safe for the infant as well.¹⁶³

Resistance. Because ACTG 076 specifically studied antiretroviral-therapy-naïve women, the effects of previous antiretroviral therapy on prophylaxis efficacy are of interest. Prophylaxis appears to remain beneficial, even in women with an extensive previous history of antiretroviral drug use.^{162,166} However, limited data suggest that maternal–infant transmission of virus resistant to antiretroviral drugs may occur in these women.¹⁶² The frequency and significance of this occurrence are unclear. Whether short-term use of zidovudine during pregnancy is associated with induction of viral resistance to antiretroviral agents is also unclear at this time.

Pediatric Efficacy. No well-controlled studies have evaluated the effect of prophylaxis in HIV-infected adolescent girls to prevent maternal–infant HIV transmission, although adult data are applicable.

Recommendation. Antiretroviral prophylaxis of maternal–infant HIV transmission is indicated when the potential benefits of drug therapy are believed to outweigh the risks to the mother or the infant (Table 4). The CDC prophylaxis regimen consists of three separate components: antepartum, intrapartum, and neonatal. As many as possible of these components should be used in prophylaxis, depending on the time of identification of eligible patients and the availability of care. Although some form of antiretroviral prophylaxis is recommended or offered in all scenarios, therapy should be instituted only after consultation with the woman and careful discussion of the potential benefits and risks involved. Decisions about the use of antiretroviral drugs during pregnancy should be made only after careful assessment of many factors, including the degree of maternal immunodeficiency (based on CD4+ lymphocyte count), the risk for maternal disease progression (based on viral load measurements), history of prior or current antiretroviral drug therapy, gestational age, and supportive care needs. Decisions about the initiation or continuation of therapy should be based on the same factors used for similar decisions in nonpregnant women, with additional consideration of the risk to the fetus and the infant. Current recommendations stress that the antiviral regimens should be selected with consideration of the proven benefit of antiretroviral therapy for the health of the infected woman as well as the potential reduction in risk of HIV transmission to the child. Ultimately, the final decision to accept or reject zidovudine treatment recommended for the woman and her child is the right and responsibility of the woman.¹⁶⁹ Recommendations also generally address four scenarios:

1. Pregnant HIV-infected women (with any CD4+ lymphocyte count) who are at >14 weeks' gestation and without a history of extensive (more than six months) antiretroviral therapy: recommend or offer all components of prophylaxis.
2. Pregnant HIV-infected women who have a history of extensive previous antiretroviral therapy before pregnancy: recommend or offer all components of prophylaxis.
3. Pregnant HIV-infected women who have not received antepartum antiretroviral therapy and who are in labor: recommend or offer intrapartum and neonatal components of prophylaxis.
4. Infants born to HIV-infected women who have received no intrapartum antiretroviral therapy: recommend or offer neonatal component of prophylaxis. It is advised that therapy for the infant be initiated as soon as possible (preferably within hours) after delivery. No data support offering antiretroviral therapy to the infant if therapy cannot be initiated within 24 hours after delivery.

Although combination antiretroviral therapy is standard in the general treatment of HIV-infected adults, the additional benefits and risks of combination therapy for prevention of perinatal transmission are as yet undetermined. Although combination regimens are considered optimal for long-term maternal benefits, zidovudine monotherapy is acceptable if the woman wants to minimize exposure of the fetus to other drugs. Because zidovudine is the only drug that has been proven to reduce the risk of perinatal transmission, all combinations of antiretroviral agents should include zidovudine as part of the initial ther-

apeutic regimen. For patients already receiving regimens that do not include zidovudine, the addition of zidovudine or substitution of zidovudine for another nucleoside reverse-transcriptase inhibitor is recommended.¹⁶⁹ Zidovudine should be administered as follows:

- For antepartum prevention, zidovudine 100 mg orally five times daily, initiated at 14–34 weeks' gestation and continued for the remainder of the pregnancy.
- For intrapartum prevention, during labor, zidovudine 2 mg/kg i.v. over one hour, followed by 1 mg/kg/hr i.v. by continuous infusion until delivery.
- Neonatal dosage: zidovudine syrup 2 mg/kg orally every six hours for six weeks, beginning 8–12 hours after birth. (Strength of evidence for prophylaxis = A)

Pediatric Dosage. In the case of adolescent pregnancy, the adult recommendations should be used. Additional guidelines for the prevention of perinatal transmission of HIV can be found at <http://www.hivatis.org/pedguide.html>, the Web site of the HIV/AIDS Treatment Information Service.

Perinatally Acquired Herpes Simplex Virus Type 2 Infection

Background. Approximately 1500 to 2000 cases of neonatal herpes are reported each year in the United States, an annual incidence of 1 in every 7500 births. HSV-2 accounts for nearly 70% of neonatal herpes and may be acquired congenitally, natively, or postnatally. The presence of primary HSV, but probably not recurrent HSV, during pregnancy increases the frequency of spontaneous abortion twofold to fourfold and increases the frequency of preterm labor twofold. Congenital anomalies may occur with primary, recurrent, or even asymptomatic disease.¹⁷⁵

Persons at Risk. The risk of HSV infection in newborns of HSV-infected mothers is greatly increased. Cesarean birth is recommended for mothers if an HSV lesion will come into contact with the baby at the time of delivery.¹⁷⁶ The neonatal infection rates are greater in mothers with primary HSV infection than in mothers with recurrence of previously acquired HSV, 30–40% versus 3–5%, respectively.¹⁷⁵ However, distinguishing between primary and recurrent HSV infection in women on the basis of clinical findings is difficult. Most newborns infected with HSV are born to women who have asymptomatic or unrecognized infection.¹⁷⁶ HSV-1 and HSV-2 produce equal severity of disease. The use of fetal scalp monitors or other invasive instrumentation antenatally increases the risk of perinatal HSV transmission. Antiviral prophylaxis is based on the presumption that reduction in the frequency of active HSV lesions at delivery will reduce the rate of cesarean delivery, newborn HSV exposure, and subsequent neonatal HSV disease.¹⁷⁷ Nearly 1600 cesarean births must be performed to prevent one case of neonatal herpes infection (a cost per neonatal herpes case averted of \$2.5 million and a cost per quality-adjusted life-year gained of \$203,000).¹⁷⁸

Efficacy. The efficacy of prophylaxis with acyclovir in the prevention of HSV disease in newborns is not known; however, use of this regimen has been associated with a lower rate of cesarean deliveries.^{177,179} Data on prophylaxis to prevent HSV-2 are limited to a case series in mothers with

recurrent genital HSV-2,¹⁸⁰ a placebo-controlled, double-blind study of mothers with first-episode herpes,¹⁷⁷ and a placebo-controlled study in mothers with frequent recurrent genital herpes.¹⁷⁹

One series of five mothers with recurrent genital herpes (HSV-2) received different acyclovir dosages after 37 weeks' gestation, and acyclovir plasma concentrations and viral cultures from the genital area were followed until birth.¹⁸⁰ This small uncontrolled study suggests that mothers with recurrent genital HSV infection may still have asymptomatic viral shedding and transmission to the newborn despite treatment with acyclovir.

In a placebo-controlled, double-blind study, 46 pregnant women with first-episode genital herpes were randomly assigned to receive either oral acyclovir 400 mg three times daily or placebo from 36 weeks' gestation to delivery.¹⁷⁷ The frequency of symptomatic recurrent HSV lesions at the time of delivery was 8% for the acyclovir recipients and 34% for the placebo recipients, demonstrating a significant reduction in HSV disease at time of delivery. The rate of cesarean section was also lower in the treatment group than the placebo group (19% versus 40%, respectively). Apparently the obstetrician had a greater sense of security with the acyclovir group because of fewer lesions. However, no newborn in either group developed HSV disease, and there were no differences in neonatal outcomes between the groups. No benefit in reducing the risk for neonatal HSV was demonstrated, possibly because of the relatively low infection rate and the enormous number of patients needed to detect differences. Acyclovir was well tolerated by both the mother and the fetus. The results of this study suggest that acyclovir suppressive therapy decreases the rate of cesarean section in mothers with genital herpes, but no conclusive benefits for the prevention of disease in the newborn could be demonstrated.

Another study also demonstrated the benefit of oral acyclovir in reducing active HSV lesions at delivery and the cesarean delivery rate.¹⁷⁹ The study was placebo controlled but was not randomized or blinded in women with frequently recurring genital herpes (an average of three symptomatic recurrences over the last six months of pregnancy). Ninety-two women with recurrent genital herpes received either acyclovir 200 mg orally four times daily or placebo for one to two weeks before delivery. No cesarean sections were performed specifically because of the presence of herpes lesions in the acyclovir-treated group ($n = 46$), while 9 (20%) of 46 patients in the placebo group had cesarean sections because of active herpes lesions at the time of delivery. There were no cases of neonatal herpes in either group. A lower cesarean delivery rate in primary HSV-infected mothers is an important benefit to the mothers. There are no data available showing that famciclovir or valacyclovir reduces active HSV lesions at delivery or the cesarean delivery rate, although famciclovir and valacyclovir are efficacious against HSV. The CDC pregnancy outcome registry from 1984 to 1993 indicated no increased risk of birth defects among infants born to women exposed to acyclovir during pregnancy.¹⁸¹

Resistance. There are no data available on the development of resistance with perinatal prophylactic antivirals. Acyclovir-resistant HSV is most commonly reported in severely immunocompromised patients and infrequently in immunocompetent patients with extended treatment courses.¹⁸²

Pediatric Efficacy. No well-controlled studies have evaluated the effect of prophylaxis in adolescent girls to prevent maternal–infant transmission of HSV, although adult data should be applicable.

Recommendation. The efficacy of prophylactic antivirals in pregnant women with genital HSV infection is not well established, although acyclovir administration has been associated with lower cesarean delivery rates. If prophylaxis is chosen, the recommended regimen is acyclovir 400 mg orally three times daily from 36 weeks' gestation to delivery in primary HSV-infected mothers (Table 4). An alternative is valacyclovir 1 g (as the hydrochloride) orally twice a day. For mothers with frequently recurring genital HSV (six episodes a year), the recommended regimen is acyclovir 200 mg four times daily for one to four weeks before delivery. Alternatives are famciclovir orally 125 mg twice a day or valacyclovir orally 500 mg (as the hydrochloride) twice a day. Prophylaxis is not recommended in pregnant women with a remote history of genital HSV (no recent recurrence or HSV seropositive). (Strength of evidence for prophylaxis = A for prevention of cesarean delivery in mothers with primary HSV infection and B for recurrent genital HSV. Strength of evidence against prophylaxis = C for mothers with a remote history of genital HSV)

Health care professionals are encouraged to register pregnant women receiving acyclovir with the acyclovir pregnancy registry at 888-825-5249, extension 39441.

Pediatric Dosage. According to adult efficacy data, acyclovir is associated with lower cesarean delivery rates in HSV-infected mothers and lower risks inherent in the surgical procedure. Adolescents should receive the adult dosage of acyclovir: acyclovir 400 mg orally three times daily from 36 weeks' gestation to delivery in primary HSV-infected adolescents. An alternative is valacyclovir 1 g (as the hydrochloride) orally twice a day. Acyclovir 200 mg orally four times daily for one to four weeks before delivery is recommended for mothers with frequently recurring genital HSV (six episodes a year). Alternatives are famciclovir orally 125 mg twice a day or valacyclovir orally 500 mg (as the hydrochloride) twice a day. Prophylaxis is not recommended in pregnant adolescents with a remote history of genital HSV (no recent recurrence or HSV seropositive).

Perinatally Acquired Group B Streptococcal Infection

Background. Group B streptococci are the pathogens most frequently implicated in neonatal sepsis in the United States and are directly implicated in 20% of all episodes of peripartum sepsis.¹⁸³ Two distinct disease types—early onset and late onset—have been described. Early-onset sepsis (less than seven days after birth) results from intrauterine infection and is more common than late-onset disease (seven days to three months).^{184,185} Early-onset disease is associated with a higher mortality rate.¹⁸⁵ It is estimated that 0.2–0.5% of all neonates in the United States develop sepsis involving group B streptococci, with a fatality rate of 25%.^{183,184} The annual morbidity and mortality rates associated with group B streptococci in the United States are approximately 12,000 infants and 50,000 pregnant women.¹⁸⁵

A pharmacoeconomic analysis showed that intrapartum prophylactic antimicrobials administered to colonized

women with labor complications (fever, rupture of membranes for more than 12 hours, or labor onset before 37 weeks of gestation) could save approximately \$16 million in direct medical costs.¹⁸⁶

Persons at Risk. Because group B streptococci are transmitted from mother to neonate during delivery, infants born to mothers with cervical or vaginal colonization are at greatest risk for sepsis. Approximately 10–34% of pregnant women have vaginal or rectal colonization.¹⁸⁷ Virtually 100% of group B streptococcal carriers can be detected when selective broth media for lower vagina and anorectum cultures are used.¹⁸⁵ Of infants born to colonized mothers, 40–73% become colonized themselves, but only 1–2% develop sepsis.^{185,187}

Several maternal factors increase the risk of infection in infants of mothers who are colonized by group B streptococci. These include gestation of less than 37 weeks, rupture of membranes more than 18 hours before delivery, fever during labor, previous delivery of an infant infected with group B streptococcal disease, group B streptococcal bacteriuria during pregnancy, high inoculum of group B streptococci in genital cultures, age of

mother of less than 20 years, low concentration of serotype-specific antibody to the group B streptococcal capsular polysaccharide in the serum, and African-American race. Multiple gestation may also be a factor.¹⁸⁷

Efficacy. Several randomized trials have demonstrated that intrapartum administration of antimicrobials is effective in reducing the rate of vertical transmission of group B streptococci.^{188–191} In one study, the frequency of early-onset group B streptococcal disease was significantly different in the infants whose mothers received prophylaxis (0%) compared with those who received no treatment (6.3%).¹⁸⁸ In a meta-analysis of controlled trials and cohort studies, the use of antimicrobial prophylaxis was associated with a 30-fold lower frequency of early-onset group B streptococcal infection.¹⁹²

Resistance. The development of resistant Enterobacteriaceae after the use of ampicillin or amoxicillin prophylaxis for group B streptococcus in women with premature rupture of the membranes has been described¹⁹³ and should be considered in the risk–benefit assessment of the use of prophylactic antimicrobials.

Table 3.
Prevention of Human Immunodeficiency Virus Infection after Occupational Exposure^a

Setting	Eligible Patients	Recommended Regimen	Alternative Regimens	Strength of Evidence ^b
Percutaneous exposure to blood	Persons with highest- and increased-risk exposure ^c	Zidovudine 300 mg p.o. b.i.d. or 200 mg p.o. t.i.d. plus lamivudine 150 mg p.o. b.i.d. plus either indinavir 800 mg p.o. t.i.d. or nelfinavir 750 mg p.o. t.i.d. for 4 wk	^d	C
	Persons with exposure of no increased risk ^e	Not recommended	Offer zidovudine 300 mg p.o. b.i.d. or 200 mg p.o. t.i.d. plus lamivudine 150 mg p.o. b.i.d. ^d	C
Other percutaneous exposure	Persons exposed to fluid containing blood, other fluid, ^f or tissue	Not recommended	Offer zidovudine 300 mg p.o. b.i.d. or 200 mg p.o. t.i.d. plus lamivudine 150 mg p.o. b.i.d. ^d	C
	Persons exposed to other fluid (e.g., urine)	Not recommended	Do not offer	C
Exposure of mucous membrane or skin ^g	Persons exposed to blood	Not recommended	Offer zidovudine 300 mg p.o. b.i.d. or 200 mg p.o. t.i.d. plus lamivudine 150 mg p.o. b.i.d.; addition of indinavir or nelfinavir is optional ^d	C
	Persons exposed to fluid containing blood, other fluid, ^f or tissue	Not recommended	Offer zidovudine 300 mg p.o. b.i.d. or 200 mg p.o. t.i.d. plus lamivudine 150 mg p.o. b.i.d. ^d	C
	Persons exposed to other fluid (e.g., urine)	Not recommended	Do not offer	C

^aAdapted from recommendations of the Centers for Disease Control and Prevention (CDC, reference 157).

^bStrength of evidence that supports the use or nonuse of prophylaxis is classified as A (levels I–III), B (levels IV–VI), or C (level VII). Level I evidence is from large, well-conducted randomized, controlled clinical trials. Level II evidence is from small, well-conducted randomized, controlled clinical trials. Level III evidence is from well-conducted cohort studies. Level IV evidence is from well-conducted case–control studies. Level V evidence is from uncontrolled studies that were not well conducted. Level VI evidence is conflicting evidence that tends to favor the recommendation. Level VII evidence is expert opinion. Strength-of-evidence classification not applied (NA) to pediatric recommendations.

^cHighest and increased-risk exposures involve a larger volume of blood (e.g., deep injury with large diameter hollow needle previously in source patient’s vein or artery, especially involving an injection of source patient’s blood) or blood containing a high titer of HIV. A high titer of HIV is defined as blood from a person with acute retroviral illness or end-stage AIDS; viral load measurement may be considered, but its use in relation to prophylaxis has not been evaluated.

^dAlternative regimens with other nucleoside reverse-transcriptase inhibitors, protease inhibitors, or nonnucleoside reverse-transcriptase inhibitors may be required. Alternative regimens may be required in certain situations (e.g., resistance of source’s virus to standard regimen).¹⁵⁷ Other regimens have not been approved by CDC.

^eThere is no increased risk if exposure was to neither a large volume of blood nor blood with a high titer of HIV (e.g., solid suture-needle injury from a source patient with asymptomatic HIV infection).

^fOther fluids include semen, vaginal secretions, and cerebrospinal, synovial, pleural, peritoneal, pericardial, and amniotic fluids.

^gFor skin exposures, the risk is increased if the fluid contains a high titer of HIV, there is prolonged contact, the exposed area is large, or the integrity of the exposed skin is visibly compromised. For skin exposures without increased risk, the risk of drug toxicity outweighs the benefit of postexposure prophylaxis.

Pediatric Efficacy. No well-controlled studies have evaluated the effect of prophylaxis in adolescent girls to prevent perinatal group B streptococcal infection, although adult data are likely to be applicable.

Recommendation. Two acceptable strategies for the prevention of perinatal group B streptococcal infection have been proposed by CDC and the American Academy of Pediatrics (AAP)/American College of Obstetricians and Gynecologists (ACOG).^{187,194} The two strategies include screening at 35–37 weeks and using only risk factors. Regardless of the strategy used, women should be given antimicrobial prophylaxis if they had a previous delivery of an infant with group B streptococcal disease or group B streptococcal bacteriuria during the pregnancy. The prenatal screening strategy includes screening all pregnant women at 35–37 weeks and offering antimicrobial prophylaxis to all pregnant women with positive group B streptococcal cultures. If the results of group B streptococcal cultures are not known at the time of labor, intrapartum prophylaxis should be administered if one of the following risk factors is present: delivery at <37 weeks' gestation (for ruptured membranes without labor at <37 weeks, group B streptococcal culture should be collected and either antimicrobials given until cultures are completed and negative or antimicrobials begun once positive culture results are available), duration of membrane rupture of ≥ 18 hours before delivery, or intrapartum fever (≥ 38 °C). The risk-factor strategy is based only on the presence of the preceding intrapartum risk factors; intrapartum antimicrobial prophylaxis is administered if one or more of these risk factors are present.

The recommendation for intrapartum therapy is penicillin G 5 million units i.v. load, then 2.5 million units i.v. every four hours until delivery (Table 4). An alternative regimen is ampicillin 2 g (as the sodium) i.v., then 1 g i.v. every four hours until delivery. Patients allergic to penicillin may receive clindamycin 900 mg (as the phosphate) i.v. every eight hours or erythromycin 500 mg (as the lactobionate) i.v. every six hours until delivery. (Strength of evidence for prophylaxis = A)

Pediatric Dosage. CDC and AAP have published official recommendations on antimicrobial prophylaxis of perinatal group B streptococcal infection and empirical management of neonates born to women receiving intrapartum chemoprophylaxis.^{176,187} Readers are referred to the adult recommendations for at-risk patients who require prophylaxis.

Opportunistic Infections in Afebrile Granulocytopenic Patients

Persons at Risk. Patients with granulocytopenia (usually defined as <500 granulocytes/mm³ for at least seven days) are at an increased risk of serious infection and death. Patients with hematologic malignancies, especially patients with acute leukemia, who are receiving antineoplastic therapy are at particular risk for infection. Patients receiving antineoplastic conditioning for bone marrow transplantation (BMT) also experience severe granulocytopenia and have significant risk of infection. Many of the studies evaluated for this review included patients with leukemia as well as patients undergoing BMT. Therefore, recommendations for patients undergoing BMT are included in this section.

The degree and duration of granulocytopenia are the greatest risk factors for the development of infection. Pa-

tients with severe granulocytopenia (<100 granulocytes/mm³) are at greatest risk. Although patients with a duration of granulocytopenia of less than one week can become febrile and require antimicrobials, they generally respond quickly to therapy.¹⁹⁵ Other risk factors include mucosal and skin lesions, indwelling catheters, instrumentation, severe periodontal disease, dental procedures, postobstructive pneumonia, status of the malignancy or organ engraftment, and compromise of other immune responses.¹⁹⁶ Patients who have granulocytopenia related to antineoplastic therapy are at greater risk of infection than patients with granulocytopenia due to other causes (e.g., aplastic anemia, HIV infection). This is presumably due to alterations in the mucosal integrity induced by chemotherapy, which allows enhanced bacterial or fungal colonization.¹⁹⁵

Another risk factor for fungal infections is the administration of broad-spectrum antimicrobials.^{197,198} Fungal infections are particularly common in patients undergoing allogeneic BMT because these patients receive an intense conditioning regimen in addition to immunosuppressive agents to prevent or treat graft-versus-host disease.¹⁹⁷

The use of colony-stimulating factors has a beneficial effect on granulocyte recovery and thus eliminates the need for extended duration of antimicrobial prophylaxis. The frequency and severity of infection are inversely related to absolute neutrophil count in patients with acute leukemia.¹⁹⁹ Colony-stimulating factors (granulocyte colony-stimulating factor, granulocyte/macrophage colony-stimulating factor, and macrophage colony-stimulating factor) have been associated with a lower severity and duration of neutropenia and infectious complications and a shorter duration of therapeutic antimicrobial administration. Colony-stimulating factors have also been associated with a shorter duration of therapeutic antimicrobials and hospitalization in BMT patients.²⁰⁰ Although the use of colony-stimulating factors in the prevention of fungal infections is controversial, there is some evidence of a beneficial effect.²⁰¹ A concern with administering colony-stimulating factors is the regrowth of leukemic blasts in the bone marrow. Because the use of colony-stimulating factors eliminates the need for prolonged prophylaxis, there is potential for use to alter or influence the interpretation of study results.

Historically, antibacterial prophylaxis has been directed primarily toward gram-negative aerobic bacteria, especially *E. coli*, *Klebsiella pneumoniae*, and *P. aeruginosa*. However, the prevalence of gram-positive bacteria (staphylococci and streptococci) is increasing, perhaps because of the increased use of indwelling catheters and the use of prophylactic regimens for selective intestinal decontamination. The most common fungal pathogens are *Candida* and *Aspergillus* species. Cytomegalovirus (CMV) infection is a major cause of morbidity in patients undergoing BMT. Before the use of antiviral prophylaxis regimens, the risk of reactivation of latent infection was 80% and the risk of a seronegative recipient acquiring CMV from either blood transfusion or seropositive marrow was 40%.²⁰²

The goal of antimicrobial prophylaxis in granulocytopenic patients is to prevent infection, the cause of death in 50–80% of these patients. Unless otherwise specified, only trials of a concurrent, randomized design were considered.

Bacterial Prophylaxis. Efficacy. Most studies of antibacterial prophylaxis were conducted in patients receiving chemotherapy for acute leukemia or undergoing BMT. Agents such as trimethoprim–sulfamethoxazole and, more recently,

the fluoroquinolones (e.g., ciprofloxacin, norfloxacin, ofloxacin) have been used to achieve a selective antimicrobial effect by reducing the aerobic bacterial flora of the colon without suppressing the anaerobic flora. This practice theoretically preserves resistance to colonization by undesirable aerobic gram-negative bacilli. Data are lacking on the use of penicillin or cephalosporins plus aminoglycosides for prophylaxis, even though a plethora of data are available on these agents for empirical treatment in febrile neutropenic patients.²⁰³ The available data demonstrate a lower number of infectious episodes.²⁰⁴⁻²³⁶ However, the lack of improvement in mortality and the risk of drug-resistant bacteria may outweigh the benefit of reducing infectious episodes. IDSA recommends against the use of routine antibacterial prophylaxis, with the exception of using trimethoprim-sulfamethoxazole for patients at risk (e.g., patients with childhood leukemias, histiocytosis, or AIDS) for *Pneumocystis carinii* pneumonitis. The quinolones may be considered for short periods if the potential for resistant organisms is appreciated and outweighed by the benefits.²⁰³

Treatment with trimethoprim-sulfamethoxazole was superior to no drug and to placebo in reducing measures of acquired infection (e.g., duration of fever, duration of antimicrobial use, number of infections, number of gram-negative bacteremias) in most,²⁰⁴⁻²⁰⁷ but not all,²³⁷ studies. Norfloxacin prophylaxis was associated with a lower rates of gram-negative infections but not gram-positive infections compared with placebo.²⁰⁸ Similarly, norfloxacin plus oral amphotericin B was associated with a lower frequency of gram-negative and overall infections compared with amphotericin B alone.²⁰⁹ With one exception,²¹⁰ vancomycin²¹¹⁻²¹³ or teicoplanin²¹⁴ was effective as prophylaxis (lower rate of gram-positive infections, catheter-related infections, and use of empirical antimicrobials).

Use of prophylactic antimicrobials in patients with granulocytopenia has become so well established that most studies do not contain a control group. Studies have focused on comparisons among the various antimicrobial regimens. Comparisons have included trimethoprim-sulfamethoxazole versus fluoroquinolones,²¹⁵⁻²²⁶ fluoroquinolones versus fluoroquinolones,^{215,227-229} fluoroquinolones with and without added coverage for gram-positive infections,²³⁰⁻²³³ and fluoroquinolone versus vancomycin plus polymyxin B.^{234,235}

Trimethoprim-sulfamethoxazole was generally superior to nalidixic acid in reducing either gram-negative or overall infection rates.^{216,226} In contrast, newer fluoroquinolones (ciprofloxacin, norfloxacin, ofloxacin) were generally associated with a lower rate of gram-negative infections than trimethoprim-sulfamethoxazole.^{218,221,223} Trimethoprim-sulfamethoxazole is generally less well tolerated than fluoroquinolones and is associated with delayed recovery from granulocytopenia.^{220,223,226} There was no significant difference in the overall infection rates between fluoroquinolones and trimethoprim-sulfamethoxazole. Prophylaxis with fluoroquinolones was associated with a higher frequency of infections by gram-positive bacteria, especially viridans streptococci.^{217,219}

Comparisons between fluoroquinolones have been the subject of several investigations.^{215,227-229} Ciprofloxacin was more effective than norfloxacin in preventing fever and microbiologically documented infection in one large trial.²²⁹ However, comparisons between ciprofloxacin and ofloxacin found no difference in efficacy.^{215,228}

The addition of an antimicrobial with gram-positive coverage (e.g., a penicillin or macrolide) to fluoroquinolones

is effective in decreasing the frequency of gram-positive infections associated with the use of quinolones alone.²³⁰⁻²³³ The combination was effective in reducing the frequency of bacteremia, especially that due to streptococcal species. Despite supportive data for reducing gram-positive bacteremia, the combination of fluoroquinolones plus prophylaxis for gram-positive bacteremia (penicillin, vancomycin, or macrolides) was not associated with a lower rate of fever-related morbidity or infection-related mortality in a meta-analysis.²³⁶

Resistance. The emergence of resistance has been a problem with the major prophylactic antibacterial agents. *E. coli* resistance to trimethoprim-sulfamethoxazole, including the isolation of a self-transferable plasmid, has been reported.^{238,239} Fluoroquinolones have also been associated with the emergence of resistant organisms, primarily gram-positive bacteria^{240,241} but also *E. coli*.²⁴²

Pediatric efficacy. Few controlled trials in pediatric patients have been reported. Among children of ages 2 to 16 years undergoing BMT, there was a lower frequency of septicemia in the group receiving i.v. ceftazidime plus teicoplanin than in the control group.²⁴³ In 44 children with granulocytopenia, norfloxacin was associated with a lower number of febrile episodes than trimethoprim-sulfamethoxazole, although there was no difference in the mean number of febrile days or the use of systemic antimicrobials.²⁴⁴ The mean ages were eight and six years, respectively. No arthropathies were noted in children receiving norfloxacin.

Fungal Prophylaxis. Efficacy. Numerous recent studies have evaluated the efficacy of antifungal prophylaxis in granulocytopenic patients with hematologic malignancies (primarily acute leukemia) or in patients receiving BMT. Both topical and systemic agents have been used. Topical agents include amphotericin B, nystatin, and clotrimazole administered orally or by inhalation.²⁴⁵⁻²⁴⁸ Systemic agents include i.v. amphotericin B and oral or i.v. azoles (e.g., fluconazole, ketoconazole, itraconazole).²⁴⁹⁻²⁵⁹ The Eastern Cooperative Oncology Group (ECOG) recommends continued clinical investigation of the use of fungal prophylaxis because of the toxicity and limited efficacy in the treatment of invasive fungal infections. ECOG recommends that fluconazole or low-dose amphotericin B be considered for patients undergoing BMT.²⁰² The risk of drug resistance and fungal colonization by less susceptible strains may outweigh the benefit of reducing infectious episodes. IDSA recommends against the routine use of antifungals, with the exception that fluconazole may be used if the frequency of systemic infection due to *C. albicans* is high and that due to other *Candida* species is low.²⁰³

Low-dose (0.1 mg/kg/day) i.v. amphotericin B was associated with a lower rate of systemic fungal infection, number of days with fever, and number of days of high-dose (1 mg/kg/day) amphotericin B treatment required in patients undergoing BMT compared with placebo.²⁴⁹ Despite being associated with a lower number of yeast colonizing the oropharyngeal area, low-dose (0.1 mg/kg/day) i.v. amphotericin B was associated with a significantly greater frequency of infusion-related adverse effects (chills, fever, nausea, and vomiting) but not systemic toxicities (electrolytes, renal function, and hepatic enzymes) compared with placebo.²⁵⁰

Oral or i.v. fluconazole or ketoconazole was associ-

Table 4.
Prevention of Perinatally Acquired Infection^a

Infection and Setting	Eligible Patients	Recommended Regimen	Alternative Regimens	Strength of Evidence ^b
HIV ^c				
Antepartum prevention of transmission	All pregnant HIV-infected women at >14 wk gestation	Zidovudine 100 mg p.o. 5 times daily, starting at 14–34 wk of gestation, continued for remainder of pregnancy	None	A
Intrapartum prevention of transmission	All pregnant HIV-infected women	During labor, zidovudine 2 mg/kg i.v. over 1 hr, then 1 mg/kg/hr i.v. continuous infusion until delivery	None	A
Prevention of neonatal infection	All neonates born to HIV-infected women	Zidovudine syrup 2 mg/kg p.o. q 6 hr for 6 wk, beginning 8–12 hr after birth	None	A
HSV-2				
Reduction of cesarean delivery rate	Women with primary genital HSV	Acyclovir 400 mg p.o. t.i.d. from 36 wk gestation to delivery ^d	Valacyclovir 1 g p.o. b.i.d.	A ^e
	Women with frequent recurrent genital HSV ^f	Acyclovir 200 mg p.o. q.i.d. for 1–4 wk before delivery ^d	Famciclovir 125 mg p.o. b.i.d. or valacyclovir 500 mg p.o. b.i.d.	B ^e
	Women with remote history of genital HSV ^g	Not recommended	None	C
Group B streptococcus ^h				
Intrapartum prevention of neonatal sepsis	Women with (1) previous delivery of infant with group B streptococcal disease or (2) group B streptococcal bacteruria during current pregnancy	Intrapartum penicillin G 5 million units i.v. load, then 2.5 million units q 4 hr until delivery	Ampicillin 2 g i.v. load, then 1 g i.v. q 4 hr until delivery, clindamycin 900 mg i.v. q 8 hr, or erythromycin 500 mg i.v. q 6 hr until delivery	A

^aHIV = human immunodeficiency virus, HSV = herpes simplex virus.

^bStrength of evidence that supports the use or nonuse of prophylaxis is classified as A (levels I–III), B (levels IV–VI), or C (level VII). Level I evidence is from large, well-conducted randomized, controlled clinical trials. Level II evidence is from small, well-conducted randomized, controlled clinical trials. Level III evidence is from well-conducted cohort studies. Level IV evidence is from well-conducted case-control studies. Level V evidence is from uncontrolled studies that were not well conducted. Level VI evidence is conflicting evidence that tends to favor the recommendation. Level VII evidence is expert opinion. Strength-of-evidence classification not applied (NA) to pediatric recommendations.

^cThe mother has the right and responsibility to accept or reject the recommendation for zidovudine treatment for herself and her child.

^dIf acyclovir is used, register patient in the acyclovir pregnancy registry (telephone 888-825-5249, extension 39441).

^eFor prevention of cesarean section.

^fFrequent means six or more herpes episodes a year.

^gRemote means no recent recurrence or woman is HSV seropositive.

^hAcceptable strategies for preventing infection include prenatal screening and considering risk factors. Regardless of strategy, antimicrobial prophylaxis should be used in all women who are eligible as indicated in the table. In prenatal screening, culture for group B streptococci is performed at 35–37 weeks of gestation, and antimicrobial prophylaxis is offered if the culture is positive. If culture results are not known at the time of labor, intrapartum prophylaxis should be administered if one of the following conditions is present: (1) delivery after 37 weeks of gestation (for ruptured membranes without labor at <37 weeks, perform group B streptococcal culture and give antimicrobials until cultures are completed and negative, or begin antimicrobials once positive culture results are available), (2) duration of membrane rupture is ≥18 hours before delivery, or (3) intrapartum fever (≥38 °C). In the risk-factor strategy, antimicrobial prophylaxis is administered if one of the numbered conditions in the previous sentence is present.

ated with a lower frequency of fungal colonization and superficial fungal infections compared with placebo in studies involving patients undergoing BMT only,²⁵⁵ hematologic malignancies only,^{253,256} and both.^{251,252,254} However, fluconazole did not have a favorable effect on infection-related health care costs and was associated with prolonged severe neutropenia.²⁵⁴ Two of these studies also found a lower use of i.v. amphotericin B for empirical therapy.^{251,255} However, with one exception,²⁵⁵ there was no significant difference in the frequency of systemic fungal infections with fluconazole prophylaxis compared with placebo.^{252–254,256} The efficacy of reducing systemic infections could not be assessed because of the small number of patients in the study.²⁵¹ Even though fluconazole was associated with a lower frequency of systemic fungal infections due to *C. albicans*, there was no difference in the frequency of non-*C. albicans* and *Torulopsis glabrata* infections between the fluconazole group and the placebo group.²⁵⁵ Itraconazole was ineffective in preventing fungal infections for patients with hematologic malignancies who were not undergoing BMT.²⁶⁰

Fluconazole was associated with a lower frequency of systemic and superficial fungal infections in a double-blind, randomized, placebo-controlled, multicenter trial in patients undergoing BMT.²⁵⁸ However, fluconazole did not prevent *C. krusei* infections. Fluconazole was associated with a lower frequency of superficial infections compared with a nystatin–miconazole combination in patients with hematologic malignancies and patients undergoing BMT.²⁴⁵ Fluconazole was associated with a lower frequency of serious infections compared with nystatin–clotrimazole in patients with hematologic malignancies and BMT patients.²⁴⁶ Ketoconazole was no more effective than oral nystatin in preventing fungal infections in patients undergoing BMT.²⁵⁹ Compared with oral amphotericin B, systemic treatment with fluconazole has been associated with a lower frequency of superficial infections in some patients with hematologic malignancies and in patients undergoing BMT.^{247,248} Other studies that involved only patients with hematologic malignancies did not demonstrate this effect.^{261–263} There was no significant difference between these treatments in the fre-

quency of systemic fungal infections.

One study compared i.v. amphotericin B with either i.v. or oral fluconazole.²⁵⁷ Although there was no significant difference in infection rates between the treatments, fluconazole was associated with a significantly greater success rate, defined as lack of discontinuation of prophylaxis due to toxicity or the decreased occurrence of a possible fungal infection.

A disadvantage of the azole antifungals is a lack of effectiveness against *Aspergillus*. A single-center trial failed to demonstrate a difference in deep mycoses between placebo (8 infections out of 76 patients) and fluconazole 400 mg/day (8 infections out of 75 patients) because the predominant mycosis was aspergillosis.²⁵⁴ The efficacy of fluconazole in preventing *Aspergillus* infections could not be determined in a multicenter trial involving 356 patients because of the low frequency of *Aspergillus*.²⁵⁸ During selection of an agent for antifungal prophylaxis, the need for coverage of *Aspergillus* should be considered.^{254,264,265}

The optimal fluconazole prophylaxis dosage has not been established. The most commonly used dosage is 400 mg/day, based on the results of a double-blind, multicenter trial in BMT patients in which the dosage was arbitrarily chosen.²⁵⁸ However, the Working Party of the British Society for Antimicrobial Chemotherapy²⁶⁵ recommends 50 mg/day on the basis of an open, randomized, multicenter trial.²⁴⁷ Dosages lower than 400 mg/day may be effective but have not been well studied.

Resistance. Resistant non-*albicans* strains of *Candida*^{258,266-269} and breakthrough infections caused by *T. glabrata*^{258,261,270} after prophylaxis with fluconazole have also been reported.

Pediatric Efficacy. Fluconazole,^{269,271} ketoconazole,^{272,273} and itraconazole²⁷³ have been used in children, although only one study was controlled.²⁷² In that study, ketoconazole was associated with a lower rate of fungal colonization but not of documented infections or fever of unknown origin requiring systemic treatment with amphotericin B.

Viral Prophylaxis. Efficacy. There are no data supporting antiviral prophylaxis for granulocytopenic patients with hematologic malignancies. There is a lack of data supporting primary antiviral prophylaxis (CMV-negative recipients, CMV-positive donors) in granulocytopenic BMT patients. Intravenous immunoglobulin (IVIG) has been associated with a lower frequency of CMV infection in CMV-seronegative recipients of allogeneic BMT.²⁷⁴

Data support the use of antivirals for secondary prophylaxis (suppressive therapy). In patients undergoing BMT who had positive cultures for CMV, prophylaxis with ganciclovir was associated with a lower rate of CMV infection and mortality compared with placebo.^{275,276} The ganciclovir i.v. dosages were 5 mg/kg (as the sodium) twice daily for the first 7 days and then once daily for the first 100 days after transplantation²⁷⁵ and 5 mg/kg daily for 5 days per week for 120 days. Intravenous acyclovir 500 mg/m² (as the sodium) three times a day for one month followed by oral acyclovir 800 mg four times daily for six months was superior to oral acyclovir 200–400 mg four times daily alone in preventing CMV infection and in improving survival.²⁷⁷ Oral acyclovir 200 mg every six hours to 400 mg five times a day for 18 to 35 days is also effective in preventing the reactivation of HSV infections in seropositive patients undergoing BMT.²⁷⁸⁻²⁸⁰

Resistance. There are no data available on the development of resistance with primary prophylaxis against CMV in granulocytopenic patients. Only one of the several studies of secondary prophylaxis evaluated the sensitivity of the viruses. No acyclovir-resistant HSV was isolated in a study of secondary prophylaxis.²⁸⁰ However, ganciclovir-resistant CMV strains during long-term ganciclovir therapy in AIDS patients have been reported.^{281,282}

Pediatric Efficacy. No well-controlled studies have yet evaluated the effect of prophylaxis for viral infections in granulocytopenic pediatric patients.

Recommendation: Bacterial Prophylaxis. Prophylaxis is generally not recommended for patients with hematologic malignancies or BMT patients who are expected to experience prolonged (seven days or more) granulocytopenia because of the lack of demonstrated improvement in mortality and the risk of drug-resistant bacteria (Table 5). Exceptions are trimethoprim-sulfamethoxazole for patients at risk (e.g., patients with childhood leukemia, histiocytosis, or AIDS) for *P. carinii* pneumonitis. The quinolones may be considered for short periods if the potential for resistant organisms is appreciated and outweighed by the benefits. The dosage is trimethoprim 160 mg and sulfamethoxazole 800 mg orally twice daily. If quinolones are used, the dosage is ciprofloxacin 500 mg orally twice daily, ciprofloxacin 400 mg (as the lactate) i.v. twice daily, or ofloxacin 200 mg orally or i.v. twice daily. Prophylaxis should start when antineoplastic therapy begins for patients with hematologic malignancies and from the start of the conditioning regimen for BMT patients. Prophylaxis should continue until the granulocyte count exceeds 500/mm³ or until fever occurs. If fever occurs, presumptive therapy with an appropriate antimicrobial should be initiated. (Strength of evidence against prophylaxis = C)

Pediatric Dosage in Bacterial Prophylaxis. Prophylaxis is not recommended for pediatric patients with hematologic malignancies or BMT patients who are expected to experience prolonged (seven days or more) granulocytopenia because of the lack of demonstrated improvement in mortality and the risk of drug-resistant bacteria. Exceptions are trimethoprim-sulfamethoxazole for pediatric patients at risk (e.g., patients with childhood leukemia, histiocytosis, or AIDS) for *P. carinii* pneumonitis. The regimen is trimethoprim 6–10 mg/kg/day and sulfamethoxazole 30–50 mg/kg/day divided twice daily. Prophylaxis should start when antineoplastic therapy begins for patients with hematologic malignancies and from the start of the conditioning regimen for BMT patients. Prophylaxis should continue until the granulocyte count exceeds 500/mm³ or until fever occurs. Although children have been treated with ciprofloxacin without the occurrence of arthropathy, further safety data are needed before widespread use can be recommended in this patient population. Norfloxacin has also been used safely in children, but data are limited.

Recommendation: Fungal Prophylaxis. Fungal prophylaxis is generally not recommended for patients with hematologic malignancies or BMT patients who are expected to experience prolonged (seven days or more) granulocytopenia. However, if the risk of *C. albicans* infection is high and the risk of infection with other *Candida* species is low, fluconazole may be an option.²⁰³ The significant risks (in-

creasing the prevalence of non-*albicans Candida* species and other more resistant fungal infections) and the associated costs should be considered. The dosage is fluconazole 400 mg orally or i.v. once daily. An alternative is i.v. amphotericin B 0.1–0.25 mg/kg/day. Prophylaxis should start when antineoplastic therapy begins for patients with hematologic malignancies and from the start of the conditioning regimen for BMT patients. Prophylaxis should be continued until the granulocyte count exceeds 500/mm³ or until fever occurs. (Strength of evidence against prophylaxis = C)

Pediatric Dosage in Fungal Prophylaxis. Fungal prophylaxis is not recommended for pediatric patients with hematologic malignancies or BMT patients who are expected to experience prolonged (seven days or more) granulocytopenia. However, if the risk of *C. albicans* infection is high and the risk of infection with other *Candida* species is low, fluconazole may be an option.²⁰³ The significant risks (increasing the prevalence of non-*albicans Candida* species and other more resistant fungal infections) and the associated costs should be considered. The dosage is fluconazole 3–5 mg/kg/day orally or i.v. for fungal prophylaxis. An alternative is i.v. amphotericin B 0.1–0.25 mg/kg/day. Prophylaxis should start when antineoplastic therapy begins for patients with hematologic malignancies and from the start of the conditioning regimen for BMT patients. Prophylaxis should be continued until the granulocyte count exceeds 500/mm³ or until fever occurs.

Recommendation: Viral Prophylaxis. Although antiviral therapy for secondary prophylaxis (suppressive therapy) is acceptable in BMT patients, antiviral therapy for primary prophylaxis is not recommended for granulocytopenic patients, including BMT patients. (Strength of evidence against primary prophylaxis = C)

Pediatric Dosage in Viral Prophylaxis. Primary prophylaxis is not recommended for granulocytopenic pediatric patients, including BMT patients.

Opportunistic Infections in HIV-Infected Persons

The prophylaxis and treatment of opportunistic infections in HIV-infected patients is a rapidly changing area of infectious diseases. Because of the intensive research being conducted and the frequent introduction of new drugs or drug regimens, this area is continually evolving. The recommendations presented in this section are based on available clinical information and the formal recommendations that were current at the time this document was prepared.²⁸³⁻²⁸⁵ Because of the rapid progression of practice related to this area, readers should be mindful of the possibility that the CDC recommendations may have been revised since publication of these guidelines.

Recommendations concerning prophylaxis of opportunistic infections in HIV-infected patients were largely based on the official guidelines of CDC and IDSA.²⁸⁴ However, there are several situations for which new information has become available since publication of the CDC guidelines and for which there are new unofficial guidelines or clinical practice standards. Formal CDC guidelines as well as newer information were used to develop the recommendations presented in this document.

Combination antiretroviral drug regimens, particu-

larly those containing protease inhibitors, are capable of increasing CD4+ lymphocyte counts by as many as 100–250 cells/mL over baseline values at the initiation of therapy. Although studies are currently being conducted, it is not yet known whether these increases in CD4+ lymphocytes induced by antiretroviral therapy are sufficient to restore immune function to the degree that drug therapies providing prophylaxis against opportunistic infections may be discontinued. Current data are insufficient to indicate whether these patients are no longer at high risk even though their CD4+ lymphocytes were significantly depleted at an earlier time. Most experts recommend that, until such data become available, prophylactic therapies be initiated on the basis of the lowest documented CD4+ lymphocyte count and that prophylactic therapies be continued regardless of subsequent therapy-induced increases in the CD4+ lymphocyte counts.²⁸⁶

Candidiasis, histoplasmosis, and coccidioidomycosis in HIV-infected persons

Background. The frequency of mucocutaneous infections due to *C. albicans* and other *Candida* species is considerably higher in HIV-infected patients, both adults and children. These infections manifest primarily as oropharyngeal, esophageal, or vulvovaginal candidiasis. The occurrence of oropharyngeal candidiasis is related to the severity of HIV disease; this infection occurs in up to 62% of previously asymptomatic persons, 43–78% of persons with AIDS-related complex, and 54–93% of persons with AIDS.²⁸⁷ Esophageal candidiasis is the AIDS-defining illness in approximately 15% of adult cases reported to CDC and 14.3% of cases in children.^{288,289} New or increased severity of vulvovaginal candidiasis has been reported in up to 52% of HIV-infected women, and the cumulative frequency of recurrent infections is approximately 33% in women.²⁹⁰ Disseminated candidiasis or other invasive infections as a complication of HIV disease are uncommon.

Disseminated histoplasmosis is the AIDS-defining illness in approximately 1% of adult cases reported to CDC and 0.4% of cases in children.^{291,292} However, this infection occurs in approximately 5% of HIV-infected patients who live in histoplasmosis-endemic areas. Disseminated histoplasmosis in endemic areas may be due to primary infection, reactivation, or reinfection.

Coccidioidomycosis is a relatively uncommon infection among HIV-infected patients, responsible for only 0.25% of AIDS-defining illnesses overall. However, as with histoplasmosis, the frequency of infection is considerably higher among HIV-infected persons living in endemic areas. Coccidioidomycosis may occur in up to 25% of HIV-infected patients living in endemic areas.²⁹³⁻²⁹⁵

Persons at Risk. Esophageal candidiasis in adults is more common among women than men (21% versus 14%, respectively), higher among blacks than whites (17% versus 14%), and higher among intravenous drug users than homosexual males (17% versus 13%).²⁸⁸ The reported median CD4+ lymphocyte counts at the time of occurrence of esophageal candidiasis were 24 cells/mL for women and 39 cells/mL for men.²⁸⁸ Low CD4+ cell count (<50 cells/mL) is the only risk factor for *Candida* colonization of various mucocutaneous sites and esophageal disease yet identified.²⁸⁸ It would appear, therefore, that the only potential indication for primary prophylaxis of mucocutaneous candidiasis is a documented CD4+ cell count of <50 cells/mL.

The risk of developing disseminated histoplasmosis also appears to be highest in AIDS patients with advanced immunosuppression (CD4+ lymphocyte count of <75 cells/mL).²⁹¹ In addition, residence in a histoplasmosis-endemic area is required in order to place patients at high risk of infection.^{292,296} Risk factors for coccidioidomycosis are similar to those for histoplasmosis, with residence in an endemic area and CD4+ lymphocyte counts of <250 cells/mL being the most significant risk factors for development of active infection.^{295,297}

Efficacy. Antifungal agents have not been shown to have clear benefit in the prophylaxis of systemic infections. One prospective, randomized trial compared oral fluconazole with clotrimazole troches for the primary prophylaxis of localized infections due to *Candida* species.²⁹⁸ After a median follow-up period of 35 months, the frequency of both oropharyngeal and esophageal candidiasis was approximately six times lower among patients receiving fluconazole. These benefits of therapy were most pronounced in patients with CD4+ lymphocyte counts of <50 cells/mL, consistent with previous observations regarding high-risk groups. However, the frequency of oropharyngeal candidiasis in fluconazole-treated patients was still 10.6%, and prophylactic therapy was not associated with a lower overall mortality among study patients.

Limited data suggest that fluconazole prophylaxis has little benefit in the prevention of disseminated histoplasmosis in HIV-infected patients; infection rates among patients receiving fluconazole did not differ significantly from rates among untreated patients.²⁹⁸⁻³⁰⁰ The role of ketoconazole and itraconazole in the prevention of histoplasmosis is currently unclear. It is also unclear whether chemoprophylaxis is of benefit in preventing coccidioidomycosis. Although active coccidioidomycosis has developed in HIV-infected persons during treatment with oral antifungal therapy for other indications, no formal prophylaxis studies have been conducted.^{295,301}

Resistance. In addition to the questionable overall benefits of prophylaxis, there are also concerns about the emergence of *Candida* resistance to azole antifungal agents among patients receiving chronic suppressive therapy. Reports have documented the development of fluconazole-resistant *Candida* species among oncology, BMT, and HIV-infected patients receiving fluconazole prophylaxis.³⁰²⁻³⁰⁴ The occurrence of infection due to non-*Candida* species that are resistant to fluconazole and amphotericin B has also been documented during long-term fluconazole prophylaxis.^{305,306}

Pediatric Efficacy. No well-controlled studies have evaluated the effect of prophylaxis of *Candida* infection, histoplasmosis, or coccidioidomycosis in children. Recommendations are provided by CDC, USPHS, and IDSA.²⁸³⁻²⁸⁵

Recommendation. *Candida.* Routine primary prophylaxis of mucocutaneous *Candida* infections is not recommended for HIV-infected adults because of the effectiveness of therapy for acute disease, infrequent occurrence of serious invasive disease, questionable mortality benefits of prophylaxis, concerns about the development of azole-resistant *Candida* species, potential for multiple drug interactions involving the azole antifungals, and costs of routine prophylaxis.^{288,307} Azole antifungal agents may be used in patients at high risk of infection (i.e., CD4+ lymphocyte count of <50

cells/mL), but these patients should be very carefully selected and therapy instituted on an individual basis and only in unusual circumstances.²⁸⁴ If primary antifungal prophylaxis is to be initiated, oral fluconazole 100–200 mg every day is preferred (Table 6). Although itraconazole has been shown to be effective in the treatment of acute candidiasis, this drug has not yet been clearly demonstrated to be effective as a prophylactic agent, and use of itraconazole is not recommended for this purpose.²⁸⁴

Disseminated histoplasmosis or coccidioidomycosis. Routine prophylaxis in HIV-infected adults is not recommended for disseminated histoplasmosis or coccidioidomycosis. In addition to the lack of substantive data on prophylaxis, the potential development of azole-resistant fungal strains and cost-effectiveness of prophylaxis are concerns that should discourage routine practice.^{283,284,286,293} Prophylactic use of azole antifungal agents, specifically itraconazole 200 mg orally every day, may be considered for patients with advanced HIV infection (CD4+ lymphocyte count of <100 cells/mL) who live in endemic areas. Patients should be carefully selected on a case-by-case basis; prophylaxis should not be routinely instituted. The oral bioavailability of itraconazole capsules has been shown to be approximately 50% lower in persons with AIDS than in healthy volunteers. In contrast, the administration of itraconazole oral solution to persons with AIDS has been shown to achieve plasma levels approximately 50–70% higher than those achieved after administration of the oral capsule. Therefore, the oral solution may be the preferred dosage form if itraconazole is to be administered in this population.^{308,309} (Strength of evidence against prophylaxis = B)

Pediatric Dosage. *Candida.* Routine primary prophylaxis of mucocutaneous *Candida* infections is not currently recommended for children. Antifungal agents may be used in patients at high risk of infection (i.e., CD4+ lymphocyte count of <750 cells/mL for children less than one year of age, <500 cells/mL for children one to five years of age, and <200 cells/mL for children six years of age or older), but these patients should be carefully selected and therapy instituted on an individual basis. Antifungal agents include nystatin (100,000 units/mL) 4–6 mL orally every six hours and topical clotrimazole 10 mg orally five times a day. The use of azole antifungal agents is not recommended in the pediatric population.

Disseminated histoplasmosis or coccidioidomycosis. Routine prophylaxis of disseminated histoplasmosis or coccidioidomycosis in HIV-infected children is not recommended. Prophylactic use of azole antifungal agents (fluconazole 3–6 mg/kg orally every day or itraconazole 2–5 mg/kg orally every 12–24 hours) may be considered for patients with advanced HIV infection (i.e., CD4+ lymphocyte count of <750 cells/mL for children less than one year of age, <500 cells/mL for children one to five years of age, and <200 cells/mL for children six years of age or older) who live in endemic areas (Table 6). Patients should be carefully selected on a case-by-case basis; prophylaxis should not be routinely instituted.

***Cryptococcus Neoformans* Infections in HIV-Infected Persons**

Background. Infection with *Cryptococcus neoformans* is a

major cause of morbidity and mortality among patients infected with HIV. The most frequent manifestation in HIV-infected patients is cryptococcal meningitis; this infection occurs as the AIDS-defining illness in approximately 6% of all patients with advanced HIV disease and is associated with mortality rates of 25–40%.^{298,310,311} Children are less prone to development of cryptococcal meningitis, with infection reported in approximately 1% of pediatric AIDS cases.³¹⁰

Persons at Risk. Cryptococcal disease is assumed to represent primary infection as a result of environmental exposure. Although the primary environmental source of cryptococcal exposure is unknown, exposure to areas heavily contaminated with pigeon droppings has been associated with high rates of infection (although not necessarily clinical disease).³¹⁰ Persons with HIV infection working or living in contaminated areas may be at increased risk of cryptococcal meningitis. African-American race appears to be an independent risk factor for cryptococcal disease.³¹⁰ The most consistently identified risk factor for cryptococcal disease in HIV-infected persons is the CD4+ lymphocyte count. The highest risk of cryptococcal meningitis is associated with CD4+ lymphocyte counts of <100 cells/mL.^{300,312} In a study of fluconazole prophylaxis, 78% of AIDS patients who developed cryptococcal disease had CD4+ lymphocyte counts of <50 cells/mL.²⁹⁸ Thus, the patients at highest risk of cryptococcal infections are those with HIV infection and a CD4+ lymphocyte count of <50 cells/mL.^{284,285} Such patients may be considered for prophylaxis, although these risk factors do not constitute a true indication for therapy.

Efficacy. A retrospective study of patients receiving fluconazole for other indications found the rate of cryptococcal infections to be only 0.3%, compared with 4.8% in untreated control patients.³⁰⁰ Two additional case-control studies also demonstrated a significantly lower rate of cryptococcal disease in patients receiving fluconazole for other reasons.^{313,314} Only one prospective, randomized trial has specifically evaluated primary prophylaxis.²⁹⁸ The frequency of cryptococcal infections was approximately 1% in patients receiving oral fluconazole, compared with 7% among patients receiving clotrimazole troches. This overall difference in infection rates was significant and was most pronounced for patients with CD4+ lymphocyte counts of <50 cells/mL. However, no difference in mortality was demonstrated between groups. It must again be emphasized that this finding is applicable only to primary prophylactic therapies and not to regimens for secondary prophylaxis.

Resistance. There are concerns about the emergence of azole-resistant *C. neoformans* strains during prolonged fluconazole prophylaxis. In addition, the cost-effectiveness of prophylaxis for this indication remains to be established.

Pediatric Efficacy. No well-controlled studies have evaluated the effect of prophylaxis of cryptococcal disease in pediatric patients. Recommendations are provided by CDC, USPHS, and IDSA.^{283,284}

Recommendation. In the absence of demonstrated survival benefits for prophylaxis and given the concerns about development of azole-resistant strains and cost-effectiveness, prophylaxis of cryptococcal disease should not be routinely recommended for HIV-infected adults.²⁸⁴ If prophylaxis is to

be used, the recommended regimen is fluconazole 200 mg orally every day (Table 6). Although itraconazole 200 mg orally every day is recommended by CDC as an alternative to fluconazole, at least one clinical study has shown fluconazole to be superior to itraconazole in this setting.³¹⁵ Patients should be carefully selected on an individual basis and should be evaluated for factors that may place them at high risk of infection (CD4+ lymphocyte count of <50 cells/mL and residence in an endemic geographic area). (Strength of evidence against prophylaxis = A)

Pediatric Dosage. Primary prophylaxis for cryptococcal disease in pediatric patients is not recommended. As is the case for adults, there are no data on the value of routine prophylaxis of HIV-infected children. Prophylactic use of azole antifungal agents (fluconazole 3–6 mg/kg orally every day or itraconazole 2–5 mg/kg orally every 12–24 hours) may be considered for patients with advanced HIV infection (i.e., CD4+ lymphocyte count of <750 cells/mL for children less than one year of age, <500 cells/mL for children one to five years of age, and <200 cells/mL for children six years of age or older) who live in endemic areas. However, patients should be carefully selected on a case-by-case basis; prophylaxis should not be routinely instituted.

Disseminated *Mycobacterium Avium* Complex Infection in HIV-Infected Persons

Background. Infection with *Mycobacterium avium* complex (MAC) occurs as a late-stage complication of HIV infection. Disseminated, nonpulmonary MAC infection is an AIDS-defining illness and may involve infection of the blood, bone marrow, liver, spleen, GI tract, and other body sites.³¹⁶ Disseminated MAC develops in 12–25% of adults with AIDS and is associated with a higher risk of death.³¹⁷ Disseminated MAC is also an important opportunistic infection in children and occurs in approximately 6% of children with AIDS; the frequency is somewhat higher (approximately 13%) in children with hemophilia- or transfusion-related HIV infection.³¹⁸ Because disseminated MAC commonly occurs in both adults and children with AIDS and is associated with a significant mortality risk, CDC issued formal recommendations for prophylaxis of MAC in 1993; these were updated in 1995 and again in 1997.^{284,307,319}

Persons at Risk. Disseminated MAC infection is most common in HIV-infected persons with CD4+ lymphocyte counts of <100 cells/mL; more than 93% of all MAC infections occur in patients with very low CD4+ lymphocyte counts.^{316,320} In one study, the median CD4+ lymphocyte count at time of MAC diagnosis was only 13 cells/mL.³²⁰ Two randomized, controlled trials of rifabutin prophylaxis against disseminated MAC disease demonstrated a significantly lower frequency of infection in adult patients with CD4+ lymphocyte counts of <100 cells/mL.³²¹ The original recommendations, therefore, specified that prophylaxis against MAC infection should be instituted in all HIV-positive adults with CD4+ lymphocyte counts of <100 cells/mL.³¹⁹ However, subsequent analysis of the prophylaxis trials revealed that rifabutin prophylaxis was associated with a lower frequency of MAC bacteremia only in patients with CD4+ lymphocyte counts of <50–75 cells/mL; beneficial effects were not significant with CD4+ lymphocyte counts of 75–99 cells/mL.³¹⁶

In children, as in adults, the risk of development of disseminated MAC infection is directly related to decreasing CD4+ lymphocyte counts.³¹⁸ However, the median CD4+ lymphocyte count is usually higher than in adults when disseminated MAC disease occurs.³¹⁸

Efficacy. Two randomized, double-blind, placebo-controlled trials established the efficacy of rifabutin for the prophylaxis of disseminated MAC disease in patients with advanced HIV infection.³²¹ In the first trial, MAC bacteremia developed in 8% of patients receiving rifabutin prophylaxis, compared with 17% of patients receiving placebo. This twofold significant difference in the rate of disseminated MAC disease was also demonstrated in the second study; bacteremia developed in 9% and 18% of patients treated with rifabutin and placebo, respectively. Beneficial effects of rifabutin prophylaxis on symptoms, signs, and laboratory markers of advanced HIV disease were also observed in the treatment groups. However, the difference in survival rates between the rifabutin and placebo groups is unclear; this difference was not significant in the original analysis but was subsequently found to be significant (26% difference in mortality) when complete follow-up data were analyzed at a later date.³²² The overall observed failure rate of rifabutin prophylaxis (8%) and the frequent adverse effects necessitating rifabutin discontinuation (16%) in these studies have tempered enthusiasm for prophylaxis with this agent. In addition, rifabutin has clinically significant drug–drug interactions with the protease inhibitors, making it less than ideal for many persons with advanced HIV infection. Finally, there are concerns about the development of rifamycin resistance among other mycobacterial strains (e.g., *M. tuberculosis*) as a consequence of widespread rifabutin use.

In a randomized, double-blind, placebo-controlled trial of clarithromycin as prophylaxis against disseminated MAC disease in patients with AIDS and CD4+ lymphocyte counts of <100 cells/mL, the rate of MAC infection was 16% in the placebo group but only 6% among patients receiving clarithromycin.³²³ Clarithromycin treatment was associated with significantly lower mortality than placebo (32% versus 41%, respectively). The observation that 58% of MAC organisms isolated from patients receiving clarithromycin were subsequently clarithromycin resistant has raised concerns about the long-term suitability of this agent.³¹⁶ Clarithromycin has also been shown to be more effective than rifabutin in the prevention of disseminated MAC disease, although a clear survival benefit was not shown.³²⁴ Although associated with fewer drug interactions, clarithromycin is an inhibitor of the cytochrome P-450 system, particularly the 3A isoenzyme, and thus has the potential for causing drug interactions with the protease inhibitors and other agents metabolized by this pathway.³²⁵ Patients should therefore be closely monitored during therapy that includes both clarithromycin and protease inhibitors.

Azithromycin has also been evaluated for the prophylaxis of disseminated MAC disease. A prospective, randomized, double-blind trial compared once-weekly azithromycin, rifabutin, or both agents in combination in high-risk AIDS patients with CD4+ lymphocyte counts of <100 cells/mL.³²⁶ The risk of infection in the azithromycin group was significantly lower than in the rifabutin group (7.6% versus 15.3%, respectively). The risk of infection was even lower with combination therapy (2.8% infection rate); however, dose-limiting adverse effects were significantly more frequent in this group. No survival benefits were demonstrated in any

treatment group. The results of this study indicate that azithromycin may also be considered an appropriate agent for the prevention of disseminated MAC disease in high-risk patients.

Resistance. Drug-resistant MAC disease occurred in 58% of persons taking clarithromycin,³²³ 11% of persons taking azithromycin,³²⁶ and no persons taking rifabutin.^{321,326} As stated previously, there are concerns about the development of rifamycin resistance among other mycobacterial strains, such as *M. tuberculosis*, because of widespread rifabutin use; as yet there are few data on the relevance of these concerns.

CDC originally recommended rifabutin as the preferred agent for routine MAC prophylaxis.³⁰⁷ However, rifabutin has several disadvantages, including lack of demonstrated survival benefits in randomized, controlled studies; treatment failures; adverse effect rates; and potentially significant drug interactions. More recent data indicate that clarithromycin and azithromycin are the agents of choice for this indication. Clarithromycin has demonstrated survival benefits, is well tolerated, and is associated with fewer clinically significant drug interactions than rifabutin. Azithromycin also has demonstrated efficacy in reducing the frequency of disseminated MAC disease, has demonstrated efficacy in reducing other bacterial infections, has the potential advantage of once-weekly dosing, is well tolerated, and is not a significant inhibitor of cytochrome P-450. Because of proven and potential benefits of the macrolide antimicrobials, relative to rifabutin, clarithromycin and azithromycin are the preferred agents for primary prophylaxis of disseminated MAC disease. The combination of clarithromycin and rifabutin is no more effective than clarithromycin alone and should not be used. Although possibly more effective than azithromycin monotherapy, the combination of azithromycin and rifabutin is also associated with more adverse effects, higher cost, potential for drug interactions, and disadvantages that affect patient adherence; this combination is therefore not recommended.^{284,285}

Pediatric Efficacy. No well-controlled studies have evaluated the effect of prophylaxis in the pediatric population. Recommendations are provided by CDC, USPHS, and IDSA.²⁸³⁻²⁸⁵

Recommendation. Prophylaxis against MAC in HIV-infected adults is recommended when the CD4+ lymphocyte count is <50–75 cells/mL (Table 7). The recommended regimen is oral azithromycin 1200 mg weekly or oral clarithromycin 500 mg twice daily. Rifabutin 300 mg every day orally, either alone or in combination with azithromycin, is recommended as an alternative agent. Selection of a specific agent should be based on individual patient characteristics and concurrent medications. (Strength of evidence for prophylaxis = A)

Pediatric Dosage. Although prophylaxis of MAC infection in children has not been rigorously evaluated, primary prophylaxis is presumed to be effective and is recommended in the following groups of children: six years of age or older with a CD4+ lymphocyte count of <50 cells/mL, two to six years of age with a CD4+ lymphocyte count of <75 cells/mL, one to two years of age with a CD4+ lymphocyte count of <500 cells/mL, and less than one year of age with a CD4+ lymphocyte count of <750 cells/mL. Oral azithromycin 20

mg/kg (up to a maximum of 1200 mg) once each week or clarithromycin 7.5 mg/kg (up to a maximum of 500 mg) every 12 hours is the preferred regimen for prophylaxis in these groups. Azithromycin 5 mg/kg (up to a maximum of 250 mg) every day may be used as an alternative. Rifabutin 300 mg every day orally for children 6–12 years old and 5 mg/kg every day orally for children less than 6 years old is recommended as an alternative agent when clarithromycin and azithromycin are poorly tolerated.

P. carinii Pneumonia in HIV-Infected Persons

Background. *P. carinii* pneumonia (PCP) is the most common serious opportunistic infection among HIV-infected persons in the United States. Approximately 51% of all adults and adolescents diagnosed with AIDS between 1982 and 1992 had one or more episodes of PCP. The total number of cases of PCP in the United States is estimated at approximately 60,000 per year.³²⁷ Although the overall percentage of PCP infection among persons with AIDS decreased from 61% to 43% during that time, PCP remained the most common AIDS-defining condition. The annual incidence of PCP was 4.2% in 1985 and decreased to 2.5% in 1991, presumably as a result of widespread, effective efforts at prophylaxis.³²⁸ The most recent CDC recommendations for primary prophylaxis of PCP in both adults and children were issued in 1995.^{307,329}

PCP is also the most common AIDS-defining condition among children, being reported in 37% of pediatric AIDS cases reported to CDC through 1992.³¹⁸ The incidence of PCP during the first year of life is approximately 12–13%. This incidence has not decreased substantially in spite of the availability of effective prophylaxis, largely because of the failure to identify children born to HIV-infected mothers in time to promptly begin prophylaxis.³³⁰

PCP is an important cause of mortality among adults with AIDS; the mortality rate for first episodes is approximately 15–18%.³³¹ Each episode of PCP among adults is associated with a mean hospital stay of 14.4 days at a cost of \$13,485.³³¹ Prophylaxis of PCP has important implications for medical resource use and prevention of morbidity and mortality for HIV-infected persons.

Persons at Risk. Among HIV-infected adults, the risk for developing PCP increases dramatically when the CD4+ lymphocyte count falls below 200 cells/mL. The yearly incidence of PCP is approximately 18% in patients with ≤ 200 cells/mL, compared with 7% in all HIV-infected persons with a CD4+ lymphocyte count of >200 cells/mL.^{332,333} Most cases of PCP occur in persons with CD4+ lymphocyte counts of <50 cells/mL. Although CD4+ lymphocyte counts are the most important marker for risk of development of PCP, unexplained fever (>100 °F for two weeks or more) and oropharyngeal candidiasis have also been identified as independent risk factors for PCP.^{332,334}

Among HIV-infected children, the risk of PCP is

Table 5.
Prevention of Opportunistic Infection in Nonpediatric and Pediatric Patients with Granulocytopenia or Receiving Bone Marrow Transplant

Infection	Eligible Patients	Recommended Regimen	Alternative Regimens	Strength of Evidence ^a
Bacterial	Patients expected to have granulocyte count of $<500/\text{mm}^3$ for ≥ 7 days	Not recommended ^b	For adult patients, trimethoprim 160 mg with sulfamethoxazole 800 mg p.o. b.i.d., ciprofloxacin 500 mg p.o. b.i.d. or 400 mg i.v. b.i.d., or ofloxacin 200 mg i.v. or p.o. b.i.d. ^c	C
			For pediatric patients, trimethoprim 6–10 mg/kg/day with sulfamethoxazole 30–50 mg/kg/day p.o. (divided into two daily doses) ^c	NA
Fungal	Patients expected to have granulocyte count of $<500/\text{mm}^3$ for ≥ 7 days	Not recommended ^d	For adult patients, fluconazole 400 mg i.v. or p.o. daily or amphotericin B 0.1–0.25 mg/kg/day i.v. ^c	C
			For pediatric patients, fluconazole 3–5 mg/kg/day i.v. or p.o. daily or amphotericin B 0.1–0.25 mg/kg/day i.v. ^c	NA
Viral	Patients with positive cytomegalovirus culture after transplantation	Primary prophylaxis is not recommended	For adult and pediatric patients with bone marrow transplant, secondary prophylaxis (suppressive therapy) includes ganciclovir i.v. for at least 3 mo or acyclovir i.v. for 1 mo followed by oral acyclovir	C ^e

^aStrength of evidence that supports the use or nonuse of prophylaxis is classified as A (levels I–III), B (levels IV–VI), or C (level VII). Level I evidence is from large, well-conducted randomized, controlled clinical trials. Level II evidence is from small, well-conducted randomized, controlled clinical trials. Level III evidence is from well-conducted cohort studies. Level IV evidence is from well-conducted case-control studies. Level V evidence is from uncontrolled studies that were not well conducted. Level VI evidence is conflicting evidence that tends to favor the recommendation. Level VII evidence is expert opinion. Strength-of-evidence classification not applied (NA) to pediatric recommendations.

^bExceptions are (1) trimethoprim–sulfamethoxazole for patients at risk (e.g., those with childhood leukemias, histiocytosis, or AIDS) for *Pneumocystis carinii* pneumonia and (2) quinolones for short periods if the potential for resistant organisms is appreciated and outweighed.

^cProphylaxis should start when antineoplastic therapy begins (for patients with hematologic malignancies) or when the conditioning regimen begins (for patients receiving bone marrow transplants) and continue until the granulocyte count exceeds 500 cells/mm³ or until fever occurs. If fever occurs, presumptive therapy with appropriate antimicrobials should be initiated.

^dIf the risk of infection with *Candida albicans* is high but the risk of infection with other *Candida* species is low, then fluconazole may be an option. The significant risks (e.g., increasing the prevalence of non-*albicans* *Candida* species and other more resistant fungal infections) and the costs associated with those risks should be considered before prophylaxis is started.

^eApplies to the recommendation against primary prophylaxis for nonpediatric patients.

highest among infants less than one year of age. More than 50% of cases of PCP occur in children of three to six months of age in whom HIV infection was perinatally acquired.^{335,336} The need for prophylaxis is difficult to correlate with CD4+ lymphocyte counts in children less than one year of age, and cell counts may fall very rapidly between measurements; children under one year of age are thus considered at high risk for PCP, regardless of CD4+ lymphocyte counts.^{330,336} Correlation of PCP infection with CD4+ lymphocyte counts is more reliable in older children; 84% of children one to five years of age had CD4+ lymphocyte counts of ≤ 500 cells/mL at the time of PCP diagnosis, and 100% of children six years of age or older had CD4+ lymphocyte counts of ≤ 200 cells/mL. The risk of PCP and the need for primary prophylaxis are thus based on CD4+ lymphocyte counts in children one year of age or older.

Efficacy. Randomized, placebo-controlled studies have demonstrated that prophylaxis very effectively reduces the frequency of PCP among HIV-infected adults. Compared with patients receiving no prophylactic therapy in whom PCP infection rates were 29–53% per year, patients receiving PCP prophylaxis had infection rates of 0–5% per year.^{337–342} Prophylactic efficacy has been demonstrated for a number of agents and regimens, and current recommendations include several regimens. Although adverse effects have been associated with PCP prophylaxis in 2–40% of patients, the risk of such adverse effects is acceptable compared with the potential benefits. Routine PCP prophylaxis is therefore justified for all patients who meet the indications for prophylaxis.

Recent CDC recommendations list several regimens for prophylaxis of PCP in adults.²⁸⁴ Trimethoprim–sulfamethoxazole has repeatedly been shown to be extremely effective in patients who can tolerate potential adverse effects of therapy.^{337,340,341,343,344} Trimethoprim–sulfamethoxazole is therefore the preferred therapy for PCP prophylaxis because of excellent efficacy, ability to prevent extrapulmonary *Pneumocystis* infection, prophylactic efficacy against both *Toxoplasma gondii* and systemic bacterial infections as well as PCP, and low cost. Other recommended regimens that have shown efficacy comparable to that of trimethoprim–sulfamethoxazole include dapsone, dapsone plus pyrimethamine, and aerosolized pentamidine.^{327,338,340}

For persons unable to tolerate trimethoprim–sulfamethoxazole, dapsone is usually preferred over aerosolized pentamidine because of increased efficacy in persons with very low CD4+ lymphocyte counts (< 100 cells/mL), ease of administration, lower expense, and efficacy in the prophylaxis of toxoplasmosis. It is worth noting that dapsone prophylaxis is considerably less effective at total daily doses of < 100 mg³⁴⁰; therefore, persons who do not tolerate dapsone at this dosage should receive either dapsone in combination with pyrimethamine or aerosolized pentamidine. Although previously the preferred agent for PCP prophylaxis, aerosolized pentamidine is now considered an alternative to trimethoprim–sulfamethoxazole because of lesser efficacy in persons with a CD4+ lymphocyte count of < 100 cells/mL, higher costs, failure to protect against extrapulmonary *Pneumocystis* infection, and lack of prophylactic efficacy against toxoplasmosis.²⁸⁴

Resistance. The inability to culture *P. carinii* has impeded identification of resistance. Although antimicrobial resistance is a potential mechanism for failure of PCP prophylaxis, clinical treatment failures related to the occurrence of drug

resistance have not been demonstrated with trimethoprim–sulfamethoxazole^{338,340} or aerosolized pentamidine.^{338,339}

Pediatric Efficacy. Although no randomized, placebo-controlled trials of PCP prophylaxis have been conducted in children, a recent retrospective study showed that the risk for PCP among children receiving prophylaxis was more than four times lower than in those who were not (yearly infection rate of 4% versus 25%, respectively).³⁴⁵ Observational studies have also demonstrated a lower frequency of PCP among children who received prophylaxis compared with those who did not.³³⁰ Pediatric recommendations are provided by CDC, USPHS, and IDSA.^{284,285}

Recommendation. Primary prophylaxis against PCP in adults is indicated for patients at high risk (HIV-infected adults with CD4+ lymphocyte counts of ≤ 200 cells/mL, unexplained fever of > 100 °F for two or more weeks, or a history of oropharyngeal candidiasis) (Table 7). Trimethoprim 160 mg and sulfamethoxazole 800 mg orally every day is the recommended regimen. Alternatives are trimethoprim 80 mg and sulfamethoxazole 400 mg orally every day, trimethoprim 160 mg and sulfamethoxazole 800 mg orally three times a week, dapsone 50 mg orally twice daily or 100 mg orally every day, dapsone 50 mg orally every day plus pyrimethamine 50 mg orally every week plus leucovorin 25 mg (as the calcium) orally every week, dapsone 200 mg orally every week plus pyrimethamine 75 mg orally every week plus leucovorin 25 mg orally every week, and aerosolized pentamidine isethionate 300 mg/month by Respigard II nebulizer (Marquest Medical Products). (Strength of evidence for prophylaxis = A)

Pediatric Dosage. Children born to HIV-infected mothers should be administered prophylaxis beginning at four to six weeks of age; prophylaxis should be discontinued if the child is subsequently determined to be HIV-negative. The need for prophylaxis after the age of 12 months is determined on the basis of age-specific CD4+ lymphocyte counts. PCP prophylaxis is indicated for children one to five years of age in whom the CD4+ lymphocyte count falls to ≤ 500 cells/mL or a CD4+ lymphocyte percentage of $< 15\%$. In children 6–12 years of age, PCP prophylaxis is indicated for CD4+ lymphocyte counts of ≤ 200 cells/mL or a CD4+ lymphocyte percentage of $< 15\%$.

Trimethoprim 150 mg/m²/day and sulfamethoxazole 750 mg/m²/day in two divided doses orally three times a week on consecutive days is the preferred regimen in all children between the ages of one month and five years. Alternative dosages are not proven to be effective in this age group and are not recommended. Children 6–12 years of age may receive the preferred regimen administered in a single daily dose; an alternative schedule in this age group is the same dose given daily in two divided doses, or two divided doses three times a week on alternate days. Children unable to tolerate trimethoprim–sulfamethoxazole should receive dapsone 2 mg/kg (not to exceed 100 mg) every day orally, aerosolized pentamidine isethionate 300 mg every month for children five years old or older, or pentamidine isethionate i.v. 4 mg/kg every two to four weeks.

Toxoplasmic Encephalitis in HIV-Infected Persons

Background. Toxoplasmic encephalitis (TE) is one of the

most important neurologic complications of HIV infection in adults. Infections due to *T. gondii* are second only to cryptococcal meningitis as common AIDS-related infections of the CNS. Studies from the United States and Europe have shown TE to be the AIDS-defining illness in 5% to 23% of cases.^{346,347} TE is associated with early mortality in approximately 16% of patients, and 40–50% of surviving patients will have residual neurologic deficits.³⁴⁸ Although primary prophylaxis against PCP has been widely adopted for many years, prophylaxis for *T. gondii* infections has not previously been widespread. Improved understanding of the epidemiology of and risk factors for toxoplasmosis, as well as recent studies demonstrating that *Pneumocystis* prophylaxis regimens are also effective against toxoplasmosis, have led to official recommendations for the primary prophylaxis of TE in HIV-infected adults.²⁸⁴

Unlike with adults, TE as a complication of AIDS is relatively rare in children. The infection accounted for <1% of AIDS-defining illnesses in pediatric cases reported to CDC through 1992.³⁴⁶ TE in children is more likely to be the result of maternal–fetal transmission of toxoplasmosis by HIV-infected mothers.³⁴⁶ Because of the very low frequency, there are currently no formal recommendations for prophylaxis of toxoplasma infections in children.

Persons at Risk. It is believed that *T. gondii* infections in HIV-infected persons are due to reactivation of latent infection originally acquired much earlier in life. The risk of TE is therefore associated with the presence of immunoglobulin G antibodies to *Toxoplasma* that indicate previous infection. Approximately 5–40% of HIV-infected adults are seropositive for *Toxoplasma*^{349,350}; the risk of developing TE in this population is approximately 27-fold higher than among HIV-infected persons who are seronegative.³⁴⁷ HIV-infected persons who are both seropositive for immunoglobulin G to *Toxoplasma* and have CD4+ lymphocyte counts of <100 cells/mL have a 10–50% risk of developing TE.^{347,349,351}

Efficacy. Both retrospective and prospective, comparative studies have demonstrated that trimethoprim–sulfamethoxazole effectively prevents the occurrence of TE in high-risk patients. Prophylaxis with trimethoprim 160 mg and sulfamethoxazole 800 mg daily is associated with the development of TE in 0–3% of patients, compared with 33–48% of persons receiving no prophylaxis.^{340,348,352–354} Trimethoprim–sulfamethoxazole is preferred for prophylaxis of toxoplasmosis because of its demonstrated efficacy against PCP as well as TE, conferring the ability of a single prophylactic regimen to be effective against two important opportunistic infections.

Dapsone alone appears to be less effective. Although one comparative study showed dapsone to be as effective as trimethoprim–sulfamethoxazole or aerosolized pentamidine,³⁴⁰ other animal and human studies have had conflicting results regarding dapsone's efficacy for this indication. The combination of dapsone and pyrimethamine appears to be more effective than dapsone alone. Three open, prospective trials demonstrated that dapsone plus pyrimethamine and leucovorin effectively prevents the occurrence of toxoplasmosis, has comparable efficacy to that of trimethoprim–sulfamethoxazole, and is superior to aerosolized pentamidine.^{352,353,355,356} In these studies, the frequency of TE in the dapsone–pyrimethamine groups ranged from 0% to 14%, compared with infection rates of 2% in patients receiving trimethoprim–sulfamethoxazole and 25% in patients receiving

aerosolized pentamidine. Combination therapy with dapsone plus pyrimethamine is thus appropriate alternative therapy for prophylaxis of TE and PCP in patients unable to tolerate recommended regimens of trimethoprim–sulfamethoxazole.²⁸⁴

Pyrimethamine alone is also unacceptable as prophylaxis against TE. Although two studies have shown pyrimethamine to be effective,^{357,358} an additional study showed no difference in the frequency of TE between the pyrimethamine-treated group and the placebo group.³⁵⁹ Additional studies are needed to determine the role of pyrimethamine monotherapy in patients unable to tolerate either trimethoprim–sulfamethoxazole or dapsone-containing regimens for prophylaxis of TE.

Pediatric Efficacy. No well-controlled studies have yet evaluated the efficacy of TE prophylaxis in the pediatric population. Pediatric recommendations are provided by USPHS and IDSA.²⁸⁴

Recommendation. Primary prophylaxis against TE in all HIV-infected adults is not routinely recommended. Rather, prophylaxis should be reserved for carefully selected high-risk patients with advanced disease. Avoiding exposure to *T. gondii* is an important aspect of disease prevention. Because the risk of acquiring new strains of *Toxoplasma* is unknown, seropositive and seronegative persons who are infected with HIV should be advised about preventive practices. These include eating red meats only if they have been well cooked; practicing hand washing after gardening, yard work, or other outdoor activities; and, if there is a cat in the household, changing the litter box daily to prevent maturation of infectious oocysts.³⁴⁶

Primary prophylaxis against TE is indicated only for HIV-infected patients with advanced disease (CD4+ lymphocyte counts of <100 cells/mL) who are also immunoglobulin G seropositive for *T. gondii* (Table 7). Trimethoprim 160 mg and sulfamethoxazole 800 mg orally every day is the preferred regimen for all patients who are able to tolerate the drug. Alternative dosages are trimethoprim 80 mg and sulfamethoxazole 400 mg orally every day and trimethoprim 160 mg and sulfamethoxazole 800 mg orally three times a week. Dapsone 50 mg orally every day plus pyrimethamine 50 mg every week is an acceptable alternative regimen in patients unable to tolerate trimethoprim–sulfamethoxazole. Leucovorin 25 mg (as the calcium) orally every week may also be administered with this regimen to prevent hematologic toxicity. Dapsone alone, pyrimethamine alone, and aerosolized pentamidine are not recommended as alternative regimens because of insufficient efficacy data or demonstrated inferior efficacy. (Strength of evidence against primary prophylaxis = A)

Pediatric Dosage. Primary prophylaxis against TE in HIV-infected pediatric patients is not recommended. In children with immunoglobulin G antibody seropositive to *T. gondii* and a CD4+ lymphocyte count indicating severe immunosuppression (<12 months of age with CD4+ lymphocyte counts of <750 cells/mL or a CD4+ lymphocyte percentage of <15%, 1–5 years of age with a CD4+ lymphocyte count of <500 cells/mL or a CD4+ lymphocyte percentage of <15%, or 6–12 years of age with a CD4+ lymphocyte count of <200 cells/mL or a CD4+ lymphocyte percentage of <15%), secondary prophylaxis may be an option and should be administered with trimethoprim 150 mg/m²/day and

Table 6.
Prevention of Fungal Infections in Patients Infected with Human Immunodeficiency Virus

Infection	Eligible Patients ^a	Recommended Regimen ^b	Alternative Regimens	Strength of Evidence ^c
Mucocutaneous candidiasis	Adults with CD4+ < 50 ^d	Not recommended	Fluconazole 100–200 mg p.o. daily	B
	Children 1–5 yr old with CD4+ < 500 or ≥6 yr old with CD4+ < 200 ^d	Not recommended	Nystatin suspension (100,000 units/mL) 4–6 mL p.o. q 6 hr or clotrimazole troches 10 mg p.o. 5 times daily	NA
Disseminated histoplasmosis	Adult residents of endemic area with CD4+ < 100 ^d	Not recommended	Itraconazole ^e 200 mg p.o. daily	B
	Pediatric residents of endemic area 1–5 yr old with CD4+ < 500 or ≥6 yr old with CD4+ < 200 ^d	Not recommended	Itraconazole ^e 2–5 mg/kg p.o. q 12–24 hr, fluconazole 3–6 mg/kg p.o. q 24 hr	NA
Coccidioidomycosis	Adult residents of endemic area with CD4+ < 100 ^d	Not recommended	Itraconazole ^e 200 mg p.o. daily	B
	Pediatric residents of endemic area 1–5 yr old with CD4+ < 500 or ≥6 yr old with CD4+ < 200	Not recommended	Itraconazole ^e 2–5 mg/kg p.o. q 12–24 hr, fluconazole 3–6 mg/kg p.o. q 24 hr	NA
Cryptococcal meningitis	Adult residents of endemic area with CD4+ < 50 ^d	Not recommended	Fluconazole 200 mg p.o. daily or itraconazole 200 mg p.o. daily	A
	Pediatric residents of endemic area 1–5 yr old with CD4+ < 500 or ≥6 yr old with CD4+ < 200	Not recommended	Fluconazole 3–6 mg/kg p.o. daily or itraconazole 2–5 mg/kg p.o. q 12–24 hr	NA

^aCriteria are for patients infected with the human immunodeficiency virus. CD4+ = CD4+ lymphocyte count (cells/μL).

^bRefer to recommendation of Centers for Disease Control and Prevention for detailed information and dosage for children younger than one year (reference 284).

^cStrength of evidence that supports the use or nonuse of prophylaxis is classified as A (levels I–III), B (levels IV–VI), or C (level VII). Level I evidence is from large, well-conducted randomized, controlled clinical trials. Level II evidence is from small, well-conducted randomized, controlled clinical trials. Level III evidence is from well-conducted cohort studies. Level IV evidence is from well-conducted case–control studies. Level V evidence is from uncontrolled studies that were not well conducted. Level VI evidence is conflicting evidence that tends to favor the recommendation. Level VII evidence is expert opinion. Strength-of-evidence classification not applied (NA) to pediatric recommendations.

^dPatients should be carefully selected and therapy instituted on an individual basis.

^eOral solution may be the preferred dosage form.

sulfamethoxazole 750 mg/m²/day orally every day. An alternative regimen for children one month old and older is dapsone 2 mg/kg or 15 mg/m² (not to exceed 25 mg) orally every day plus pyrimethamine 1 mg/kg orally every day plus leucovorin 5 mg (as the calcium) orally every three days.

CMV Disease in HIV-Infected Persons

Background. CMV is the cause of significant morbidity and mortality among persons with advanced HIV disease. CMV disease, manifested either as retinitis or involvement of other organs, was the AIDS-defining illness in 9.4% of AIDS cases in adults and 9.3% of cases in children reported to CDC through 1992.³⁶⁰ CMV retinitis occurs in approximately 25–40% of all adults with AIDS.^{361,362} However, the true importance of CMV in HIV-infected patients is better illustrated by the fact that 75–90% of patients examined at autopsy have evidence of CMV infection of the retina, brain, GI tract, lungs, or adrenal glands.^{363,364} Further, CMV is an immediate cause of death in 30% of patients dying of AIDS-related complications.³⁶⁵ Prevention and effective management of CMV disease is clearly an important issue in the treatment of HIV-infected persons.

Persons at Risk. Although primary infection may occur in HIV-infected persons, CMV disease usually represents a reactivation of latent infection; 95–98% of homosexual men and injection drug users with HIV infection are seropositive for antibodies to CMV at the time of diagnosis.³⁶⁶ Reactivation of CMV infection is closely related to the degree of HIV-associated immunosuppression. HIV-infected persons with CD4+ lymphocyte counts of <200 cells/mL are at increased risk of developing CMV disease, while those with

CD4+ lymphocyte counts of <100 cells/mL are at even greater risk.^{365,367} Retinitis due to CMV occurs primarily in patients with CD4+ lymphocyte counts of <50 cells/mL; the median time to development of retinitis in adults with this advanced degree of HIV disease is six months.³⁶⁸ Viremia has also been demonstrated to be a significant predictor of the development of CMV disease in HIV-infected patients. One study demonstrated the probability of patients with CMV viremia developing CMV disease to be nearly 80% within one year of the first positive blood culture; these patients had a 22-fold higher risk of CMV disease than HIV-infected patients without viremia.³⁶⁹ Measurements of CMV viral load may also be of value in the identification of high-risk patients. Detection and quantitation of CMV DNA in plasma by polymerase chain reaction have been demonstrated to be more useful than either urine or blood cultures in identifying patients at high risk for later developing CMV disease.³⁷⁰

Routine prophylaxis of CMV disease is not yet recommended. However, prophylaxis for HIV-infected adults with CD4+ lymphocyte counts of <50 cells/mL and who are also seropositive for antibodies to CMV may be considered for selected patients.²⁸⁴ Further information about the use of CMV viral load data to identify high-risk patients will be available in the future and may also eventually assist clinicians with decisions to institute CMV prophylaxis.

Efficacy. High-dose oral acyclovir is not effective in preventing CMV. A double-blind, placebo-controlled trial of oral acyclovir 800 mg orally four times a day demonstrated virtually no difference in the occurrence of CMV disease between treated and placebo groups.³⁷¹ However, a prospective, randomized, double-blind, placebo-controlled study

Table 7.
Prevention of Opportunistic Infection in Patients Infected with Human Immunodeficiency Virus^a

Infection	Eligible Patients ^b	Recommended Regimen	Alternative Regimens	Strength of Evidence ^c
Disseminated <i>Mycobacterium avium</i> complex	Adults with CD4+ < 50–75	Azithromycin 1200 mg p.o. weekly or clarithromycin 500 mg p.o. b.i.d.	Rifabutin 300 mg p.o. daily with or without azithromycin 1200 mg p.o. weekly	A
	Children 6–12 yr old with CD4+ < 50	Azithromycin 20 mg/kg (maximum 1200 mg) p.o. weekly or clarithromycin 7.5 mg/kg (maximum 500 mg) p.o. q 12 hr	Rifabutin 300 mg p.o. daily or azithromycin 5 mg/kg (maximum 250 mg) p.o. daily	NA
	Children 2–6 yr old with CD4+ < 75, 1–2 yr old with CD4+ < 500, or < 1 yr old with CD4+ < 750	Azithromycin 20 mg/kg (maximum 1200 mg) p.o. weekly or clarithromycin 7.5 mg/kg (maximum 500 mg) p.o. q 12 hr	Rifabutin 5 mg/kg p.o. daily when suspension available or azithromycin 5 mg/kg (maximum 250 mg) p.o. daily	NA
PCP	Adult or adolescent >12 yr old with CD4+ ≤ 200, unexplained fever for ≥2 wk, or history of oropharyngeal candidiasis	TMP 160 mg and SMX 800 mg p.o. daily, TMP 80 mg and SMX 400 mg p.o. daily, or TMP 160 mg and SMX 800 mg p.o. thrice weekly	Dapsone 50 mg p.o. b.i.d. or 100 mg p.o. daily; dapsone 50 mg p.o. daily plus pyrimethamine 50 mg and leucovorin 25 mg p.o. weekly; dapsone 200 mg, pyrimethamine 75 mg, and leucovorin 25 mg p.o. weekly; or aerosolized pentamidine 300 mg monthly via Respirgard II nebulizer	A
	Children 6–12 yr old not previously receiving PCP prophylaxis with CD4+ ≤ 200 or < 15%	TMP 150 mg/m ² /day and SMX 750 mg/m ² /day p.o. in 2 divided doses thrice weekly on consecutive days, in single daily dose thrice weekly on consecutive days, in 2 divided doses daily, or in 2 divided doses thrice weekly on alternate days	Dapsone 2 mg/kg (maximum 100 mg) p.o. daily, pentamidine 4 mg/kg i.v. q 2–4 wk, or aerosolized pentamidine 300 mg monthly via Respirgard II nebulizer	NA
	Children 1–5 yr old not previously receiving PCP prophylaxis with CD4+ ≤ 500 or < 15%	TMP 150 mg/m ² /day and SMX 750 mg/m ² /day p.o. in 2 divided doses thrice weekly on consecutive days	Dapsone 2 mg/kg (maximum 100 mg) p.o. daily or pentamidine 4 mg/kg i.v. q 2–4 wk	NA
<i>Toxoplasma gondii</i> encephalitis	Adult with IgG antibody seropositive for <i>Toxoplasma</i> and CD4+ < 100	Primary prophylaxis not recommended	TMP 160 mg and SMX 800 mg p.o. daily, TMP 80 mg and SMX 400 mg p.o. daily, TMP 160 mg and SMX 800 mg p.o. thrice weekly, or dapsone 50 mg p.o. daily, pyrimethamine 50 mg, leucovorin 25 mg p.o. weekly, and SMX 750 mg/m ² /day	A ^d
	Children ≥6 yr old with IgG antibody seropositive for <i>Toxoplasma</i> and CD4+ < 200 or < 15% or 1–5 yr old with IgG antibody seropositive for <i>Toxoplasma</i> and CD4+ < 500 or < 15%	Primary prophylaxis not recommended	TMP 150 mg/m ² /day p.o. in 2 divided daily doses, or dapsone 2 mg/kg or 15 mg/m ² (maximum 25 mg) p.o. daily, pyrimethamine 1 mg/kg p.o. daily, and leucovorin 5 mg p.o. q 3 days	NA
CMV disease	Adult with CD4+ < 50 and positive for CMV antibody	Primary prophylaxis not recommended	Ganciclovir 1000 mg p.o. t.i.d.	B ^d
	Children ≥6 yr old with CD4+ < 200 or < 15% and positive for CMV antibody or 1–5 yr old with CD4+ < 500 or < 15% and positive for CMV antibody	Primary prophylaxis not recommended	Oral ganciclovir under investigation but not yet recommended for use	NA
Primary HSV	Adult and pediatric patients susceptible to HSV as determined by seronegativity for antibody to HSV	Primary prophylaxis not recommended	None	C ^e

Continued on next page

Table 7 (continued)

Infection	Eligible Patients ^b	Recommended Regimen	Alternative Regimens	Strength of Evidence ^c
Primary VZV	Adult and pediatric patients susceptible to VZV as determined by having no prior VZV infection, by being seronegative for antibody to VZV, and having no history of significant exposure to persons with active varicella or herpes zoster	Primary prophylaxis not recommended	Immunoprophylaxis in susceptible patients ^f	C ^e

^aCD4+ = CD4+ lymphocyte count (cells/μL), TMP = trimethoprim, SMX = sulfamethoxazole, PCP = *Pneumocystis carinii* pneumonia, IgG = immunoglobulin G, CMV = cytomegalovirus, HSV = herpes simplex virus, VZV = varicella zoster virus.

^bCriteria are for patients infected with the human immunodeficiency virus.

^cStrength of evidence that supports the use or nonuse of prophylaxis is classified as A (levels I–III), B (levels IV–VI), or C (level VII). Level I evidence is from large, well-conducted randomized, controlled clinical trials. Level II evidence is from small, well-conducted randomized, controlled clinical trials. Level III evidence is from well-conducted cohort studies. Level IV evidence is from well-conducted case-control studies. Level V evidence is from uncontrolled studies that were not well conducted. Level VI evidence is conflicting evidence that tends to favor the recommendation. Level VII evidence is expert opinion. Strength-of-evidence classification not applied (NA) to pediatric recommendations.

^dFor primary prophylaxis.

^eAgainst primary prophylaxis in nonpediatric patients.

^fRefer to recommendation of Centers for Disease Control and Prevention for detailed information (reference 284).

evaluating the efficacy of ganciclovir for preventing CMV disease yielded some impressive results.³⁷² Patients enrolled in this study, nearly 90% of whom had CD4+ lymphocyte counts of <50 cells/mL, were randomly assigned to receive either ganciclovir 1000 mg orally three times a day or placebo. The study was stopped after a median follow-up period of 367 days when interim analysis revealed that the rates of both overall CMV disease and CMV retinitis were 50% lower among patients receiving ganciclovir. Although not significant, there was also a trend toward a higher rate of survival among patients receiving ganciclovir.

Oral ganciclovir may prove to have an important role in the prevention of CMV disease. However, the routine use of ganciclovir is not yet recommended because of several concerns. An unpublished study showed that oral ganciclovir does not prevent CMV disease. However, there were methodological differences between the two studies. First, in the study by Spector et al.,³⁷² patients underwent dilated ophthalmoscope examination at regular intervals, while Crumpacker³⁷³ defined endpoints clinically. Second, as with prophylaxis of various fungal infections, there are additional concerns about the true mortality benefits of prophylaxis, the toxicity of oral ganciclovir, the development of ganciclovir-resistant CMV strains during long-term ganciclovir therapy, and the cost-effectiveness of routine prophylaxis. Although oral ganciclovir is promising, until these concerns have been adequately addressed, the routine use of ganciclovir prophylaxis in HIV-infected patients at risk of CMV disease cannot be advocated.

Resistance. There are no data on the development of resistance with prophylaxis against CMV. However, ganciclovir-resistant CMV strains during long-term ganciclovir therapy have been reported.^{281,282}

Pediatric Efficacy. No well-controlled studies have yet evaluated the effect of prophylaxis for CMV in pediatric patients. Pediatric recommendations are not provided by CDC, USPHS, or IDSA.²⁸⁴

Recommendation. Primary prophylaxis of CMV disease is not routinely recommended because of insufficient data

demonstrating clinical efficacy versus benefits and concerns about the development of drug-resistant CMV strains during long-term antiviral use. The use of oral ganciclovir 1000 mg three times a day has been recommended in carefully selected patients who are seropositive for antibodies to CMV and have advanced HIV infection (CD4+ lymphocyte count of <50 cells/mL) (Table 7). (Strength of evidence against primary prophylaxis = B)

Pediatric Dosage. Primary prophylaxis against CMV is not recommended for pediatric patients. Primary prophylaxis with ganciclovir may eventually be an option for patients who are seropositive for antibodies to CMV and have severe immunosuppression. Although currently under study, the efficacy of oral ganciclovir for primary prophylaxis is not yet demonstrated to be beneficial in children and is not recommended at this time.

Herpes Simplex and Varicella-Zoster Virus Infections in HIV-Infected Persons

Background. HSV infections are common in all populations. In adults in the United States, seroprevalence rates are >80% for HSV-1 (oral mucosal lesions) and 20–30% for HSV-2 (genital lesions).³⁶⁰ In HIV-infected persons, reactivation of HSV occurs frequently and can result in chronic mucocutaneous disease; however, disseminated HSV disease occurs rarely.³⁷⁴ Varicella-zoster virus (VZV) is the cause of varicella or chickenpox, a childhood disease that occurs in more than 90% of persons. Although VZV infection in HIV-negative children is usually self-limiting and without complication, primary infections in HIV-infected children and adults may be associated with severe disease that may occasionally be fatal (usually because of pulmonary complications).³⁶⁰ Adults with HIV infection are approximately nine times more likely than HIV-negative persons to develop recurrent VZV (herpes zoster or shingles).³⁷⁵ Because seroprevalence of both HSV and VZV are so common in the general population, measures to prevent primary infection with these viruses are valid only for HIV-infected individuals who are still seronegative.

Persons at Risk. HSV reactivation is common in HIV-infected persons. Reactivation appears more common with HSV-2 than with HSV-1, and reactivation of both strains appears to be relatively independent of the stage of HIV disease.³⁶⁰ Severe mucocutaneous HSV disease does not commonly appear until advanced HIV disease (CD4+ lymphocyte count of <100 cells/mL) is present. There are no known risk factors for more severe complications of reactivated HSV infection (meningitis, encephalitis).³⁶⁰ Maternally transmitted primary HSV infections in children are not usually clinically serious, but features of reactivated HSV are similar to those seen in HIV-infected adults.

No other clear risk factors for herpes zoster in HIV-infected persons have yet been identified,³⁶⁰ although there appears to be an association between a decreasing CD4+ lymphocyte count and the severity of VZV disease in HIV-infected children.³⁷⁶

Efficacy. Other than measures designed to prevent exposure to HSV, no other strategies have been proven effective in the prevention of primary HSV infections. The role of acyclovir or other antiviral agents in the prophylaxis of primary HSV infections is unknown; therefore chemoprophylaxis of HSV is not recommended. This is particularly true in light of the frequent occurrence (11–17% of patients) of acyclovir-resistant HSV in HIV-infected persons receiving long-term acyclovir therapy.³⁷⁷

Although data from controlled studies are lacking, CDC has issued recommendations that varicella-zoster immune globulin (VZIG) be administered to susceptible (no history of prior infection or VZV seronegative) HIV-infected adults after significant exposure to persons with active VZV infections.²⁸⁴ The need for VZIG should be evaluated on an individual basis according to the HIV-infected patient's medical condition and the degree of exposure. Significant exposure is defined as more than one hour of household contact or exposure to a VZV-infected patient in the same room or an adjacent bed.²⁸⁴ When indicated, VZIG should be administered within 96 hours after exposure. Other forms of antiviral chemoprophylaxis have not been adequately studied and are not recommended. In addition, use of the live-attenuated varicella vaccine for prevention of primary VZV infection is not recommended because of a lack of efficacy and safety studies in HIV-infected persons.²⁸⁴

Resistance. There are no data on the development of resistance as a result of primary prophylaxis against HSV or VZV. Acyclovir-resistant HSV is most commonly reported in severely immunocompromised patients and infrequently in immunocompetent patients with extended treatment courses.¹⁸²

Pediatric Efficacy. Although data from controlled studies are lacking, CDC, USPHS, and IDSA have issued recommendations that VZIG be administered to susceptible (no history of prior infection or VZV seronegative) HIV-infected children after significant exposure to persons with active VZV infections.²⁸⁴

Recommendation. Primary chemoprophylaxis for HSV and VZV is not recommended. Because severe HSV disease in all age groups is a result of reactivation rather than primary infection, and because HSV-2 reactivation is much more

problematic than HSV-1, prophylaxis efforts are directed toward prevention of primary infections in persons seronegative for antibodies to HSV-2.^{307,360} This is most effectively accomplished through the use of latex condoms by sexually active HIV-infected adults rather than chemoprophylaxis.^{283,307} HIV-infected persons with no reliable history of VZV infection or documented seronegativity for antibodies to VZV are possibly susceptible to primary infection and should avoid exposure to individuals with either varicella or herpes zoster.³⁶⁰

Because of the increased severity of primary VZV infection in HIV-infected adults, susceptible persons should be administered VZIG after significant exposure to persons with active varicella or herpes zoster.^{283,307} For detailed information on immunoprophylaxis, readers are referred to the CDC guidelines.²⁸⁴ No other forms of prophylaxis are indicated. (Strength of evidence against primary prophylaxis = C)

Pediatric Dosage. Primary chemoprophylaxis for HSV and VZV is not recommended for pediatric patients. Because of the higher severity of primary VZV infection in HIV-infected children, susceptible persons should be administered VZIG after significant exposure to persons with active varicella or herpes zoster.²⁸⁴ For detailed information on immunoprophylaxis, readers are referred to the CDC guidelines.²⁸⁴ No other forms of prophylaxis are indicated.

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