CHAPTER 51

Clinical Use of Antimicrobial Agents

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CASE STUDY

A 51-year-old alcoholic patient presents to the emergency department with fever, headache, neck stiffness, and altered mental status for 12 hours. Vital signs are blood pressure 90/55 mm Hg, pulse 120/min, respirations 30/min, temperature 40°C [104°F] rectal. The patient is minimally responsive to voice and does not follow commands. Examination is significant for a right third cranial nerve palsy and nuchal rigidity. Laboratory results show a white blood cell count of 24,000/mm^3 with left shift, but other hematologic and chemistry values are within normal limits. An emergency CT scan of the head is normal. Blood cultures are obtained, and a lumbar puncture reveals the following cerebrospinal fluid (CSF) values: white blood cells 5000/mm^3, red blood cells 10/mm^3, protein 200 mg/dL, glucose 15 mg/dL (serum glucose 96 taken at same time). CSF Gram stain reveals gram-positive cocci in pairs. What is the most likely diagnosis in this patient? What organisms should be treated empirically? Are there other pharmacologic interventions to consider before initiating antimicrobial therapy?

The development of antimicrobial drugs represents one of the most important advances in therapeutics, both in the control or cure of serious infections and in the prevention and treatment of infectious complications of other therapeutic modalities such as cancer chemotherapy, immunosuppression, and surgery. However, evidence is overwhelming that antimicrobial agents are vastly overprescribed in outpatient settings in the United States, and the availability of antimicrobial agents without prescription in many developing countries has—by facilitating the development of resistance—already severely limited therapeutic options in the treatment of life-threatening infections. Therefore, the clinician should first determine whether antimicrobial therapy is warranted for a given patient. The specific questions one should ask include the following:

1. Is an antimicrobial agent indicated on the basis of clinical findings? Or is it prudent to wait until such clinical findings become apparent?
2. Have appropriate clinical specimens been obtained to establish a microbiologic diagnosis?
3. What are the likely etiologic agents for the patient's illness?
4. What measures should be taken to protect individuals exposed to the index case to prevent secondary cases, and what measures should be implemented to prevent further exposure?
5. Is there clinical evidence (eg, from well-executed clinical trials) that antimicrobial therapy will confer clinical benefit for the patient?

Once a specific cause is identified based on specific microbiologic tests, the following further questions should be considered:

1. If a specific microbial pathogen is identified, can a narrower-spectrum agent be substituted for the initial empiric drug?
2. Is one agent or a combination of agents necessary?
3. What are the optimal dose, route of administration, and duration of therapy?
4. What specific tests (eg, susceptibility testing) should be undertaken to identify patients who will not respond to treatment?
5. What adjunctive measures can be undertaken to eradicate the infection? For example, is surgery feasible for removal of devitalized tissue or foreign bodies—or drainage of an abscess—into which antimicrobial agents may be unable to penetrate?

Is it possible to decrease the dosage of immunosuppressive therapy in patients who have undergone organ transplantation? Is it possible to reduce morbidity or mortality due to the infection by reducing host immunologic response to the infection (eg, by the use of corticosteroids for the treatment of severe *Pneumocystis jiroveci* pneumonia or meningitis due to *Streptococcus pneumoniae*)?

EMPIRIC ANTIMICROBIAL THERAPY

Antimicrobial agents are frequently used before the pathogen responsible for a particular illness or the susceptibility to a particular antimicrobial agent is known. This use of antimicrobial agents is called empiric (or presumptive) therapy and is based on experience with a particular clinical entity. The usual justification for empiric therapy is the hope that early intervention will improve the outcome; in the best cases, this has been established by placebo-controlled, double-blind prospective clinical trials. For example, treatment of febrile episodes in neutropenic cancer patients with empiric antimicrobial therapy has been demonstrated to have impressive morbidity and mortality benefits even though the specific bacterial agent responsible for fever is determined for only a minority of such episodes.

Finally, there are many clinical entities, such as certain episodes of community-acquired pneumonia, in which it is difficult to identify a specific pathogen. In such cases, a clinical response to empiric therapy may be an important clue to the likely pathogen.

Frequently, the signs and symptoms of infection diminish as a result of empiric therapy, and microbiologic test results become available that establish a specific microbiologic diagnosis. At the time that the pathogenic organism responsible for the illness is identified, empiric therapy is optimally modified to **definitive therapy,** which is typically narrower in coverage and is given for an appropriate duration based on the results of clinical trials or experience when clinical trial data are not available.

Approach to Empiric Therapy

Initiation of empiric therapy should follow a specific and systematic approach.

A. Formulate a Clinical Diagnosis of Microbial Infection

Using all available data, the clinician should determine that there is anatomic evidence of infection (eg, pneumonia, cellulitis, sinusitis).

B. Obtain Specimens for Laboratory Examination

Examination of stained specimens by microscopy or simple examination of an uncentrifuged sample of urine for white blood cells and bacteria may provide important etiologic clues in a very short time. Cultures of selected anatomic sites (blood, sputum, urine, cerebrospinal fluid, and stool) and nonculture methods (antigen testing, polymerase chain reaction, and serology) may also confirm specific etiologic agents.

C. Formulate a Microbiologic Diagnosis

The history, physical examination, and immediately available laboratory results (eg, Gram stain of urine or sputum) may provide highly specific information. For example, in a young man with urethritis and a Gram-stained smear from the urethral meatus demonstrating intracellular gram-negative diplococci, the most likely pathogen is *Neisseria gonorrhoeae*. In the latter instance, however, the clinician should be aware that a significant number of patients with gonococcal urethritis have uninformative Gram stains for the organism and that a significant number of patients with gonococcal urethritis harbor concurrent chlamydial infection that is not demonstrated on the Gram-stained smear.

D. Determine the Necessity for Empiric Therapy

Whether or not to initiate empiric therapy is an important clinical decision based partly on experience and partly on data from clinical trials. Empiric therapy is indicated when there is a significant risk of serious morbidity if therapy is withheld until a specific pathogen is detected by the clinical laboratory.

In other settings, empiric therapy may be indicated for public health reasons rather than for demonstrated superior outcome of therapy in a specific patient. For example, urethritis in a young sexually active man usually requires treatment for *N gonorrhoeae* and *Chlamydia trachomatis* despite the absence of microbiologic confirmation at the time of diagnosis. Because the risk of noncompliance with follow-up visits in this patient population may lead to further transmission of these sexually transmitted pathogens, empiric therapy is warranted.

E. Institute Treatment

Selection of empiric therapy may be based on the microbiologic diagnosis or a clinical diagnosis without available microbiologic clues. If no microbiologic information is available, the antimicrobial spectrum of the agent or agents chosen must necessarily be broader, taking into account the most likely pathogens responsible for the patient's illness.

Choice of Antimicrobial Agent

Selection from among several drugs depends on **host factors** that include the following: (1) concomitant disease states (eg, AIDS, neutropenia due to the use of cytotoxic chemotherapy, organ transplantation, severe chronic liver or kidney disease) or the use of immunosuppressive medications; (2) prior adverse drug effects; (3) impaired elimination or detoxification of the drug (may be genetically predetermined but more frequently is associated with impaired renal or hepatic function due to underlying disease); (4) age of the patient; (5) pregnancy status; and (6) epidemiologic exposure (eg, exposure to a sick family member or pet, recent hospitalization, recent travel, occupational exposure, or new sexual partner).

Pharmacologic factors include (1) the kinetics of absorption, distribution, and elimination; (2) the ability of the drug to be delivered to the site of infection; (3) the potential toxicity of an agent; and (4) pharmacokinetic or pharmacodynamic interactions with other drugs.

Knowledge of the **susceptibility** of an organism to a specific agent in a hospital or community setting is important in the selection of empiric therapy. Pharmacokinetic differences among agents with similar antimicrobial spectrums may be exploited to reduce the frequency of dosing (eg, ceftriaxone may be conveniently given once every 24 hours). Finally, increasing consideration is being given to the cost of antimicrobial therapy, especially when multiple agents with comparable efficacy and toxicity are available for a specific infection. Changing from intravenous to oral antibiotics for prolonged administration can be particularly cost-effective.

Brief guides to empiric therapy based on presumptive microbial diagnosis and site of infection are given in Tables 51–1 and 51–2.

ANTIMICROBIAL THERAPY OF INFECTIONS WITH KNOWN ETIOLOGY

INTERPRETATION OF CULTURE RESULTS

Properly obtained and processed specimens for culture frequently yield reliable information about the cause of infection. The lack of a confirmatory microbiologic diagnosis may be due to the following:

1. Sample error, eg, obtaining cultures after antimicrobial agents have been administered, or contamination of specimens sent for culture
2. Noncultivable or slow-growing organisms (*Histoplasma capsulatum, Bartonella* or *Brucella* species), in which cultures are often discarded before sufficient growth has occurred for detection
3. Requesting *bacterial* cultures when infection is due to other organisms
4. Not recognizing the need for special media or isolation techniques (eg, charcoal yeast extract agar for isolation of legionella species, shell-vial tissue culture system for rapid isolation of cytomegalovirus)

Even in the setting of a classic infectious disease for which isolation techniques have been established for decades (eg, pneumococcal pneumonia, pulmonary tuberculosis, streptococcal pharyngitis), the sensitivity of the culture technique may be inadequate to identify all cases of the disease.

GUIDING ANTIMICROBIAL THERAPY OF ESTABLISHED INFECTIONS

Susceptibility Testing

Testing bacterial pathogens in vitro for their susceptibility to antimicrobial agents is extremely valuable in confirming susceptibility, ideally to a narrow-spectrum nontoxic antimicrobial drug. Tests measure the concentration of drug required to inhibit growth of the organism (**minimal inhibitory concentration [MIC]**) or to kill the organism (**minimal bactericidal concentration [MBC]**). The results of these tests can then be correlated with known drug concentrations in various body compartments. Only MICs are routinely measured in most infections, whereas in infections in which bactericidal therapy is required for eradication of infection (eg, meningitis, endocarditis, sepsis in the granulocytopenic host), MBC measurements occasionally may be useful.

Specialized Assay Methods

A. Beta-Lactamase Assay

For some bacteria (eg, *Haemophilus* species), the susceptibility patterns of strains are similar except for the production of β lactamase. In these cases, extensive susceptibility testing may not be required, and a direct test for β lactamase using a chromogenic β-lactam substrate (nitrocephin disk) may be substituted.

B. Synergy Studies

Synergy studies are in vitro tests that attempt to measure synergistic, additive, indifferent, or antagonistic drug interactions. In general, these tests have not been standardized and have not correlated well with clinical outcome. (See section on Antimicrobial Drug Combinations for details.)

MONITORING THERAPEUTIC RESPONSE: DURATION OF THERAPY

The therapeutic response may be monitored microbiologically or clinically. Cultures of specimens taken from infected sites should eventually become sterile or demonstrate eradication of the pathogen and are useful for documenting recurrence or relapse. Follow-up cultures may also be useful for detecting superinfections or the development of resistance. Clinically, the patient's systemic manifestations of infection (malaise, fever, leukocytosis) should abate, and the clinical findings should improve (eg, as shown by clearing of radiographic infiltrates or lessening hypoxemia in pneumonia).

The duration of definitive therapy required for cure depends on the pathogen, the site of infection, and host factors (immunocompromised patients generally require longer courses of treatment). Precise data on duration of therapy exist for some infections (eg, streptococcal pharyngitis, syphilis, gonorrhea, tuberculosis, and cryptococcal meningitis). In many other situations, duration of therapy is determined empirically. For recurrent infections (eg, sinusitis, urinary tract infections), longer courses of antimicrobial therapy or surgical intervention are frequently necessary for eradication.

Clinical Failure of Antimicrobial Therapy

When the patient has an inadequate clinical or microbiologic response to antimicrobial therapy selected by in vitro susceptibility testing, systematic investigation should be undertaken to determine the cause of failure. Errors in susceptibility testing are rare, but the original results should be confirmed by repeat testing. Drug dosing and absorption should be scrutinized and tested directly using serum measurements, pill counting, or directly observed therapy.

The clinical data should be reviewed to determine whether the patient's immune function is adequate and, if not, what can be

TABLE 51–1 Empiric antimicrobial therapy based on microbiologic etiology.

Suspected or Proven Disease or Pathogen	Drugs of First Choice	Alternative Drugs
Gram-negative cocci (aerobic)		
Moraxella (Branhamella) catarrhalis	TMP-SMZ,[1] cephalosporin (second- or third-generation)[2]	Quinolone,[3] macrolide[4]
Neisseria gonorrhoeae	Ceftriaxone, cefixime	Spectinomycin, azithromycin
Neisseria meningitides	Penicillin G	Chloramphenicol, ceftriaxone, cefotaxime
Gram-negative rods (aerobic)		
E coli, Klebsiella, Proteus	Cephalosporin (first- or second-generation),[2] TMP-SMZ[1]	Quinolone,[3] aminoglycoside[5]
Enterobacter, Citrobacter, Serratia	TMP-SMZ,[1] quinolone,[3] carbapenem[6]	Antipseudomonal penicillin,[7] aminoglycoside,[5] cefepime
Shigella	Quinolone[3]	TMP-SMZ,[1] ampicillin, azithromycin, ceftriaxone
Salmonella	Quinolone,[3] ceftriaxone	Chloramphenicol, ampicillin, TMP-SMZ[1]
Campylobacter jejuni	Erythromycin or azithromycin	Tetracycline, quinolone[3]
Brucella species	Doxycycline + rifampin or aminoglycoside[5]	Chloramphenicol + aminoglycoside[5] or TMP-SMZ[1]
Helicobacter pylori	Proton pump inhibitor + amoxicillin + clarithromycin	Bismuth + metronidazole + tetracycline + proton pump inhibitor
Vibrio species	Tetracycline	Quinolone,[3] TMP-SMZ[1]
Pseudomonas aeruginosa	Antipseudomonal penicillin ± aminoglycoside[5]	Antipseudomonal penicillin ± quinolone,[3] cefepime, ceftazidime, antipseudomonal carbapenem,[6] or aztreonam ± aminoglycoside[5]
Burkholderia cepacia (formerly *Pseudomonas cepacia*)	TMP-SMZ[1]	Ceftazidime, chloramphenicol
Stenotrophomonas maltophilia (formerly *Xanthomonas maltophilia*)	TMP-SMZ[1]	Minocycline, ticarcillin-clavulanate, tigecycline, ceftazidime, quinolone[3]
Legionella species	Azithromycin or quinolone[3]	Clarithromycin, erythromycin
Gram-positive cocci (aerobic)		
Streptococcus pneumoniae	Penicillin[8]	Doxycycline, ceftriaxone, antipneumococcal quinolone,[3] macrolide,[4] linezolid
Streptococcus pyogenes (group A)	Penicillin, clindamycin	Erythromycin, cephalosporin (first-generation)[2]
Streptococcus agalactiae (group B)	Penicillin (± aminoglycoside[5])	Vancomycin
Viridans streptococci	Penicillin	Cephalosporin (first- or third-generation),[2] vancomycin
Staphylococcus aureus		
β-Lactamase negative	Penicillin	Cephalosporin (first-generation),[2] vancomycin
β-Lactamase positive	Penicillinase-resistant penicillin[9]	As above
Methicillin-resistant	Vancomycin	TMP-SMZ,[1] minocycline, linezolid, daptomycin, tigecycline
Enterococcus species[10]	Penicillin ± aminoglycoside[5]	Vancomycin ± aminoglycoside[5]
Gram-positive rods (aerobic)		
Bacillus species (non-*anthracis*)	Vancomycin	Imipenem, quinolone,[3] clindamycin
Listeria species	Ampicillin (± aminoglycoside[5])	TMP-SMZ[1]
Nocardia species	Sulfadiazine, TMP-SMZ[1]	Minocycline, imipenem, amikacin, linezolid
Anaerobic bacteria		
Gram-positive (clostridia, *Peptococcus, Actinomyces, Peptostreptococcus*)	Penicillin, clindamycin	Vancomycin, carbapenem,[6] chloramphenicol
Clostridium difficile	Metronidazole	Vancomycin, bacitracin
Bacteroides fragilis	Metronidazole	Chloramphenicol, carbapenem,[6] β-lactam–β-lactamase-inhibitor combinations, clindamycin

(*continued*)

TABLE 51–1 Empiric antimicrobial therapy based on microbiologic etiology. (Continued)

Suspected or Proven Disease or Pathogen	Drugs of First Choice	Alternative Drugs
Fusobacterium, Prevotella, Porphyromonas	Metronidazole, clindamycin, penicillin	As for *B fragilis*
Mycobacteria		
Mycobacterium tuberculosis	Isoniazid + rifampin + ethambutol + pyrazinamide	Streptomycin, moxifloxacin, amikacin, ethionamide, cycloserine, PAS, linezolid
Mycobacterium leprae		
Multibacillary	Dapsone + rifampin + clofazimine	
Paucibacillary	Dapsone + rifampin	
Mycoplasma pneumoniae	Tetracycline, erythromycin	Azithromycin, clarithromycin, quinolone[3]
Chlamydia		
C trachomatis	Tetracycline, azithromycin	Clindamycin, ofloxacin
C pneumoniae	Tetracycline, erythromycin	Clarithromycin, azithromycin
C psittaci	Tetracycline	Chloramphenicol
Spirochetes		
Borrelia recurrentis	Doxycycline	Erythromycin, chloramphenicol, penicillin
Borrelia burgdorferi		
Early	Doxycycline, amoxicillin	Cefuroxime axetil, penicillin
Late	Ceftriaxone	
Leptospira species	Penicillin	Tetracycline
Treponema species	Penicillin	Tetracycline, azithromycin, ceftriaxone
Fungi		
Aspergillus species	Voriconazole	Amphotericin B, itraconazole, caspofungin
Blastomyces species	Amphotericin B	Itraconazole, fluconazole
Candida species	Amphotericin B, echinocandin[11]	Fluconazole, itraconazole, voriconazole
Cryptococcus	Amphotericin B ± flucytosine (5-FC)	Fluconazole, voriconazole
Coccidioides immitis	Amphotericin B	Fluconazole, itraconazole, voriconazole, posaconazole
Histoplasma capsulatum	Amphotericin B	Itraconazole
Mucoraceae (*Rhizopus, Absidia*)	Amphotericin B	Posaconazole
Sporothrix schenckii	Amphotericin B	Itraconazole

[1]Trimethoprim-sulfamethoxazole (TMP-SMZ) is a mixture of one part trimethoprim plus five parts sulfamethoxazole.

[2]First-generation cephalosporins: cefazolin for parenteral administration; cefadroxil or cephalexin for oral administration. Second-generation cephalosporins: cefuroxime for parenteral administration; cefaclor, cefuroxime axetil, cefprozil for oral administration. Third-generation cephalosporins: ceftazidime, cefotaxime, ceftriaxone for parenteral administration; cefixime, cefpodoxime, ceftibuten, cefdinir, cefditoren for oral administration. Fourth-generation cephalosporin: cefepime for parenteral administration. Cephamycins: cefoxitin and cefotetan for parenteral administration.

[3]Quinolones: ciprofloxacin, gemifloxacin, levofloxacin, moxifloxacin, norfloxacin, ofloxacin. Norfloxacin is not effective for the treatment of systemic infections. Gemifloxacin, levofloxacin, and moxifloxacin have excellent activity against pneumococci. Ciprofloxacin and levofloxacin have good activity against *Pseudomonas aeruginosa.*

[4]Macrolides: azithromycin, clarithromycin, dirithromycin, erythromycin.

[5]Generally, streptomycin and gentamicin are used to treat infections with gram-positive organisms, whereas gentamicin, tobramycin, and amikacin are used to treat infections with gram-negatives.

[6]Carbapenems: doripenem, ertapenem, imipenem, meropenem. Ertapenem lacks activity against enterococci, *Acinetobacter,* and *P aeruginosa.*

[7]Antipseudomonal penicillin: piperacillin, piperacillin/tazobactam, ticarcillin/clavulanic acid.

[8]See footnote 3 in Table 51–2 for guidelines on the treatment of penicillin-resistant pneumococcal meningitis.

[9]Parenteral nafcillin or oxacillin; oral dicloxacillin.

[10]There is no regimen that is reliably bactericidal for vancomycin-resistant enterococcus for which there is extensive clinical experience; daptomycin has bactericidal activity in vitro. Regimens that have been reported to be efficacious include nitrofurantoin (for urinary tract infection); potential regimens for bacteremia include daptomycin, linezolid, and dalfopristin/quinupristin.

[11]Echinocandins: anidulafungin, caspofungin, micafungin.

TABLE 51–2 Empiric antimicrobial therapy based on site of infection.

Presumed Site of Infection	Common Pathogens	Drugs of First Choice	Alternative Drugs
Bacterial endocarditis			
Acute	*Staphylococcus aureus*	Vancomycin + gentamicin	Penicillinase-resistant penicillin[1] + gentamicin
Subacute	*Viridans* streptococci, enterococci	Penicillin + gentamicin	Vancomycin + gentamicin
Septic arthritis			
Child	*H influenzae, S aureus,* β-hemolytic streptococci	Ceftriaxone	Ampicillin-sulbactam
Adult	*S aureus,* Enterobacteriaceae	Cefazolin	Vancomycin, quinolone
Acute otitis media, sinusitis	*H influenzae, S pneumoniae, M catarrhalis*	Amoxicillin	Amoxicillin-clavulanate, cefuroxime axetil, TMP-SMZ
Cellulitis	*S aureus,* group A streptococcus	Penicillinase-resistant penicillin, cephalosporin (first-generation)[2]	Vancomycin, clindamycin, linezolid, daptomycin
Meningitis			
Neonate	Group B streptococcus, *E coli, Listeria*	Ampicillin + cephalosporin (third-generation)	Ampicillin + aminoglycoside, chloramphenicol, meropenem
Child	*H influenzae,* pneumococcus, meningococcus	Ceftriaxone or cefotaxime ± vancomycin[3]	Chloramphenicol, meropenem
Adult	Pneumococcus, meningococcus	Ceftriaxone, cefotaxime	Vancomycin + ceftriaxone or cefotaxime[3]
Peritonitis due to ruptured viscus	Coliforms, *B fragilis*	Metronidazole + cephalosporin (third-generation), piperacillin/tazobactam	Carbapenem, tigecycline
Pneumonia			
Neonate	As in neonatal meningitis		
Child	Pneumococcus, *S aureus, H influenzae*	Ceftriaxone, cefuroxime, cefotaxime	Ampicillin-sulbactam
Adult (community-acquired)	Pneumococcus, *Mycoplasma, Legionella, H influenzae, S aureus, C pneumonia,* coliforms	**Outpatient:** Macrolide,[4] amoxicillin, tetracycline	**Outpatient:** Quinolone
		Inpatient: Macrolide[4] + cefotaxime, ceftriaxone, ertapenem, or ampicillin	**Inpatient:** Doxycycline + cefotaxime, ceftriaxone, ertapenem, or ampicillin; respiratory quinolone[5]
Septicemia[6]	Any	Vancomycin + cephalosporin (third-generation) or piperacillin/tazobactam or imipenem or meropenem	
Septicemia with granulocytopenia	Any	Antipseudomonal penicillin + aminoglycoside; ceftazidime; cefepime; imipenem or meropenem; consider addition of systemic antifungal therapy if fever persists beyond 5 days of empiric therapy	

[1]See footnote 9, Table 51–1.

[2]See footnote 2, Table 51–1.

[3]When meningitis with penicillin-resistant pneumococcus is suspected, empiric therapy with this regimen is recommended.

[4]Erythromycin, clarithromycin, or azithromycin (an azalide) may be used.

[5]Quinolones used to treat pneumonococcal infections include levofloxacin, moxifloxacin, and gemifloxacin.

[6]Adjunctive immunomodulatory drugs such as drotrecogin-alfa can also be considered for patients with severe sepsis.

done to maximize it. For example, are adequate numbers of granulocytes present and are HIV infection, malnutrition, or underlying malignancy present? The presence of abscesses or foreign bodies should also be considered. Finally, culture and susceptibility testing should be repeated to determine whether superinfection has occurred with another organism or whether the original pathogen has developed drug resistance.

ANTIMICROBIAL PHARMACODYNAMICS

The time course of drug concentration is closely related to the antimicrobial effect at the site of infection and to any toxic effects. Pharmacodynamic factors include pathogen susceptibility testing, drug bactericidal versus bacteriostatic activity, drug synergism, antagonism, and postantibiotic effects. Together with pharmacokinetics,

pharmacodynamic information permits the selection of optimal antimicrobial dosage regimens.

Bacteriostatic versus Bactericidal Activity

Antibacterial agents may be classified as bacteriostatic or bactericidal (Table 51–3). For agents that are primarily bacteriostatic, inhibitory drug concentrations are much lower than bactericidal drug concentrations. In general, cell wall-active agents are bactericidal, and drugs that inhibit protein synthesis are bacteriostatic.

The classification of antibacterial agents as bactericidal or bacteriostatic has limitations. Some agents that are considered to be bacteriostatic may be bactericidal against selected organisms. On the other hand, enterococci are inhibited but not killed by vancomycin, penicillin, or ampicillin used as single agents.

Bacteriostatic and bactericidal agents are equivalent for the treatment of most infectious diseases in immunocompetent hosts. Bactericidal agents should be selected over bacteriostatic ones in circumstances in which local or systemic host defenses are impaired. Bactericidal agents are required for treatment of endocarditis and other endovascular infections, meningitis, and infections in neutropenic cancer patients.

Bactericidal agents can be divided into two groups: agents that exhibit **concentration-dependent killing** (eg, aminoglycosides and quinolones) and agents that exhibit **time-dependent killing** (eg, β lactams and vancomycin). For drugs whose killing action is concentration-dependent, the rate and extent of killing increase with increasing drug concentrations. Concentration-dependent killing is one of the pharmacodynamic factors responsible for the efficacy of once-daily dosing of aminoglycosides.

For drugs whose killing action is time-dependent, bactericidal activity continues as long as serum concentrations are greater than the MBC. Drug concentrations of time-dependent killing agents that lack a postantibiotic effect should be maintained above the MIC for the entire interval between doses.

TABLE 51–3 Bactericidal and bacteriostatic antibacterial agents.

Bactericidal Agents	Bacteriostatic Agents
Aminoglycosides	Chloramphenicol
Bacitracin	Clindamycin
β-Lactam antibiotics	Ethambutol
Daptomycin	Macrolides
Glycopeptide antibiotics	Nitrofurantoin
Isoniazid	Novobiocin
Ketolides	Oxazolidinones
Metronidazole	Sulfonamides
Polymyxins	Tetracyclines
Pyrazinamide	Tigecycline
Quinolones	Trimethoprim
Rifampin	
Streptogramins	

Postantibiotic Effect

Persistent suppression of bacterial growth after limited exposure to an antimicrobial agent is known as the postantibiotic effect (PAE). The PAE can be expressed mathematically as follows:

$$PAE = T - C$$

where T is the time required for the viable count in the test (in vitro) culture to increase tenfold above the count observed immediately before drug removal and C is the time required for the count in an untreated culture to increase tenfold above the count observed immediately after completion of the same procedure used on the test culture. The PAE reflects the time required for bacteria to return to logarithmic growth.

Proposed mechanisms include (1) slow recovery after reversible nonlethal damage to cell structures; (2) persistence of the drug at a binding site or within the periplasmic space; and (3) the need to synthesize new enzymes before growth can resume. Most antimicrobials possess significant in vitro PAEs (≥ 1.5 hours) against susceptible gram-positive cocci (Table 51–4). Antimicrobials with significant PAEs against susceptible gram-negative bacilli are limited to carbapenems and agents that inhibit protein or DNA synthesis.

In vivo PAEs are usually much longer than in vitro PAEs. This is thought to be due to **postantibiotic leukocyte enhancement (PALE)** and exposure of bacteria to subinhibitory antibiotic concentrations. The efficacy of once-daily dosing regimens is in part due to the PAE. Aminoglycosides and quinolones possess concentration-dependent PAEs; thus, high doses of aminoglycosides given once daily result in enhanced bactericidal activity and extended PAEs. This combination of pharmacodynamic effects allows aminoglycoside serum concentrations that are below the MICs of target organisms to remain effective for extended periods of time.

PHARMACOKINETIC CONSIDERATIONS

Route of Administration

Many antimicrobial agents have similar pharmacokinetic properties when given orally or parenterally (ie, tetracyclines, trimethoprim-sulfamethoxazole, quinolones, chloramphenicol, metronidazole, clindamycin, rifampin, linezolid, and fluconazole). In most cases, oral therapy with these drugs is equally effective, is less costly, and results in fewer complications than parenteral therapy.

The intravenous route is preferred in the following situations: (1) for critically ill patients; (2) for patients with bacterial meningitis or endocarditis; (3) for patients with nausea, vomiting, gastrectomy, or diseases that may impair oral absorption; and (4) when giving antimicrobials that are poorly absorbed following oral administration.

TABLE 51–4 Antibacterial agents with in vitro postantibiotic effects ≥ 1.5 hours.

Against Gram-Positive Cocci	Against Gram-Negative Bacilli
Aminoglycosides	Aminoglycosides
Carbapenems	Carbapenems
Cephalosporins	Chloramphenicol
Chloramphenicol	Quinolones
Clindamycin	Rifampin
Daptomycin	Tetracyclines
Glycopeptide antibiotics	Tigecycline
Ketolides	
Macrolides	
Oxazolidinones	
Penicillins	
Quinolones	
Rifampin	
Streptogramins	
Sulfonamides	
Tetracyclines	
Tigecycline	
Trimethoprim	

Conditions That Alter Antimicrobial Pharmacokinetics

Various diseases and physiologic states alter the pharmacokinetics of antimicrobial agents. Impairment of renal or hepatic function may result in decreased elimination. Table 51–5 lists drugs that require dosage reduction in patients with renal or hepatic insufficiency. Failure to reduce antimicrobial agent dosage in such patients may cause toxic effects. Conversely, patients with burns, cystic fibrosis, or trauma may have increased dosage requirements for selected agents. The pharmacokinetics of antimicrobials is also altered in the elderly, in neonates, and in pregnancy.

Drug Concentrations in Body Fluids

Most antimicrobial agents are well distributed to most body tissues and fluids. Penetration into the cerebrospinal fluid is an exception. Most do not penetrate uninflamed meninges to an appreciable extent. In the presence of meningitis, however, the cerebrospinal fluid concentrations of many antimicrobials increase (Table 51–6).

Monitoring Serum Concentrations of Antimicrobial Agents

For most antimicrobial agents, the relation between dose and therapeutic outcome is well established, and serum concentration monitoring is unnecessary for these drugs. To justify routine serum concentration monitoring, it should be established (1) that a direct relationship exists between drug concentrations and efficacy or toxicity; (2) that substantial interpatient variability exists in serum concentrations on standard doses; (3) that a small difference exists between therapeutic and toxic serum concentrations; (4) that the clinical efficacy or toxicity of the drug is delayed or difficult to measure; and (5) that an accurate assay is available.

In clinical practice, serum concentration monitoring is routinely performed on patients receiving aminoglycosides. Despite the lack of supporting evidence for its usefulness or need, serum vancomycin concentration monitoring is also widespread. Flucytosine serum concentration monitoring has been shown to reduce toxicity when doses are adjusted to maintain peak concentrations below 100 mcg/mL.

■ MANAGEMENT OF ANTIMICROBIAL DRUG TOXICITY

Owing to the large number of antimicrobials available, it is usually possible to select an effective alternative in patients who develop serious drug toxicity (Table 51–1). However, for some infections there are no effective alternatives to the drug of choice. For example, in patients with neurosyphilis who have a history of

TABLE 51–5 Antimicrobial agents that require dosage adjustment or are contraindicated in patients with renal or hepatic impairment.

Dosage Adjustment Needed in Renal Impairment	Contraindicated in Renal Impairment	Dosage Adjustment Needed in Hepatic Impairment
Acyclovir, amantadine, aminoglycosides, aztreonam, carbapenems, cephalosporins,[1] clarithromycin, colistin, cycloserine, daptomycin, didanosine, emtricitabine, ethambutol, ethionamide, famciclovir, fluconazole, flucytosine, foscarnet, ganciclovir, lamivudine, penicillins,[3] pyrazinamide, quinolones, [4] rimantadine, stavudine, telavancin, telbivudine, telithromycin, tenofovir, terbinafine, trimethoprim-sulfamethoxazole, valacyclovir, vancomycin, zidovudine	Cidofovir, methenamine, nalidixic acid, nitrofurantoin, sulfonamides (long-acting), tetracyclines[2]	Amprenavir, atazanavir, chloramphenicol, clindamycin, erythromycin, fosamprenavir, indinavir, metronidazole, rimantadine, tigecycline

[1]Except ceftriaxone.

[2]Except doxycycline and possibly minocycline.

[3]Except antistaphylococcal penicillins (eg, nafcillin and dicloxacillin).

[4]Except moxifloxacin.

TABLE 51–6 Cerebrospinal fluid (CSF) penetration of selected antimicrobials.

Antimicrobial Agent	CSF Concentration (Uninflamed Meninges) as % of Serum Concentration	CSF Concentration (Inflamed Meninges) as % of Serum Concentration
Ampicillin	2–3	2–100
Aztreonam	2	5
Cefepime	0–2	4–12
Cefotaxime	22.5	27–36
Ceftazidime	0.7	20–40
Ceftriaxone	0.8–1.6	16
Cefuroxime	20	17–88
Ciprofloxacin	6–27	26–37
Imipenem	3.1	11–41
Meropenem	0–7	1–52
Nafcillin	2–15	5–27
Penicillin G	1–2	8–18
Sulfamethoxazole	40	12–47
Trimethoprim	< 41	12–69
Vancomycin	0	1–53

anaphylaxis to penicillin, it is necessary to perform skin testing and desensitization to penicillin. It is important to obtain a clear history of drug allergy and other adverse drug reactions. A patient with a documented antimicrobial allergy should carry a card with the name of the drug and a description of the reaction. Cross-reactivity between penicillins and cephalosporins is less than 10%. Cephalosporins may be administered to patients with penicillin-induced maculopapular rashes but should be avoided in patients with a history of penicillin-induced immediate hypersensitivity reactions. On the other hand, aztreonam does not cross-react with penicillins and can be safely administered to patients with a history of penicillin-induced anaphylaxis. For mild reactions, it may be possible to continue therapy with use of adjunctive agents or dosage reduction.

Adverse reactions to antimicrobials occur with increased frequency in several groups, including neonates, geriatric patients, renal failure patients, and AIDS patients. Dosage adjustment of the drugs listed in Table 51–5 is essential for the prevention of adverse effects in patients with renal failure. In addition, several agents are contraindicated in patients with renal impairment because of increased rates of serious toxicity (Table 51–5). See the preceding chapters for discussions of specific drugs.

Polypharmacy also predisposes to drug interactions. Although the mechanism is not known, AIDS patients have an unusually high incidence of toxicity to a number of drugs, including clindamycin, aminopenicillins, and sulfonamides. Many of these reactions, including rash and fever, may respond to dosage reduction or treatment with corticosteroids and antihistamines. Other examples are discussed in the preceding chapters and in Chapter 66.

ANTIMICROBIAL DRUG COMBINATIONS

RATIONALE FOR COMBINATION ANTIMICROBIAL THERAPY

Most infections should be treated with a single antimicrobial agent. Although indications for combination therapy exist, antimicrobial combinations are often overused in clinical practice. The unnecessary use of antimicrobial combinations increases toxicity and costs and may occasionally result in reduced efficacy due to antagonism of one drug by another. Antimicrobial combinations should be selected for one or more of the following reasons:

1. To provide broad-spectrum empiric therapy in seriously ill patients.
2. To treat polymicrobial infections (such as intra-abdominal abscesses, which typically are due to a combination of anaerobic and aerobic gram-negative organisms, and enterococci). The antimicrobial combination chosen should cover the most common known or suspected pathogens but need not cover all possible pathogens. The availability of antimicrobials with excellent polymicrobial coverage (eg, β-lactamase inhibitor combinations or carbapenems) may reduce the need for combination therapy in the setting of polymicrobial infections.
3. To decrease the emergence of resistant strains. The value of combination therapy in this setting has been clearly demonstrated for tuberculosis.
4. To decrease dose-related toxicity by using reduced doses of one or more components of the drug regimen. The use of flucytosine in combination with amphotericin B for the treatment of cryptococcal meningitis in non–HIV-infected patients allows for a reduction in amphotericin B dosage with decreased amphotericin B-induced nephrotoxicity.
5. To obtain enhanced inhibition or killing. This use of antimicrobial combinations is discussed in the paragraphs that follow.

SYNERGISM & ANTAGONISM

When the inhibitory or killing effects of two or more antimicrobials used together are significantly greater than expected from their effects when used individually, synergism is said to result. Synergism is marked by a fourfold or greater reduction in the MIC or MBC of each drug when used in combination versus when used alone. Antagonism occurs when the combined inhibitory or killing effects of two or more antimicrobial drugs are significantly less than observed when the drugs are used individually.

Mechanisms of Synergistic Action

The need for synergistic combinations of antimicrobials has been clearly established for the treatment of enterococcal endocarditis. Bactericidal activity is essential for the optimal management of

bacterial endocarditis. Penicillin or ampicillin in combination with gentamicin or streptomycin is superior to monotherapy with a penicillin or vancomycin. When tested alone, penicillins and vancomycin are only bacteriostatic against susceptible enterococcal isolates. When these agents are combined with an aminoglycoside, however, bactericidal activity results. The addition of gentamicin or streptomycin to penicillin allows for a reduction in the duration of therapy for selected patients with viridans streptococcal endocarditis. Some evidence exists that synergistic combinations of antimicrobials may be of benefit in the treatment of gram-negative bacillary infections in febrile neutropenic cancer patients and in systemic infections caused by *Pseudomonas aeruginosa*.

Other synergistic antimicrobial combinations have been shown to be more effective than monotherapy with individual components. Trimethoprim-sulfamethoxazole has been successfully used for the treatment of bacterial infections and *P jiroveci* (*carinii*) pneumonia.* β-Lactamase inhibitors restore the activity of intrinsically active but hydrolyzable β lactams against organisms such as *Staphylococcus aureus* and *Bacteroides fragilis*. Three major mechanisms of antimicrobial synergism have been established:

1. **Blockade of sequential steps in a metabolic sequence:** Trimethoprim-sulfamethoxazole is the best-known example of this mechanism of synergy (see Chapter 46). Blockade of the two sequential steps in the folic acid pathway by trimethoprim-sulfamethoxazole results in a much more complete inhibition of growth than achieved by either component alone.
2. **Inhibition of enzymatic inactivation:** Enzymatic inactivation of β-lactam antibiotics is a major mechanism of antibiotic resistance. Inhibition of β lactamase by β-lactamase inhibitor drugs (eg, sulbactam) results in synergism.
3. **Enhancement of antimicrobial agent uptake:** Penicillins and other cell wall-active agents can increase the uptake of aminoglycosides by a number of bacteria, including staphylococci, enterococci, streptococci, and *P aeruginosa*. Enterococci are thought to be intrinsically resistant to aminoglycosides because of permeability barriers. Similarly, amphotericin B is thought to enhance the uptake of flucytosine by fungi.

Mechanisms of Antagonistic Action

There are few clinically relevant examples of antimicrobial antagonism. The most striking example was reported in a study of patients with pneumococcal meningitis. Patients who were treated with the combination of penicillin and chlortetracycline had a mortality rate of 79% compared with a mortality rate of 21% in patients who received penicillin monotherapy (illustrating the first mechanism set forth below).

The use of an antagonistic antimicrobial combination does not preclude other potential beneficial interactions. For example, rifampin may antagonize the action of anti-staphylococcal penicillins or vancomycin against staphylococci. However, the aforementioned antimicrobials may prevent the emergence of resistance to rifampin.

Two major mechanisms of antimicrobial antagonism have been established:

1. **Inhibition of cidal activity by static agents:** Bacteriostatic agents such as tetracyclines and chloramphenicol can antagonize the action of bactericidal cell wall-active agents because cell wall-active agents require that the bacteria be actively growing and dividing.
2. **Induction of enzymatic inactivation:** Some gram-negative bacilli, including enterobacter species, *P aeruginosa, Serratia marcescens,* and *Citrobacter freundii,* possess inducible β lactamases. β-Lactam antibiotics such as imipenem, cefoxitin, and ampicillin are potent inducers of β-lactamase production. If an inducing agent is combined with an intrinsically active but hydrolyzable β lactam such as piperacillin, antagonism may result.

ANTIMICROBIAL PROPHYLAXIS

Antimicrobial agents are effective in preventing infections in many settings. Antimicrobial prophylaxis should be used in circumstances in which efficacy has been demonstrated and benefits outweigh the risks of prophylaxis. Antimicrobial prophylaxis may be divided into surgical prophylaxis and nonsurgical prophylaxis.

Surgical Prophylaxis

Surgical wound infections are a major category of nosocomial infections. The estimated annual cost of surgical wound infections in the United States is $1.5 billion.

The National Research Council (NRC) Wound Classification Criteria have served as the basis for recommending antimicrobial prophylaxis. NRC criteria consist of four classes [see Box: National Research Council (NRC) Wound Classification Criteria].

The Study of the Efficacy of Nosocomial Infection Control (SENIC) identified four independent risk factors for postoperative wound infections: operations on the abdomen, operations lasting more than 2 hours, contaminated or dirty wound classification, and at least three medical diagnoses. Patients with at least two SENIC risk factors who undergo clean surgical procedures have an increased risk of developing surgical wound infections and should receive antimicrobial prophylaxis.

Surgical procedures that necessitate the use of antimicrobial prophylaxis include contaminated and clean-contaminated operations, selected operations in which postoperative infection may be catastrophic such as open heart surgery, clean procedures that involve placement of prosthetic materials, and any procedure in an immunocompromised host. The operation should carry a significant risk of postoperative site infection or cause significant bacterial contamination.

General principles of antimicrobial surgical prophylaxis include the following:

1. The antibiotic should be active against common surgical wound pathogens; unnecessarily broad coverage should be avoided.
2. The antibiotic should have proved efficacy in clinical trials.

**Pneumocystis jiroveci* is a fungal organism found in humans (*P carinii* infects animals) that responds to antiprotozoal drugs. See Chapter 52.

National Research Council (NRC) Wound Classification Criteria

Clean: Elective, primarily closed procedure; respiratory, gastrointestinal, biliary, genitourinary, or oropharyngeal tract not entered; no acute inflammation and no break in technique; expected infection rate ≤ 2%.

Clean contaminated: Urgent or emergency case that is otherwise clean; elective, controlled opening of respiratory, gastrointestinal, biliary, or oropharyngeal tract; minimal spillage or minor break in technique; expected infection rate ≤ 10%.

Contaminated: Acute nonpurulent inflammation; major technique break or major spill from hollow organ; penetrating trauma less than 4 hours old; chronic open wounds to be grafted or covered; expected infection rate about 20%.

Dirty: Purulence or abscess; preoperative perforation of respiratory, gastrointestinal, biliary, or oropharyngeal tract; penetrating trauma more than 4 hours old; expected infection rate about 40%.

3. The antibiotic must achieve concentrations greater than the MIC of suspected pathogens, and these concentrations must be present at the time of incision.
4. The shortest possible course—ideally a single dose—of the most effective and least toxic antibiotic should be used.
5. The newer broad-spectrum antibiotics should be reserved for therapy of resistant infections.
6. If all other factors are equal, the least expensive agent should be used.

The proper selection and administration of antimicrobial prophylaxis are of utmost importance. Common indications for surgical prophylaxis are shown in Table 51–7. Cefazolin is the prophylactic agent of choice for head and neck, gastroduodenal, biliary tract, gynecologic, and clean procedures. Local wound infection patterns should be considered when selecting antimicrobial prophylaxis. The selection of vancomycin over cefazolin may be necessary in hospitals with high rates of methicillin-resistant *S aureus* or *S epidermidis* infections. The antibiotic should be present in adequate concentrations at the operative site before incision and throughout the procedure; initial dosing is dependent on the volume of distribution, peak levels, clearance, protein binding, and bioavailability. Parenteral agents should be administered during the interval beginning 60 minutes before incision; administration up to the time of incision is preferred. In cesarean section, the antibiotic is administered after umbilical cord clamping. If short-acting agents such as cefoxitin are used, doses should be repeated if the procedure exceeds 3–4 hours in duration. Single-dose prophylaxis is effective for most procedures and results in decreased toxicity and antimicrobial resistance.

Improper administration of antimicrobial prophylaxis leads to excessive surgical wound infection rates. Common errors in antibiotic prophylaxis include selection of the wrong antibiotic,

TABLE 51–7 Recommendations for surgical antimicrobial prophylaxis.

Type of Operation	Common Pathogens	Drug of Choice
Cardiac (with median sternotomy)	Staphylococci, enteric gram-negative rods	Cefazolin
Noncardiac, thoracic	Staphylococci, streptococci, enteric gram-negative rods	Cefazolin
Vascular (abdominal and lower extremity)	Staphylococci, enteric gram-negative rods	Cefazolin
Neurosurgical (craniotomy)	Staphylococci	Cefazolin
Orthopedic (with hardware insertion)	Staphylococci	Cefazolin
Head and neck (with entry into the oropharynx)	*S aureus,* oral flora	Cefazolin + metronidazole
Gastroduodenal (high-risk patients[1])	*S aureus,* oral flora, enteric gram-negative rods	Cefazolin
Biliary tract (high-risk patients[2])	*S aureus,* enterococci, enteric gram-negative rods	Cefazolin
Colorectal (elective surgery)	Enteric gram-negative rods, anaerobes	Oral erythromycin plus neomycin[3]
Colorectal (emergency surgery or obstruction)	Enteric gram-negative rods, anaerobes	Cefoxitin, cefotetan, or cefazolin + metronidazole
Appendectomy, nonperforated	Enteric gram-negative rods, anaerobes	Cefoxitin or cefazolin + metronidazole
Hysterectomy	Enteric gram-negative rods, anaerobes, enterococci, group B streptococci	Cefazolin or cefoxitin
Cesarean section	Enteric gram-negative rods, anaerobes, enterococci, group B streptococci	Cefazolin[4]

[1]Gastric procedures for cancer, ulcer, bleeding, or obstruction; morbid obesity; suppression of gastric acid secretion.

[2]Age > 60, acute cholecystitis, prior biliary tract surgery, common duct stones, jaundice, or diabetes mellitus.

[3]In conjunction with mechanical bowel preparation.

[4]Administer immediately following cord clamping.

TABLE 51–8 Recommendations for nonsurgical antimicrobial prophylaxis.

Infection to Be Prevented	Indication(s)	Drug of Choice	Efficacy
Anthrax	Suspected exposure	Ciprofloxacin or doxycycline	Proposed effective
Cholera	Close contacts of a case	Tetracycline	Proposed effective
Diphtheria	Unimmunized contacts	Penicillin or erythromycin	Proposed effective
Endocarditis	Dental, oral, or upper respiratory tract procedures[1] in at-risk patients[2]	Amoxicillin or clindamycin	Proposed effective
Genital herpes simplex	Recurrent infection (≥ 4 episodes per year)	Acyclovir	Excellent
Perinatal herpes simplex type 2 infection	Mothers with primary HSV or frequent recurrent genital HSV	Acyclovir	Proposed effective
Group B streptococcal (GBS) infection	Mothers with cervical or vaginal GBS colonization and their newborns with one or more of the following: (a) onset of labor or membrane rupture before 37 weeks' gestation, (b) prolonged rupture of membranes (> 12 hours), (c) maternal intrapartum fever, (d) history of GBS bacteriuria during pregnancy, (e) mothers who have given birth to infants who had early GBS disease or with a history of streptococcal bacteriuria during pregnancy	Ampicillin or penicillin	Excellent
Haemophilus influenzae type B infection	Close contacts of a case in incompletely immunized children (> 48 months old)	Rifampin	Excellent
HIV infection	Health care workers exposed to blood after needle-stick injury	Tenofovir/emtricitabine ± lopinavir/ritonavir	Good
	Pregnant HIV-infected women who are at ≥ 14 weeks of gestation; newborns of HIV-infected women for the first 6 weeks of life, beginning 8–12 hours after birth	HAART[3]	Excellent
Influenza A and B	Unvaccinated geriatric patients, immunocompromised hosts, and health care workers during outbreaks	Oseltamivir	Good
Malaria	Travelers to areas endemic for chloroquine-susceptible disease	Chloroquine	Excellent
	Travelers to areas endemic for chloroquine-resistant disease	Mefloquine, doxycycline, or atovaquone/proguanil	Excellent
Meningococcal infection	Close contacts of a case	Rifampin, ciprofloxacin, or ceftriaxone	Excellent
Mycobacterium avium complex	HIV-infected patients with CD4 count < 75/μL	Azithromycin, clarithromycin, or rifabutin	Excellent
Otitis media	Recurrent infection	Amoxicillin	Good
Pertussis	Close contacts of a case	Azithromycin	Excellent
Plague	Close contacts of a case	Tetracycline	Proposed effective
Pneumococcemia	Children with sickle cell disease or asplenia	Penicillin	Excellent
Pneumocystis jiroveci pneumonia (PCP)	High-risk patients (eg, AIDS, leukemia, transplant)	Trimethoprim-sulfamethoxazole, dapsone, or atovaquone	Excellent
Rheumatic fever	History of rheumatic fever or known rheumatic heart disease	Benzathine penicillin	Excellent
Toxoplasmosis	HIV-infected patients with IgG antibody to *Toxoplasma* and CD4 count < 100/μL	Trimethoprim-sulfamethoxazole	Good
Tuberculosis	Persons with positive tuberculin skin tests and one or more of the following: (a) HIV infection, (b) close contacts with newly diagnosed disease, (c) recent skin test conversion, (d) medical conditions that increase the risk of developing tuberculosis, (e) age < 35	Isoniazid, rifampin, or pyrazinamide	Excellent
Urinary tract infections (UTI)	Recurrent infection	Trimethoprim-sulfamethoxazole	Excellent

[1]Prophylaxis is recommended for the following: dental procedures that involve manipulation of gingival tissue or the periapical region of teeth or perforation of the oral mucosa, and invasive procedure of the respiratory tract that involves incision or biopsy of the respiratory mucosa, such as tonsillectomy and adenoidectomy.

[2]Prophylaxis should be targeted to those with the following risk factors: prosthetic heart valves, previous bacterial endocarditis, congenital cardiac malformations, cardiac transplantation patients who develop cardiac valvulopathy.

[3]Highly active antiretroviral therapy. See http://www.hivatis.org/ for updated guidelines.

administering the first dose too early or too late, failure to repeat doses during prolonged procedures, excessive duration of prophylaxis, and inappropriate use of broad-spectrum antibiotics.

Nonsurgical Prophylaxis

Nonsurgical prophylaxis includes the administration of antimicrobials to prevent colonization or asymptomatic infection as well as the administration of drugs following colonization by or inoculation of pathogens but before the development of disease. Nonsurgical prophylaxis is indicated in individuals who are at high risk for temporary exposure to selected virulent pathogens and in patients who are at increased risk for developing infection because of underlying disease (eg, immunocompromised hosts). Prophylaxis is most effective when directed against organisms that are predictably susceptible to antimicrobial agents. Common indications and drugs for nonsurgical prophylaxis are listed in Table 51–8.

REFERENCES

American Thoracic Society: Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. Am J Respir Crit Care Med 2005;171:388.

Antimicrobial prophylaxis for surgery. Treat Guidel Med Lett 2009;7:47.

Baddour LM et al: Infective endocarditis: Diagnosis, antimicrobial therapy, and management of complications. Circulation 2005;111:3167.

Blumberg HM et al: American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America: Treatment of tuberculosis. Am J Respir Crit Care Med 2003;167:603.

Bochner BS et al: Anaphylaxis. N Engl J Med 1991;324:1785.

Bratzler DW et al: Antimicrobial prophylaxis for surgery: An advisory statement from the National Surgical Infection Prevention Project. Clin Infect Dis 2004;38:1706.

Gonzales R et al: Principles of appropriate antibiotic use for treatment of acute respiratory tract infections in adults: Background, specific aims, and methods. Ann Intern Med 2001;134:479.

Guidelines for prevention and treatment of opportunistic infections in HIV-infected adults and adolescents. Recommendations of the National Institutes of Health (NIH), the Centers for Disease Control and Prevention (CDC), and the HIV Medicine Association of the Infectious Diseases Society of America (HIVMA/IDSA). AIDSinfo April 10, 2009. http://AIDSinfo.nih.gov

Jones RN, Pfaller MA: Bacterial resistance: A worldwide problem. Diagn Microbiol Infect Dis 1998;31:379.

Kaye KS, Kaye D: Antibacterial therapy and newer agents. Infect Dis Clin North Am 2009;23:757.

Mandell LA et al: Infectious Diseases Society of America/American Thoracic Society Consensus guidelines on the management of community-acquired pneumonia in adults. Clin Infect Dis 2007;44:S27.

Mazuski JE: Surgical infections. Surg Clin North Am 2009;89:295.

National Nosocomial Infections Surveillance (NNIS) System Report, Data Summary from January 1992–June 2004, issued October 2004. Am J Infect Control 2004;32:470.

Sexually transmitted diseases treatment guidelines 2006. Centers for Disease Control and Prevention. MMWR Morb Mortal Wkly Rep 2006;54(RR-11):1.

Tunkel AR et al: Practice guidelines for the management of bacterial meningitis. Clin Infect Dis 2004;39:1267.

Wilson W et al: Prevention of infective endocarditis: Guidelines from the American Heart Association. Circulation 2007;116:1736.

CASE STUDY ANSWER

The most likely diagnosis for this patient is *Streptococcus pneumoniae* meningitis, the most common bacterial cause of meningitis in adults. Other possible microbiologic etiologies include *Neisseria meningitidis, Listeria monocytogenes,* and enteric gram-negative bacilli. Intravenous antimicrobials to which local strains of these organisms are sensitive should be started while awaiting culture and sensitivity results. In addition, the use of dexamethasone has also been demonstrated to reduce mortality in adults with pneumococcal meningitis in conjunction with appropriate antimicrobial therapy.

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CHAPTER 52

Antiprotozoal Drugs

Philip J. Rosenthal, MD

CASE STUDY

A 5-year-old American girl presents with a 1-week history of intermittent chills, fever, and sweats. She had returned home 2 weeks earlier after leaving the United States for the first time to spend 3 weeks with her grandparents in Nigeria. She received all standard childhood immunizations, but no additional treatment before travel, since her parents have returned to their native Nigeria frequently without medical consequences. Three days ago, the child was seen in an outpatient clinic and diagnosed with a viral syndrome. Examination reveals a lethargic child, with a temperature of 39.8°C (103.6°F) and splenomegaly. She has no skin rash or lymphadenopathy. Initial laboratory studies are remarkable for hematocrit 29.8%, platelets 45,000/mm^3, creatinine 2.5 mg/dL (220 µmol/L), and mildly elevated bilirubin and transaminases. A blood smear shows ring forms of *Plasmodium falciparum* at 1.5% parasitemia. What treatment should be started?

MALARIA

Malaria is the most important parasitic disease of humans and causes hundreds of millions of illnesses per year. Four species of plasmodium typically cause human malaria: *Plasmodium falciparum, P vivax, P malariae,* and *P ovale.* A fifth species, *P knowlesi,* is primarily a pathogen of monkeys, but has recently been recognized to cause illness, including severe disease, in humans in Asia. Although all of the latter species may cause significant illness, *P falciparum* is responsible for the majority of serious complications and deaths. Drug resistance is an important therapeutic problem, most notably with *P falciparum.*

PARASITE LIFE CYCLE

An anopheline mosquito inoculates plasmodium sporozoites to initiate human infection (Figure 52–1). Circulating sporozoites rapidly invade liver cells, and exoerythrocytic stage tissue schizonts mature in the liver. Merozoites are subsequently released from the liver and invade erythrocytes. Only erythrocytic parasites cause clinical illness. Repeated cycles of infection can lead to the infection of many erythrocytes and serious disease. Sexual stage gametocytes also develop in erythrocytes before being taken up by mosquitoes, where they develop into infective sporozoites.

In *P falciparum* and *P malariae* infection, only one cycle of liver cell invasion and multiplication occurs, and liver infection ceases spontaneously in less than 4 weeks. Thus, treatment that eliminates erythrocytic parasites will cure these infections. In *P vivax* and *P ovale* infections, a dormant hepatic stage, the hypnozoite, is not eradicated by most drugs, and subsequent relapses can therefore occur after therapy directed against erythrocytic parasites. Eradication of both erythrocytic and hepatic parasites is required to cure these infections and usually requires two or more drugs.

DRUG CLASSIFICATION

Several classes of antimalarial drugs are available (Table 52–1 and Figure 52–2). Drugs that eliminate developing or dormant liver forms are called **tissue schizonticides;** those that act on erythrocytic parasites are **blood schizonticides;** and those that kill sexual stages and prevent transmission to mosquitoes are **gametocides.** No single available agent can reliably effect a **radical cure,** ie, eliminate both hepatic and erythrocytic stages. Few available agents are **causal prophylactic drugs,** ie, capable of preventing erythrocytic infection. However, all effective chemoprophylactic agents kill erythrocytic parasites before they increase sufficiently in number to cause clinical disease.

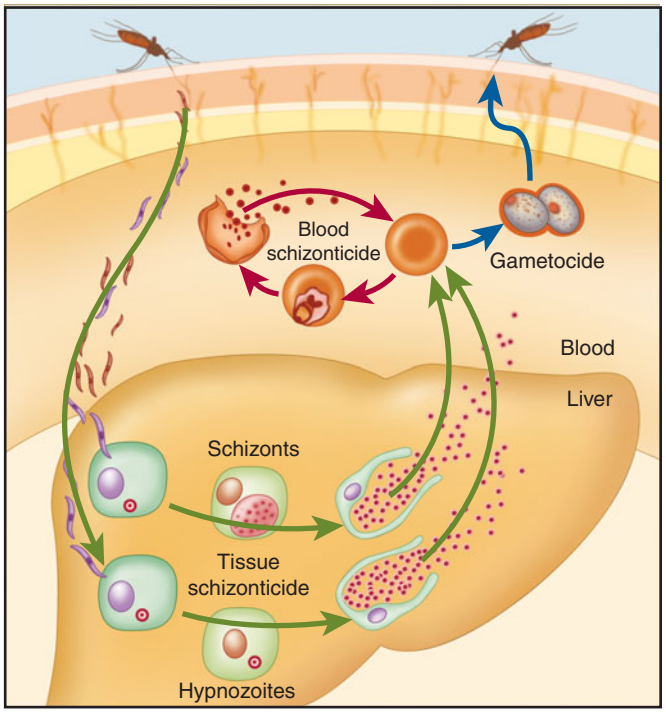

FIGURE 52–1 Life cycle of malaria parasites. Only the asexual erythrocytic stage of infection causes clinical malaria. All effective antimalarial treatments are blood schizonticides that kill this stage. (Reproduced, with permission, from Baird JK: Effectiveness of antimalarial drugs. N Engl J M 2005;352:1565.)

CHEMOPROPHYLAXIS & TREATMENT

When patients are counseled on the prevention of malaria, it is imperative to emphasize measures to prevent mosquito bites (eg, with insect repellents, insecticides, and bed nets), because parasites are increasingly resistant to multiple drugs and no chemoprophylactic regimen is fully protective. Current recommendations from the Centers for Disease Control and Prevention (CDC) include the use of chloroquine for chemoprophylaxis in the few areas infested by only chloroquine-sensitive malaria parasites (principally the Caribbean and Central America west of the Panama Canal), mefloquine or Malarone* for most other malarious areas, and doxycycline for areas with a very high prevalence of multidrug-resistant falciparum malaria (principally border areas of Thailand) (Table 52–2). CDC recommendations should be checked regularly (Phone: 770-488-7788; Internet: http://www.cdc.gov/malaria), because these may change in response to changing resistance patterns and increasing experience with new drugs. In some circumstances, it may be appropriate for travelers to carry supplies of drugs with them in case they develop a febrile illness when medical attention is unavailable. Regimens for self-treatment include new artemisinin-based combination therapies (see below), which are widely available internationally (and, in the case of Coartem**, in the USA); Malarone; mefloquine; and quinine. Most authorities do not recommend routine terminal chemoprophylaxis with primaquine to eradicate dormant hepatic stages of *P vivax* and *P ovale* after travel, but this may be appropriate in some circumstances, especially for travelers with major exposure to these parasites.

Multiple drugs are available for the treatment of malaria that presents in the USA (Table 52–3). Most nonfalciparum infections and falciparum malaria from areas without known resistance should be treated with chloroquine. For vivax malaria from areas with suspected chloroquine resistance, including Indonesia and Papua New Guinea, other therapies effective against falciparum malaria may be used. Vivax and ovale malaria should subsequently be treated with primaquine to eradicate liver forms. Uncomplicated falciparum malaria from most areas is typically treated with Malarone or oral quinine, but new artemisinin-based combinations are increasingly the international standard of care, and one combination, Coartem, is now available in the USA. Other agents that are generally effective against resistant falciparum malaria include mefloquine and halofantrine, both of which have toxicity concerns at treatment dosages. Severe falciparum malaria is treated with intravenous artesunate, quinidine, or quinine (intravenous quinine is not available in the USA).

CHLOROQUINE

Chloroquine has been the drug of choice for both treatment and chemoprophylaxis of malaria since the 1940s, but its usefulness against *P falciparum* has been seriously compromised by drug resistance. It remains the drug of choice in the treatment of sensitive *P falciparum* and other species of human malaria parasites.

Chemistry & Pharmacokinetics

Chloroquine is a synthetic 4-aminoquinoline (Figure 52–2) formulated as the phosphate salt for oral use. It is rapidly and almost completely absorbed from the gastrointestinal tract, reaches maximum plasma concentrations in about 3 hours, and is rapidly distributed to the tissues. It has a very large apparent volume of distribution of 100–1000 L/kg and is slowly released from tissues and metabolized. Chloroquine is principally excreted in the urine with an initial half-life of 3–5 days but a much longer terminal elimination half-life of 1–2 months.

Antimalarial Action & Resistance

When not limited by resistance, chloroquine is a highly effective blood schizonticide. It is also moderately effective against gametocytes of *P vivax, P ovale,* and *P malariae* but not against those of *P falciparum.* Chloroquine is not active against liver stage parasites. Chloroquine probably acts by concentrating in parasite food

*Malarone is a proprietary formulation of atovaquone plus proguanil.

**Coartem is a proprietary formulation of artemether and lumefantrine.

TABLE 52–1 Major antimalarial drugs.

Drug	Class	Use
Chloroquine	4-Aminoquinoline	Treatment and chemoprophylaxis of infection with sensitive parasites
Amodiaquine[1]	4-Aminoquinoline	Treatment of infection with some chloroquine-resistant *P falciparum* strains and in fixed combination with artesunate
Piperaquine[1]	Bisquinoline	Treatment of *P falciparum* infection in fixed combination with dihydroartemisinin
Quinine	Quinoline methanol	Oral and intravenous[1] treatment of *P falciparum* infections
Quinidine	Quinoline methanol	Intravenous therapy of severe infections with *P falciparum*
Mefloquine	Quinoline methanol	Chemoprophylaxis and treatment of infections with *P falciparum*
Primaquine	8-Aminoquinoline	Radical cure and terminal prophylaxis of infections with *P vivax* and *P ovale*; alternative chemoprophylaxis for all species
Sulfadoxine-pyrimethamine (Fansidar)	Folate antagonist combination	Treatment of infections with some chloroquine-resistant *P falciparum,* including combination with artesunate; intermittent preventive therapy in endemic areas
Atovaquone-proguanil (Malarone)	Quinone-folate antagonist combination	Treatment and chemoprophylaxis of *P falciparum* infection
Doxycycline	Tetracycline	Treatment (with quinine) of infections with *P falciparum;* chemoprophylaxis
Halofantrine[1]	Phenanthrene methanol	Treatment of *P falciparum* infections
Lumefantrine[2]	Amyl alcohol	Treatment of *P falciparum* malaria in fixed combination with artemether (Coartem)
Artemisinins (artesunate, artemether,[2] dihydro-artemisinin[1])	Sesquiterpene lactone endoperoxides	Treatment of *P falciparum* infections; oral combination therapies for uncomplicated disease; intravenous artesunate for severe disease

[1]Not available in the USA.

[2]Available in the USA only as the fixed combination Coartem.

vacuoles, preventing the biocrystallization of the hemoglobin breakdown product, heme, into hemozoin, and thus eliciting parasite toxicity due to the buildup of free heme.

Resistance to chloroquine is now very common among strains of *P falciparum* and uncommon but increasing for *P vivax.* In *P falciparum,* mutations in a putative transporter, PfCRT, have been correlated with resistance. Chloroquine resistance can be reversed by certain agents, including verapamil, desipramine, and chlorpheniramine, but the clinical value of resistance-reversing drugs is not established.

Clinical Uses

A. Treatment

Chloroquine is the drug of choice in the treatment of nonfalciparum and sensitive falciparum malaria. It rapidly terminates fever (in 24–48 hours) and clears parasitemia (in 48–72 hours) caused by sensitive parasites. It is still used to treat falciparum malaria in some areas with widespread resistance, in particular much of Africa, owing to its safety, low cost, antipyretic properties, and partial activity, but continued use of chloroquine for this purpose is discouraged, especially in nonimmune individuals. Chloroquine has been replaced by other drugs, principally artemisinin-based combination therapies, as the standard therapy to treat falciparum malaria in most endemic countries. Chloroquine does not eliminate dormant liver forms of *P vivax* and *P ovale,* and for that reason primaquine must be added for the radical cure of these species.

B. Chemoprophylaxis

Chloroquine is the preferred chemoprophylactic agent in malarious regions without resistant falciparum malaria. Eradication of *P vivax* and *P ovale* requires a course of primaquine to clear hepatic stages.

C. Amebic Liver Abscess

Chloroquine reaches high liver concentrations and may be used for amebic abscesses that fail initial therapy with metronidazole (see below).

Adverse Effects

Chloroquine is usually very well tolerated, even with prolonged use. Pruritus is common, primarily in Africans. Nausea, vomiting, abdominal pain, headache, anorexia, malaise, blurring of vision, and urticaria are uncommon. Dosing after meals may reduce some adverse effects. Rare reactions include hemolysis in glucose-6-phosphate dehydrogenase (G6PD)-deficient persons, impaired hearing, confusion, psychosis, seizures, agranulocytosis, exfoliative dermatitis, alopecia, bleaching of hair, hypotension,

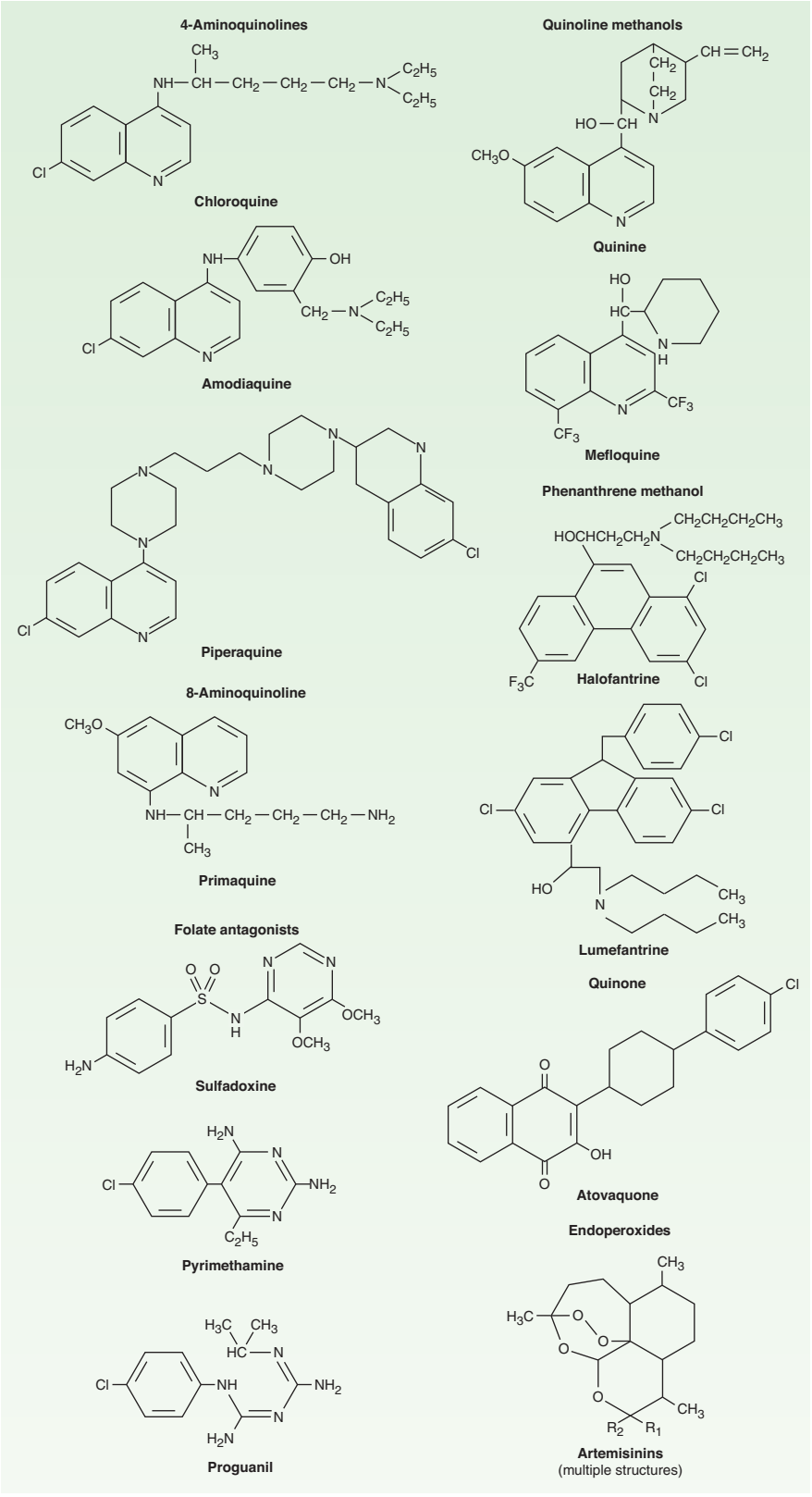

FIGURE 52–2 Structural formulas of antimalarial drugs.

TABLE 52–2 Drugs for the prevention of malaria in travelers.[1]

Drug	Use[2]	Adult Dosage[3]
Chloroquine	Areas without resistant *P falciparum*	500 mg weekly
Malarone	Areas with chloroquine-resistant *P falciparum*	1 tablet (250 mg atovaquone/100 mg proguanil) daily
Mefloquine	Areas with chloroquine-resistant *P falciparum*	250 mg weekly
Doxycycline	Areas with multidrug-resistant *P falciparum*	100 mg daily
Primaquine[4]	Terminal prophylaxis of *P vivax* and *P ovale* infections; alternative for primary prevention	52.6 mg (30 mg base) daily for 14 days after travel; for primary prevention 52.6 mg (30 mg base) daily

[1]Recommendations may change, as resistance to all available drugs is increasing. See text for additional information on toxicities and cautions. For additional details and pediatric dosing, see CDC guidelines (phone: 877-FYI-TRIP; http://www.cdc.gov). Travelers to remote areas should consider carrying effective therapy (see text) for use if they develop a febrile illness and cannot reach medical attention quickly.

[2]Areas without known chloroquine-resistant *P falciparum* are Central America west of the Panama Canal, Haiti, Dominican Republic, Egypt, and most malarious countries of the Middle East. Malarone or mefloquine are currently recommended for other malarious areas except for border areas of Thailand, where doxycycline is recommended.

[3]For drugs other than primaquine, begin 1–2 weeks before departure (except 2 days before for doxycycline and Malarone) and continue for 4 weeks after leaving the endemic area (except 1 week for Malarone). All dosages refer to salts.

[4]Screen for glucose-6-phosphate dehydrogenase (G6PD) deficiency before using primaquine.

TABLE 52–3 Treatment of malaria.

Clinical Setting	Drug Therapy[1]	Alternative Drugs
Chloroquine-sensitive *P falciparum* and *P malariae* infections	Chloroquine phosphate, 1 g, followed by 500 mg at 6, 24, and 48 hours *or* Chloroquine phosphate, 1 g at 0 and 24 hours, then 0.5 g at 48 hours	
P vivax and *P ovale* infections	Chloroquine (as above), then (if G6PD normal) primaquine, 52.6 (30 mg base) for 14 days	For infections from Indonesia, Papua New Guinea, and other areas with suspected resistance: therapies listed for uncomplicated chloroquine-resistant *P falciparum* plus primaquine
Uncomplicated infections with chloroquine-resistant *P falciparum*	Coartem (artemether, 20 mg, plus lumefantrine, 120 mg), four tablets twice daily for 3 days	Malarone, four tablets (total of 1 g atovaquone, 400 mg proguanil) daily for 3 days *or* Mefloquine, 15 mg/kg once or 750 mg, then 500 mg in 6–8 hours *or* Quinine sulfate, 650 mg 3 times daily for 3 days, plus doxycycline, 100 mg twice daily for 7 days, or clindamycin, 600 mg twice daily for 7 days *or* Other artemisinin-based combination regimens (see Table 52–4)
Severe or complicated infections with *P falciparum*	Artesunate,[2] 2.4 mg/kg IV, every 12 hours for 1 day, then daily for 2 additional days; follow with 7-day oral course of doxycycline or clindamycin or full treatment course of Coartem, Malarone, or mefloquine *or* Quinidine gluconate,[4,5] 10 mg/kg IV over 1–2 hours, then 0.02 mg/kg IV/min *or* Quinidine gluconate[4,5] 15 mg/kg IV over 4 hours, then 7.5 mg/kg IV over 4 hours every 8 hours	Artemether,[3] 3.2 mg/kg IM, then 1.6 mg/kg/d IM; follow with oral therapy as for artesunate *or* Quinine dihydrochloride,[3–5] 20 mg/kg IV, then 10 mg/kg every 8 hours

[1]All dosages are oral and refer to salts unless otherwise indicated. See text for additional information on all agents, including toxicities and cautions. See CDC guidelines (phone: 770-488-7788; http://www.cdc.gov) for additional information and pediatric dosing.

[2]Available in the United States only on an investigational basis through the CDC (phone: 770-488-7788).

[3]Not available in the USA.

[4]Cardiac monitoring should be in place during intravenous administration of intravenous quinidine or quinine. Change to an oral regimen as soon as the patient can tolerate it.

[5]Avoid loading doses in persons who have received quinine, quinidine, or mefloquine in the prior 24 hours.

G6PD, glucose-6-phosphate dehydrogenase.

and electrocardiographic changes (QRS widening, T-wave abnormalities). The long-term administration of high doses of chloroquine for rheumatologic diseases (see Chapter 36) can result in irreversible ototoxicity, retinopathy, myopathy, and peripheral neuropathy. These abnormalities are rarely if ever seen with standard-dose weekly chemoprophylaxis, even when given for prolonged periods. Large intramuscular injections or rapid intravenous infusions of chloroquine hydrochloride can result in severe hypotension and respiratory and cardiac arrest. Parenteral administration of chloroquine is best avoided, but if other drugs are not available for parenteral use, it should be infused slowly.

Contraindications & Cautions

Chloroquine is contraindicated in patients with psoriasis or porphyria, in whom it may precipitate acute attacks of these diseases. It should generally not be used in those with retinal or visual field abnormalities or myopathy. Chloroquine should be used with caution in patients with a history of liver disease or neurologic or hematologic disorders. The antidiarrheal agent kaolin and calcium- and magnesium-containing antacids interfere with the absorption of chloroquine and should not be co-administered with the drug. Chloroquine is considered safe in pregnancy and for young children.

OTHER QUINOLINES

Amodiaquine is closely related to chloroquine, and it probably shares mechanisms of action and resistance with that drug. Amodiaquine has been widely used to treat malaria because of its low cost, limited toxicity, and, in some areas, effectiveness against chloroquine-resistant strains of *P falciparum.* Reports of toxicities of amodiaquine, including agranulocytosis, aplastic anemia, and hepatotoxicity, have limited use of the drug in recent years. However, recent reevaluation has shown that serious toxicity from amodiaquine is rare, and it may be used as a replacement for chloroquine in areas with high rates of resistance but limited resources. The most important current use of amodiaquine is in combination therapy. The World Health Organization (WHO) lists amodiaquine plus artesunate as a recommended therapy for falciparum malaria in areas with resistance to older drugs (Table 52–4). This combination is now available as a single tablet (ASAQ, Arsucam, Coarsucam) and is the first-line therapy for the treatment of uncomplicated falciparum malaria in many countries in Africa. Another combination, amodiaquine plus sulfadoxine-pyrimethamine, remains reasonably effective for the treatment of falciparum malaria in many areas with some resistance to the individual drugs, and it is a preferred alternative treatment if artemisinin-containing therapies are unavailable. Chemoprophylaxis with amodiaquine is best avoided because of its apparent increased toxicity with long-term use.

Piperaquine is a bisquinoline that was used widely to treat chloroquine-resistant falciparum malaria in China in the 1970s through the 1980s, but its use waned after resistance became widespread. Recently, piperaquine has been combined with dihydroartemisinin in co-formulated tablets (Artekin, Duocotecxin) that have shown excellent efficacy and safety for the treatment of falciparum malaria, without apparent drug resistance. Piperaquine has a longer half-life (~ 28 days) than amodiaquine (~ 14 days), mefloquine (~ 14 days), or lumefantrine (~ 4 days), leading to a longer period of post-treatment prophylaxis with dihydroartemisinin-piperaquine than with the other leading artemisinin-based combinations; this feature should be particularly advantageous in high transmission areas. Dihydroartemisinin-piperaquine is now the first-line therapy for the treatment of uncomplicated malaria in Vietnam.

TABLE 52–4 WHO recommendations for the treatment of falciparum malaria.

Regimen	Notes
Artemether-lumefantrine (Coartem, Riamet)	Co-formulated; first-line therapy in many countries; approved in the USA
Artesunate-amodiaquine (ASAQ, Arsucam, Coarsucam)	Co-formulated; first-line therapy in many African countries
Artesunate-mefloquine	Co-formulated; first-line therapy in parts of Southeast Asia and South America
Dihydroartemisinin-piperaquine (Artekin, Duocotecxin)	Co-formulated; first-line therapy in some countries in Southeast Asia
Artesunate-sulfadoxine-pyrimethamine	First-line therapy in some countries, but efficacy lower than other regimens in most areas

World Health Organization: Guidelines for the Treatment of Malaria. World Health Organization. Geneva, 2010.

ARTEMISININ & ITS DERIVATIVES

Artemisinin **(qinghaosu)** is a sesquiterpene lactone endoperoxide (Figure 52–2), the active component of an herbal medicine that has been used as an antipyretic in China for over 2000 years. Artemisinin is insoluble and can only be used orally. Analogs have been synthesized to increase solubility and improve antimalarial efficacy. The most important of these analogs are **artesunate** (water-soluble; useful for oral, intravenous, intramuscular, and rectal administration), **artemether** (lipid-soluble; useful for oral, intramuscular, and rectal administration), and **dihydroartemisinin** (water-soluble; useful for oral administration).

Chemistry & Pharmacokinetics

Artemisinin and its analogs are rapidly absorbed, with peak plasma levels occurring in 1–2 hours and half-lives of 1–3 hours after oral administration. Artemisinin, artesunate, and artemether are rapidly metabolized to the active metabolite dihydroartemisinin. Drug levels appear to decrease after a number of days of therapy.

Antimalarial Action & Resistance

The artemisinins are now widely available around the world. However, artemisinin monotherapy for the treatment of uncomplicated malaria is now strongly discouraged. Rather, co-formulated artemisinin-based combination therapies are recommended to improve efficacy and prevent the selection of artemisinin-resistant parasites. The oral combination regimen Coartem (artemether-lumefantrine) was approved by the Food and Drug Administration (FDA) in 2009, and may be considered the new first-line therapy in the USA for uncomplicated falciparum malaria, although the drug may not be widely available. Intravenous artesunate was made available by the CDC in 2007; use of the drug can be initiated by contact with the CDC, which will release the drug for appropriate indications (falciparum malaria with signs of severe disease or inability to take oral medications) from stocks stored around the USA.

Artemisinin and its analogs are very rapidly acting blood schizonticides against all human malaria parasites. Artemisinins have no effect on hepatic stages. The antimalarial activity of artemisinins may result from the production of free radicals that follows the iron-catalyzed cleavage of the artemisinin endoperoxide bridge in the parasite food vacuole or from inhibition of a parasite calcium ATPase. Artemisinin resistance is not yet an important problem, but *P falciparum* isolates with diminished in vitro susceptibility to artemether have recently been described. In addition, increasing rates of treatment failure and increases in parasite clearance times after use of artesunate or artesunate-mefloquine in parts of Cambodia may be early signs of a worrisome decrease in artesunate efficacy.

Clinical Uses

Artemisinin-based combination therapy is now the standard for treatment of uncomplicated falciparum malaria in nearly all areas endemic for falciparum malaria. These regimens were developed because the short plasma half-lives of the artemisinins led to unacceptably high recrudescence rates after short-course therapy, which were reversed by inclusion of longer-acting drugs. Combination therapy also helps to protect against the selection of artemisinin resistance. However, with completion of dosing after 3 days, the artemisinin components are rapidly eliminated, and so selection of resistance to partner drugs is of concern.

The WHO recommends five artemisinin-based combinations for the treatment of uncomplicated falciparum malaria (Table 52–4). One of these, artesunate-sulfadoxine-pyrimethamine is not recommended in many areas owing to unacceptable levels of resistance to sulfadoxine-pyrimethamine, but it is the first-line therapy in some countries in Asia, South America, and North Africa. The other four recommended regimens are now all available as combination formulations, although manufacturing standards may vary. Artesunate-mefloquine is highly effective in Southeast Asia, where resistance to many antimalarials is common; it is the first-line therapy in some countries in Southeast Asia and South America. This regimen is less practical for other areas, particularly Africa, because of its relatively high cost and poor tolerability. Either artesunate-amodiaquine or artemether-lumefantrine is now the standard treatment for uncomplicated falciparum malaria in most countries in Africa and some additional endemic countries on other continents. Dihydroartemisinin-piperaquine is a newer regimen that has shown excellent efficacy; it is the first-line therapy for falciparum malaria in Vietnam.

The relative efficacy and safety of artemisinin-based combination therapies are now under active investigation. In general, the leading regimens are highly efficacious, safe, and well tolerated, and they are the new standard of care for the treatment of uncomplicated falciparum malaria.

Artemisinins are also proving to have outstanding efficacy in the treatment of complicated falciparum malaria. Large randomized trials and meta-analyses have shown that intramuscular artemether has an efficacy equivalent to that of quinine and that intravenous artesunate is superior to intravenous quinine in terms of parasite clearance time and—most important—patient survival. Intravenous artesunate also has a superior side-effect profile compared with that of intravenous quinine or quinidine. Thus, intravenous artesunate will likely replace quinine as the standard of care for the treatment of severe falciparum malaria, although it is not yet widely available in most areas. Artesunate and artemether have also been effective in the treatment of severe malaria when administered rectally, offering a valuable treatment modality when parenteral therapy is not available.

Adverse Effects & Cautions

Artemisinins are generally very well tolerated. The most commonly reported adverse effects are nausea, vomiting, diarrhea, and dizziness, and these may often be due to underlying malaria rather than the medications. Rare serious toxicities include neutropenia, anemia, hemolysis, elevated liver enzymes, and allergic reactions. Irreversible neurotoxicity has been seen in animals, but only after doses much higher than those used to treat malaria. Artemisinins have been embryotoxic in animal studies, but rates of congenital abnormalities, stillbirths, and abortions were not elevated, compared with those of controls, in women who received artemisinins during pregnancy. Based on this information and the significant risk of malaria during pregnancy, the WHO recommends artemisinin-based combination therapies for the treatment of uncomplicated falciparum malaria during the second and third trimesters of pregnancy, intravenous artesunate or quinine for the treatment of severe malaria during the first trimester, and intravenous artesunate for treatment of severe malaria during the second and third trimesters.

QUININE & QUINIDINE

Quinine and quinidine remain important therapies for falciparum malaria—especially severe disease—although toxicity may complicate therapy. Resistance to quinine is uncommon but may be increasing.

Chemistry & Pharmacokinetics

Quinine is derived from the bark of the cinchona tree, a traditional remedy for intermittent fevers from South America. The

alkaloid quinine was purified from the bark in 1820, and it has been used in the treatment and prevention of malaria since that time. Quinidine, the dextrorotatory stereoisomer of quinine, is at least as effective as parenteral quinine in the treatment of severe falciparum malaria. After oral administration, quinine is rapidly absorbed, reaches peak plasma levels in 1–3 hours, and is widely distributed in body tissues. The use of a loading dose in severe malaria allows the achievement of peak levels within a few hours. The pharmacokinetics of quinine varies among populations. Individuals with malaria develop higher plasma levels of the drug than healthy controls, but toxicity is not increased, apparently because of increased protein binding. The half-life of quinine also is longer in those with severe malaria (18 hours) than in healthy controls (11 hours). Quinidine has a shorter half-life than quinine, mostly as a result of decreased protein binding. Quinine is primarily metabolized in the liver and excreted in the urine.

Antimalarial Action & Resistance

Quinine is a rapid-acting, highly effective blood schizonticide against the four species of human malaria parasites. The drug is gametocidal against *P vivax* and *P ovale* but not *P falciparum.* It is not active against liver stage parasites. The mechanism of action of quinine is unknown.

Increasing in vitro resistance of parasites from a number of areas suggests that quinine resistance will be an increasing problem. Resistance to quinine is already common in some areas of Southeast Asia, especially border areas of Thailand, where the drug may fail if used alone to treat falciparum malaria. However, quinine still provides at least a partial therapeutic effect in most patients.

Clinical Uses

A. Parenteral Treatment of Severe Falciparum Malaria

For many years, quinine dihydrochloride or quinidine gluconate have been the treatments of choice for severe falciparum malaria, although intravenous artesunate now provides an alternative for this indication. Quinine can be administered slowly intravenously or, in a dilute solution, intramuscularly, but parenteral preparations of this drug are not available in the USA. Quinidine has been the standard therapy in the USA for the parenteral treatment of severe falciparum malaria. The drug can be administered in divided doses or by continuous intravenous infusion; treatment should begin with a loading dose to rapidly achieve effective plasma concentrations. Because of its cardiac toxicity and the relative unpredictability of its pharmacokinetics, intravenous quinidine should be administered slowly with cardiac monitoring. Therapy should be changed to an effective oral agent as soon as the patient has improved and can tolerate oral medications.

B. Oral Treatment of Falciparum Malaria

Quinine sulfate is appropriate therapy for uncomplicated falciparum malaria except when the infection was transmitted in an area without documented chloroquine-resistant malaria. Quinine is commonly used with a second drug (most often doxycycline or, in children, clindamycin) to shorten quinine's duration of use (usually to 3 days) and limit toxicity. Quinine is less effective than chloroquine against other human malarias and is more toxic. Therefore, it is not used to treat infections with these parasites.

C. Malarial Chemoprophylaxis

Quinine is not generally used in chemoprophylaxis owing to its toxicity, although a daily dose of 325 mg is effective.

D. Babesiosis

Quinine is first-line therapy, in combination with clindamycin, in the treatment of infection with *Babesia microti* or other human babesial infections.

Adverse Effects

Therapeutic dosages of quinine and quinidine commonly cause tinnitus, headache, nausea, dizziness, flushing, and visual disturbances, a constellation of symptoms termed **cinchonism.** Mild symptoms of cinchonism do not warrant the discontinuation of therapy. More severe findings, often after prolonged therapy, include more marked visual and auditory abnormalities, vomiting, diarrhea, and abdominal pain. Hypersensitivity reactions include skin rashes, urticaria, angioedema, and bronchospasm. Hematologic abnormalities include hemolysis (especially with G6PD deficiency), leukopenia, agranulocytosis, and thrombocytopenia. Therapeutic doses may cause hypoglycemia through stimulation of insulin release; this is a particular problem in severe infections and in pregnant patients, who have increased sensitivity to insulin. Quinine can stimulate uterine contractions, especially in the third trimester. However, this effect is mild, and quinine and quinidine remain drugs of choice for severe falciparum malaria even during pregnancy. Intravenous infusions of the drugs may cause thrombophlebitis.

Severe hypotension can follow too-rapid intravenous infusions of quinine or quinidine. Electrocardiographic abnormalities (QT interval prolongation) are fairly common with intravenous quinidine, but dangerous arrhythmias are uncommon when the drug is administered appropriately in a monitored setting.

Blackwater fever is a rare severe illness that includes marked hemolysis and hemoglobinuria in the setting of quinine therapy for malaria. It appears to be due to a hypersensitivity reaction to the drug, although its pathogenesis is uncertain.

Contraindications & Cautions

Quinine (or quinidine) should be discontinued if signs of severe cinchonism, hemolysis, or hypersensitivity occur. It should be avoided if possible in patients with underlying visual or auditory problems. It must be used with great caution in those with underlying cardiac abnormalities. Quinine should not be given concurrently with mefloquine and should be used with caution in a patient with malaria who has previously received mefloquine chemoprophylaxis. Absorption may be blocked by aluminum-containing antacids. Quinine can raise plasma levels of warfarin and digoxin. Dosage must be reduced in renal insufficiency.

MEFLOQUINE

Mefloquine is effective therapy for many chloroquine-resistant strains of *P falciparum* and against other species. Although toxicity is a concern, mefloquine is one of the recommended chemoprophylactic drugs for use in most malaria-endemic regions with chloroquine-resistant strains.

Chemistry & Pharmacokinetics

Mefloquine hydrochloride is a synthetic 4-quinoline methanol that is chemically related to quinine. It can only be given orally because severe local irritation occurs with parenteral use. It is well absorbed, and peak plasma concentrations are reached in about 18 hours. Mefloquine is highly protein-bound, extensively distributed in tissues, and eliminated slowly, allowing a single-dose treatment regimen. The terminal elimination half-life is about 20 days, allowing weekly dosing for chemoprophylaxis. With weekly dosing, steady-state drug levels are reached over a number of weeks; this interval can be shortened to 4 days by beginning a course with three consecutive daily doses of 250 mg, although this is not standard practice. Mefloquine and acid metabolites of the drug are slowly excreted, mainly in the feces. The drug can be detected in the blood for months after the completion of therapy.

Antimalarial Action & Resistance

Mefloquine has strong blood schizonticidal activity against *P falciparum* and *P vivax,* but it is not active against hepatic stages or gametocytes. The mechanism of action of mefloquine is unknown. Sporadic resistance to mefloquine has been reported from many areas. At present, resistance appears to be uncommon except in regions of Southeast Asia with high rates of multidrug resistance (especially border areas of Thailand). Mefloquine resistance appears to be associated with resistance to quinine and halofantrine but not with resistance to chloroquine.

Clinical Uses

A. Chemoprophylaxis

Mefloquine is effective in prophylaxis against most strains of *P falciparum* and probably all other human malarial species. Mefloquine is therefore among the drugs recommended by the CDC for chemoprophylaxis in all malarious areas except for those with no chloroquine resistance (where chloroquine is preferred) and some rural areas of Southeast Asia with a high prevalence of mefloquine resistance. As with chloroquine, eradication of *P vivax* and *P ovale* requires a course of primaquine.

B. Treatment

Mefloquine is effective in treating most falciparum malaria. The drug is not appropriate for treating individuals with severe or complicated malaria, since quinine, quinidine, and artemisinins are more rapidly active, and since drug resistance is less likely with those agents. The combination of artesunate plus mefloquine showed excellent antimalarial efficacy in regions of Southeast Asia with some resistance to mefloquine, and this regimen is now one of the combination therapies recommended by the WHO for the treatment of uncomplicated falciparum malaria (Table 52–4). Artesunate-mefloquine is the first-line therapy for uncomplicated malaria in a number of countries in Asia and South America.

Adverse Effects

Weekly dosing with mefloquine for chemoprophylaxis may cause nausea, vomiting, dizziness, sleep and behavioral disturbances, epigastric pain, diarrhea, abdominal pain, headache, rash, and dizziness. Neuropsychiatric toxicities have received a good deal of publicity, but despite frequent anecdotal reports of seizures and psychosis, a number of controlled studies have found the frequency of serious adverse effects from mefloquine to be no higher than that with other common antimalarial chemoprophylactic regimens. Leukocytosis, thrombocytopenia, and aminotransferase elevations have been reported.

The latter adverse effects are more common with the higher dosages required for treatment. These effects may be lessened by administering the drug in two doses separated by 6–8 hours. The incidence of neuropsychiatric symptoms appears to be about ten times more common than with chemoprophylactic dosing, with widely varying frequencies of up to about 50% being reported. Serious neuropsychiatric toxicities (depression, confusion, acute psychosis, or seizures) have been reported in less than 1 in 1000 treatments, but some authorities believe that these toxicities are actually more common. Mefloquine can also alter cardiac conduction, and arrhythmias and bradycardia have been reported.

Contraindications & Cautions

Mefloquine is contraindicated in a patient with a history of epilepsy, psychiatric disorders, arrhythmia, cardiac conduction defects, or sensitivity to related drugs. It should not be co-administered with quinine, quinidine, or halofantrine, and caution is required if quinine or quinidine is used to treat malaria after mefloquine chemoprophylaxis. Theoretical risks of mefloquine must be balanced with the risk of contracting falciparum malaria. The CDC no longer advises against mefloquine use in patients receiving β-adrenoceptor antagonists. Mefloquine is also now considered safe in young children. Available data suggest that mefloquine is safe throughout pregnancy, although experience in the first trimester is limited. An older recommendation to avoid mefloquine use in those requiring fine motor skills (eg, airline pilots) is controversial. Mefloquine chemoprophylaxis should be discontinued if significant neuropsychiatric symptoms develop.

PRIMAQUINE

Primaquine is the drug of choice for the eradication of dormant liver forms of *P vivax* and *P ovale* and can also be used for chemoprophylaxis against all malarial species.

Chemistry & Pharmacokinetics

Primaquine phosphate is a synthetic 8-aminoquinoline (Figure 52–2). The drug is well absorbed orally, reaching peak plasma levels in

1–2 hours. The plasma half-life is 3–8 hours. Primaquine is widely distributed to the tissues, but only a small amount is bound there. It is rapidly metabolized and excreted in the urine. Its three major metabolites appear to have less antimalarial activity but more potential for inducing hemolysis than the parent compound.

Antimalarial Action & Resistance

Primaquine is active against hepatic stages of all human malaria parasites. It is the only available agent active against the dormant hypnozoite stages of *P vivax* and *P ovale.* Primaquine is also gametocidal against the four human malaria species. Primaquine acts against erythrocytic stage parasites, but this activity is too weak to play an important role. The mechanism of antimalarial action is unknown.

Some strains of *P vivax* in New Guinea, Southeast Asia, Central and South America, and other areas are relatively resistant to primaquine. Liver forms of these strains may not be eradicated by a single standard treatment with primaquine and may require repeated therapy. Because of decreasing efficacy, the standard dosage of primaquine for radical cure of *P vivax* infection was recently doubled to 30 mg base daily for 14 days.

Clinical Uses

A. Therapy (Radical Cure) of Acute Vivax and Ovale Malaria

Standard therapy for these infections includes chloroquine to eradicate erythrocytic forms and primaquine to eradicate liver hypnozoites and prevent a subsequent relapse. Chloroquine is given acutely, and therapy with primaquine is withheld until the G6PD status of the patient is known. If the G6PD level is normal, a 14-day course of primaquine is given. Prompt evaluation of the G6PD level is helpful, since primaquine appears to be most effective when instituted before completion of dosing with chloroquine.

B. Terminal Prophylaxis of Vivax and Ovale Malaria

Standard chemoprophylaxis does not prevent a relapse of vivax or ovale malaria, because the hypnozoite forms of these parasites are not eradicated by chloroquine or other available blood schizonticide agents. To markedly diminish the likelihood of relapse, some authorities advocate the use of primaquine after the completion of travel to an endemic area.

C. Chemoprophylaxis of Malaria

Primaquine has been studied as a daily chemoprophylactic agent. Daily treatment with 30 mg (0.5 mg/kg) of base provided good levels of protection against falciparum and vivax malaria. However, potential toxicities of long-term use remain a concern, and primaquine is generally recommended for this purpose only when mefloquine, Malarone, and doxycycline cannot be used.

D. Gametocidal Action

A single dose of primaquine (45 mg base) can be used as a control measure to render *P falciparum* gametocytes noninfective to mosquitoes. This therapy is of no clinical benefit to the patient but will disrupt transmission.

E. *Pneumocystis jiroveci* Infection

The combination of clindamycin and primaquine is an alternative regimen in the treatment of pneumocystosis, particularly mild to moderate disease. This regimen offers improved tolerance compared with high-dose trimethoprim-sulfamethoxazole or pentamidine, although its efficacy against severe pneumocystis pneumonia is not well studied.

Adverse Effects

Primaquine in recommended doses is generally well tolerated. It infrequently causes nausea, epigastric pain, abdominal cramps, and headache, and these symptoms are more common with higher dosages and when the drug is taken on an empty stomach. More serious but rare adverse effects are leukopenia, agranulocytosis, leukocytosis, and cardiac arrhythmias. Standard doses of primaquine may cause hemolysis or methemoglobinemia (manifested by cyanosis), especially in persons with G6PD deficiency or other hereditary metabolic defects.

Contraindications & Cautions

Primaquine should be avoided in patients with a history of granulocytopenia or methemoglobinemia, in those receiving potentially myelosuppressive drugs (eg, quinidine), and in those with disorders that commonly include myelosuppression. It is never given parenterally because it may induce marked hypotension.

Patients should be tested for G6PD deficiency before primaquine is prescribed. When a patient is deficient in G6PD, treatment strategies may consist of withholding therapy and treating subsequent relapses, if they occur, with chloroquine; treating patients with standard dosing, paying close attention to their hematologic status; or treating with weekly primaquine (45 mg base) for 8 weeks. G6PD-deficient individuals of Mediterranean and Asian ancestry are most likely to have severe deficiency, whereas those of African ancestry usually have a milder biochemical defect. This difference can be taken into consideration in choosing a treatment strategy. In any event, primaquine should be discontinued if there is evidence of hemolysis or anemia. Primaquine should be avoided in pregnancy because the fetus is relatively G6PD-deficient and thus at risk of hemolysis.

ATOVAQUONE

Atovaquone, a hydroxynaphthoquinone (Figure 52–2), was initially developed as an antimalarial agent, and as a component of **Malarone** is recommended for treatment and prevention of malaria. Atovaquone has also been approved by the FDA for the treatment of mild to moderate *P jiroveci* pneumonia.

The drug is only administered orally. Its bioavailability is low and erratic, but absorption is increased by fatty food. The drug is heavily protein-bound and has a half-life of 2–3 days. Most of the drug is eliminated unchanged in the feces. Atovaquone acts against plasmodia by disrupting mitochondrial electron transport. It is active against tissue and erythrocytic schizonts, allowing

chemoprophylaxis to be discontinued only 1 week after the end of exposure (compared with 4 weeks for mefloquine or doxycycline, which lack activity against tissue schizonts).

Initial use of atovaquone to treat malaria led to disappointing results, with frequent failures, apparently due to the selection of resistant parasites during therapy. In contrast, Malarone, a fixed combination of atovaquone (250 mg) and proguanil (100 mg), is highly effective for both the treatment and chemoprophylaxis of falciparum malaria, and it is now approved for both indications in the USA. For chemoprophylaxis, Malarone must be taken daily (Table 52–2). It has an advantage over mefloquine and doxycycline in requiring shorter periods of treatment before and after the period at risk for malaria transmission, but it is more expensive than the other agents. It should be taken with food.

Atovaquone is an alternative therapy for *P jiroveci* infection, although its efficacy is lower than that of trimethoprim-sulfamethoxazole. Standard dosing is 750 mg taken with food twice daily for 21 days. Adverse effects include fever, rash, nausea, vomiting, diarrhea, headache, and insomnia. Serious adverse effects appear to be minimal, although experience with the drug remains limited. Atovaquone has also been effective in small numbers of immunocompromised patients with toxoplasmosis unresponsive to other agents, although its role in this disease is not yet defined.

Malarone is generally well tolerated. Adverse effects include abdominal pain, nausea, vomiting, diarrhea, headache, and rash, and these are more common with the higher dosage required for treatment. Reversible elevations in liver enzymes have been reported. The safety of atovaquone in pregnancy is unknown. Plasma concentrations of atovaquone are decreased about 50% by co-administration of tetracycline or rifampin.

INHIBITORS OF FOLATE SYNTHESIS

Inhibitors of enzymes involved in folate metabolism are used, generally in combination regimens, in the treatment and prevention of malaria.

Chemistry & Pharmacokinetics

Pyrimethamine is a 2,4-diaminopyrimidine related to trimethoprim (see Chapter 46). **Proguanil** is a biguanide derivative (Figure 52–2). Both drugs are slowly but adequately absorbed from the gastrointestinal tract. Pyrimethamine reaches peak plasma levels 2–6 hours after an oral dose, is bound to plasma proteins, and has an elimination half-life of about 3.5 days. Proguanil reaches peak plasma levels about 5 hours after an oral dose and has an elimination half-life of about 16 hours. Therefore, proguanil must be administered daily for chemoprophylaxis, whereas pyrimethamine can be given once a week. Pyrimethamine is extensively metabolized before excretion. Proguanil is a prodrug; only its triazine metabolite, cycloguanil, is active. **Fansidar,** a fixed combination of the sulfonamide **sulfadoxine** (500 mg per tablet) and **pyrimethamine** (25 mg per tablet), is well absorbed. Its components display peak plasma levels within 2–8 hours and are excreted mainly by the kidneys. The average half-life of sulfadoxine is about 170 hours.

Antimalarial Action & Resistance

Pyrimethamine and proguanil act slowly against erythrocytic forms of susceptible strains of all four human malaria species. Proguanil also has some activity against hepatic forms. Neither drug is adequately gametocidal or effective against the persistent liver stages of *P vivax* or *P ovale.* Sulfonamides and sulfones are weakly active against erythrocytic schizonts but not against liver stages or gametocytes. They are not used alone as antimalarials but are effective in combination with other agents.

The mechanism of action of pyrimethamine and proguanil involves selective inhibition of plasmodial dihydrofolate reductase, a key enzyme in the pathway for synthesis of folate. Sulfonamides and sulfones inhibit another enzyme in the folate pathway, dihydropteroate synthase. As described in Chapter 46 and shown in Figure 46–2, combinations of inhibitors of these two enzymes provide synergistic activity.

Resistance to folate antagonists and sulfonamides is common in many areas for *P falciparum* and less common for *P vivax.* Resistance is due primarily to mutations in dihydrofolate reductase and dihydropteroate synthase, with increasing numbers of mutations leading to increasing levels of resistance. At present, resistance seriously limits the efficacy of sulfadoxine-pyrimethamine (Fansidar) for the treatment of malaria in most areas, but in Africa most parasites exhibit an intermediate level of resistance, such that antifolates may continue to offer some preventive efficacy against malaria. Because different mutations may mediate resistance to different agents, cross-resistance is not uniformly seen.

Clinical Uses

A. Chemoprophylaxis

Chemoprophylaxis with single folate antagonists is no longer recommended because of frequent resistance, but a number of agents are used in combination regimens. The combination of chloroquine (500 mg weekly) and proguanil (200 mg daily) was previously widely used, but with increasing resistance to both agents it is no longer recommended. Fansidar and Maloprim (the latter is a combination of pyrimethamine and the sulfone dapsone) are both effective against sensitive parasites with weekly dosing, but they are no longer recommended because of resistance and toxicity. Considering protection of populations in endemic regions, trimethoprim-sulfamethoxazole, an antifolate combination that is more active against bacteria than malaria parasites, is increasingly used as a daily prophylactic therapy for HIV-infected patients in developing countries. Although it is administered primarily to prevent typical HIV opportunistic and bacterial infections, this regimen offers partial preventive efficacy against malaria in Africa.

B. Intermittent Preventive Therapy

A new strategy for malaria control is intermittent preventive therapy, in which high-risk patients receive intermittent treatment for malaria, regardless of their infection status, typically with Fansidar, which benefits from simple dosing and prolonged activity. Considering the two highest risk groups for severe malaria in

Africa, this strategy is best validated in pregnant women and is increasingly studied in young children. Typical schedules include single doses of Fansidar during the second and third trimesters of pregnancy and monthly doses whenever children present for scheduled immunizations or, in areas with seasonal malaria, monthly doses during the transmission season. However, optimal preventive dosing schedules have not been established.

C. Treatment of Chloroquine-Resistant Falciparum Malaria

Fansidar is commonly used to treat uncomplicated falciparum malaria and until recently it was a first-line therapy for this indication in some tropical countries. Advantages of Fansidar are ease of administration (a single oral dose) and low cost. However, rates of resistance are increasing, and Fansidar is no longer a recommended therapy. In particular, Fansidar should not be used for severe malaria, since it is slower-acting than other available agents. Fansidar is also not reliably effective in vivax malaria, and its usefulness against *P ovale* and *P malariae* has not been adequately studied. A new antifolate-sulfone combination, chlorproguanil-dapsone (Lapdap), was until recently available in some African countries for the treatment of uncomplicated falciparum malaria, and the combination of chlorproguanil-dapsone and artesunate (Dacart) was under development. However, this project was discontinued in 2008 as a result of concerns about hematologic toxicity in those with G6PD deficiency, and chlorproguanil-dapsone will no longer be marketed.

D. Toxoplasmosis

Pyrimethamine, in combination with sulfadiazine, is first-line therapy in the treatment of toxoplasmosis, including acute infection, congenital infection, and disease in immunocompromised patients. For immunocompromised patients, high-dose therapy is required followed by chronic suppressive therapy. Folinic acid is included to limit myelosuppression. Toxicity from the combination is usually due primarily to sulfadiazine. The replacement of sulfadiazine with clindamycin provides an effective alternative regimen.

E. Pneumocystosis

P jiroveci is the cause of human pneumocystosis and is now recognized to be a fungus, but this organism is discussed in this chapter because it responds to antiprotozoal drugs, not antifungals. (The related species *P carinii* is now recognized to be the cause of animal infections.) First-line therapy of pneumocystosis is trimethoprim plus sulfamethoxazole (see also Chapter 46). Standard treatment includes high-dose intravenous or oral therapy (15 mg trimethoprim and 75 mg sulfamethoxazole per day in three or four divided doses) for 21 days. High-dose therapy entails significant toxicity, especially in patients with AIDS. Important toxicities include nausea, vomiting, fever, rash, leukopenia, hyponatremia, elevated hepatic enzymes, azotemia, anemia, and thrombocytopenia. Less common effects include severe skin reactions, mental status changes, pancreatitis, and hypocalcemia. Trimethoprim-sulfamethoxazole is also the standard chemoprophylactic drug for the prevention of *P jiroveci* infection in immunocompromised individuals. Dosing is one double-strength tablet daily or three times per week. The chemoprophylactic dosing schedule is much better tolerated than high-dose therapy in immunocompromised patients, but rash, fever, leukopenia, or hepatitis may necessitate changing to another drug.

Adverse Effects & Cautions

Most patients tolerate pyrimethamine and proguanil well. Gastrointestinal symptoms, skin rashes, and itching are rare. Mouth ulcers and alopecia have been described with proguanil. Fansidar is no longer recommended for chemoprophylaxis because of uncommon but severe cutaneous reactions, including erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis. Severe reactions appear to be much less common with single-dose or intermittent therapy, and use of the drug has been justified by the risks associated with falciparum malaria.

Rare adverse effects with a single dose of Fansidar are those associated with other sulfonamides, including hematologic, gastrointestinal, central nervous system, dermatologic, and renal toxicity. Maloprim is no longer recommended for chemoprophylaxis because of unacceptably high rates of agranulocytosis. Folate antagonists should be used cautiously in the presence of renal or hepatic dysfunction. Although pyrimethamine is teratogenic in animals, Fansidar has been safely used in pregnancy for therapy and as an intermittent chemoprophylactic regimen to improve pregnancy outcomes. Proguanil is considered safe in pregnancy. Folate supplements should be routinely administered during pregnancy, but in women receiving Fansidar preventive therapy, high-dose folate supplementation (eg, 5 mg daily) should probably be avoided because it may limit preventive efficacy. The standard recommended dosage of 0.4–0.6 mg daily is less likely to affect Fansidar's protective efficacy.

ANTIBIOTICS

A number of antibiotics in addition to the folate antagonists and sulfonamides are modestly active antimalarials. The antibiotics that are bacterial protein synthesis inhibitors appear to act against malaria parasites by inhibiting protein synthesis in a plasmodial prokaryote-like organelle, the apicoplast. None of the antibiotics should be used as single agents in the treatment of malaria because their action is much slower than that of standard antimalarials.

Tetracycline and doxycycline (see Chapter 44) are active against erythrocytic schizonts of all human malaria parasites. They are not active against liver stages. Doxycycline is used in the treatment of falciparum malaria in conjunction with quinine, allowing a shorter and better-tolerated course of that drug. Doxycycline is also used to complete treatment courses after initial treatment of severe malaria with intravenous quinine, quinidine, or artesunate. In all of these cases a 1-week treatment course of doxycycline is carried out. Doxycycline has also become a standard chemoprophylactic drug, especially for use in areas of Southeast Asia with high rates of resistance to other antimalarials, including mefloquine.

Doxycycline adverse effects include gastrointestinal symptoms, candidal vaginitis, and photosensitivity. Its safety in long-term chemoprophylaxis has not been extensively evaluated.

Clindamycin (see Chapter 44) is slowly active against erythrocytic schizonts and can be used after treatment courses of quinine, quinidine, or artesunate in those for whom doxycycline is not recommended, such as children and pregnant women. Azithromycin (see Chapter 44) also has antimalarial activity and is now under study as an alternative chemoprophylactic drug. Antimalarial activity of fluoroquinolones has been demonstrated, but efficacy for the therapy or chemoprophylaxis of malaria has been suboptimal.

Antibiotics also are active against other protozoans. Tetracycline and erythromycin are alternative therapies for the treatment of intestinal amebiasis. Clindamycin, in combination with other agents, is effective therapy for toxoplasmosis, pneumocystosis, and babesiosis. Spiramycin is a macrolide antibiotic that is used to treat primary toxoplasmosis acquired during pregnancy. Treatment lowers the risk of the development of congenital toxoplasmosis.

HALOFANTRINE & LUMEFANTRINE

Halofantrine hydrochloride, a phenanthrene-methanol, is effective against erythrocytic (but not other) stages of all four human malaria species. Oral absorption is variable and is enhanced with food. Because of toxicity concerns, it should not be taken with meals. Plasma levels peak 16 hours after dosing, and the half-life is about 4 days. Excretion is mainly in the feces. The mechanism of action of halofantrine is unknown. The drug is not available in the USA (although it has been approved by the FDA), but it is widely available in malaria-endemic countries.

Halofantrine (three 500-mg doses at 6-hour intervals, repeated in 1 week for nonimmune individuals) is rapidly effective against most strains of *P falciparum,* but its use is limited by irregular absorption and cardiac toxicity. It should not be used for chemoprophylaxis. Halofantrine is generally well tolerated. The most common adverse effects are abdominal pain, diarrhea, vomiting, cough, rash, headache, pruritus, and elevated liver enzymes. Of greater concern, the drug alters cardiac conduction, with dose-related prolongation of QT and PR intervals. This effect is seen with standard doses and is worsened by prior mefloquine therapy. Rare instances of dangerous arrhythmias and deaths have been reported. The drug is contraindicated in patients who have cardiac conduction defects or who have recently taken mefloquine. Halofantrine is embryotoxic in animals and therefore contraindicated in pregnancy.

Lumefantrine, an aryl alcohol related to halofantrine, is available only as a fixed-dose combination with artemether (Coartem), which is now the first-line therapy for uncomplicated falciparum malaria in many countries. In addition, Coartem is approved in many nonendemic countries, including the USA. The half-life of lumefantrine, when used in combination, is approximately 4 days. Drug levels may be altered by interactions with other drugs, including those that affect CYP3A4 metabolism, but this area has not been well studied. As with halofantrine, oral absorption is highly variable and improved when the drug is taken with food. Since lumefantrine does not engender the dangerous toxicity concerns of halofantrine, Coartem should be administered with fatty food to maximize antimalarial efficacy. Coartem is highly effective in the treatment of falciparum malaria when administered twice daily for 3 days. Coartem can cause minor prolongation of the QT interval, but this appears to be clinically insignificant, and the drug does not carry the risk of dangerous arrhythmias seen with halofantrine and quinidine. Indeed, Coartem is very well tolerated. The most commonly reported adverse events in drug trials have been gastrointestinal disturbances, headache, dizziness, rash, and pruritus, and in many cases these toxicities may have been due to underlying malaria or concomitant medications rather than to Coartem.

AMEBIASIS

Amebiasis is infection with *Entamoeba histolytica.* This organism can cause asymptomatic intestinal infection, mild to moderate colitis, severe intestinal infection (dysentery), ameboma, liver abscess, and other extraintestinal infections. The choice of drugs for amebiasis depends on the clinical presentation (Table 52–5).

Treatment of Specific Forms of Amebiasis

A. Asymptomatic Intestinal Infection

Asymptomatic carriers generally are not treated in endemic areas, but in nonendemic areas they are treated with a luminal amebicide. A tissue amebicidal drug is unnecessary. Standard luminal amebicides are diloxanide furoate, iodoquinol, and paromomycin. Each drug eradicates carriage in about 80–90% of patients with a single course of treatment. Therapy with a luminal amebicide is also required in the treatment of all other forms of amebiasis.

B. Amebic Colitis

Metronidazole plus a luminal amebicide is the treatment of choice for amebic colitis and dysentery. Tetracyclines and erythromycin are alternative drugs for moderate colitis but are not effective against extraintestinal disease. Dehydroemetine or emetine can also be used, but are best avoided because of toxicity.

C. Extraintestinal Infections

The treatment of choice for extraintestinal infections is metronidazole plus a luminal amebicide. A 10-day course of metronidazole cures over 95% of uncomplicated liver abscesses. For unusual cases in which initial therapy with metronidazole has failed, aspiration of the abscess and the addition of chloroquine to a repeat course of metronidazole should be considered. Dehydroemetine and emetine are toxic alternative drugs.

METRONIDAZOLE & TINIDAZOLE

Metronidazole, a nitroimidazole (Figure 52–3), is the drug of choice in the treatment of extraluminal amebiasis. It kills trophozoites but not cysts of *E histolytica* and effectively eradicates

TABLE 52–5 Treatment of amebiasis. Not all preparations are available in the USA.[1]

Clinical Setting	Drugs of Choice and Adult Dosage	Alternative Drugs and Adult Dosage
Asymptomatic intestinal infection	Luminal agent: Diloxanide furoate,[2] 500 mg 3 times daily for 10 days *or* Iodoquinol, 650 mg 3 times daily for 21 days *or* Paromomycin, 10 mg/kg 3 times daily for 7 days	
Mild to moderate intestinal infection	Metronidazole, 750 mg 3 times daily (or 500 mg IV every 6 hours) for 10 days *or* Tinidazole, 2 g daily for 3 days *plus* Luminal agent (see above)	Luminal agent (see above) *plus either* Tetracycline, 250 mg 3 times daily for 10 days *or* Erythromycin, 500 mg 4 times daily for 10 days
Severe intestinal infection	Metronidazole, 750 mg 3 times daily (or 500 mg IV every 6 hours) for 10 days *or* Tinidazole, 2 g daily for 3 days *plus* Luminal agent (see above)	Luminal agent (see above) *plus either* Tetracycline, 250 mg 3 times daily for 10 days *or* Dehydroemetine[2] or emetine,[2] 1 mg/kg SC or IM for 3–5 days
Hepatic abscess, ameboma, and other extraintestinal disease	Metronidazole, 750 mg 3 times daily (or 500 mg IV every 6 hours) for 10 days *or* Tinidazole, 2 g daily for 5 days *plus* Luminal agent (see above)	Dehydroemetine[2] or emetine,[2] 1 mg/kg SC or IM for 8–10 days, followed by (liver abscess only) chloroquine, 500 mg twice daily for 2 days, then 500 mg daily for 21 days *plus* Luminal agent (see above)

[1]Route is oral unless otherwise indicated. See text for additional details and cautions.

[2]Not available in the USA.

intestinal and extraintestinal tissue infections. Tinidazole, a related nitroimidazole available in the USA since 2004, appears to have similar activity and a better toxicity profile than metronidazole. It offers simpler dosing regimens and can be substituted for the indications listed below.

Pharmacokinetics & Mechanism of Action

Oral metronidazole and tinidazole are readily absorbed and permeate all tissues by simple diffusion. Intracellular concentrations rapidly approach extracellular levels. Peak plasma concentrations are reached in 1–3 hours. Protein binding of both drugs is low (10–20%); the half-life of unchanged drug is 7.5 hours for metronidazole and 12–14 hours for tinidazole. Metronidazole and its metabolites are excreted mainly in the urine. Plasma clearance of metronidazole is decreased in patients with impaired liver function.

The nitro group of metronidazole is chemically reduced in anaerobic bacteria and sensitive protozoans. Reactive reduction products appear to be responsible for antimicrobial activity. The mechanism of tinidazole is assumed to be the same.

Clinical Uses

A. Amebiasis

Metronidazole or tinidazole is the drug of choice in the treatment of all tissue infections with *E histolytica*. Neither drug is reliably effective against luminal parasites and so must be used with a luminal amebicide to ensure eradication of the infection.

B. Giardiasis

Metronidazole is the treatment of choice for giardiasis. The dosage for giardiasis is much lower—and the drug thus better tolerated—than that for amebiasis. Efficacy after a single treatment is about 90%. Tinidazole is at least equally effective.

C. Trichomoniasis

Metronidazole is the treatment of choice. A single dose of 2 g is effective. Metronidazole-resistant organisms can lead to treatment failures. Tinidazole may be effective against some of these resistant organisms.

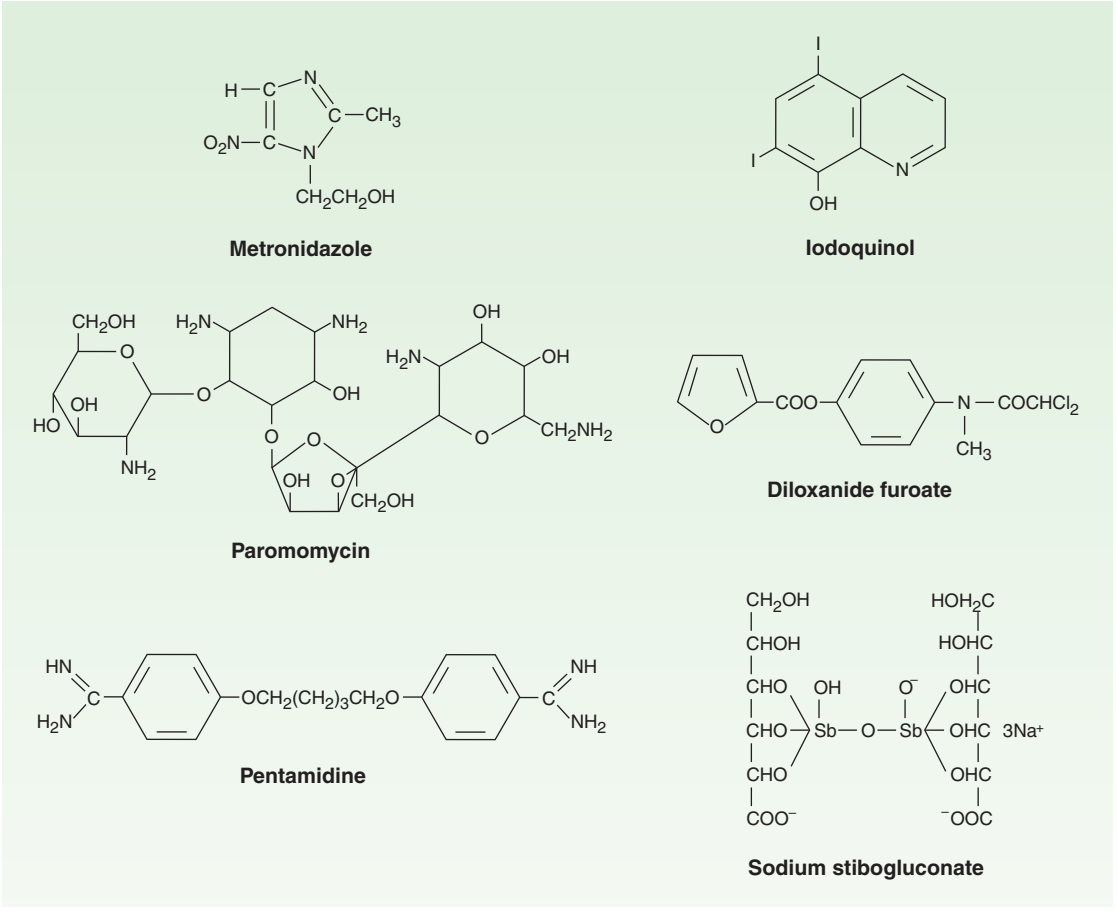

FIGURE 52–3 Structural formulas of other antiprotozoal drugs.

Adverse Effects & Cautions

Nausea, headache, dry mouth, or a metallic taste in the mouth occurs commonly. Infrequent adverse effects include vomiting, diarrhea, insomnia, weakness, dizziness, thrush, rash, dysuria, dark urine, vertigo, paresthesias, and neutropenia. Taking the drug with meals lessens gastrointestinal irritation. Pancreatitis and severe central nervous system toxicity (ataxia, encephalopathy, seizures) are rare. Metronidazole has a disulfiram-like effect, so that nausea and vomiting can occur if alcohol is ingested during therapy. The drug should be used with caution in patients with central nervous system disease. Intravenous infusions have rarely caused seizures or peripheral neuropathy. The dosage should be adjusted for patients with severe liver or renal disease. Tinidazole has a similar adverse-effect profile, although it appears to be somewhat better tolerated than metronidazole.

Metronidazole has been reported to potentiate the anticoagulant effect of coumarin-type anticoagulants. Phenytoin and phenobarbital may accelerate elimination of the drug, whereas cimetidine may decrease plasma clearance. Lithium toxicity may occur when the drug is used with metronidazole.

Metronidazole and its metabolites are mutagenic in bacteria. Chronic administration of large doses led to tumorigenicity in mice. Data on teratogenicity are inconsistent. Metronidazole is thus best avoided in pregnant or nursing women, although congenital abnormalities have not clearly been associated with use in humans.

IODOQUINOL

Iodoquinol (diiodohydroxyquin) is a halogenated hydroxyquinoline. It is an effective luminal amebicide that is commonly used with metronidazole to treat amebic infections. Pharmacokinetic data are incomplete but 90% of the drug is retained in the intestine and excreted in the feces. The remainder enters the circulation, has a half-life of 11–14 hours, and is excreted in the urine as glucuronides.

The mechanism of action of iodoquinol against trophozoites is unknown. It is effective against organisms in the bowel lumen but not against trophozoites in the intestinal wall or extraintestinal tissues.

Infrequent adverse effects include diarrhea—which usually stops after several days—anorexia, nausea, vomiting, abdominal pain, headache, rash, and pruritus. The drug may increase protein-bound serum iodine, leading to a decrease in measured ^{131}I uptake that persists for months. Some halogenated hydroxyquinolines can produce severe neurotoxicity with prolonged use at greater than recommended doses. Iodoquinol is not known to produce these

effects at its recommended dosage, and this dosage should never be exceeded.

Iodoquinol should be taken with meals to limit gastrointestinal toxicity. It should be used with caution in patients with optic neuropathy, renal or thyroid disease, or nonamebic hepatic disease. The drug should be discontinued if it produces persistent diarrhea or signs of iodine toxicity (dermatitis, urticaria, pruritus, fever). It is contraindicated in patients with intolerance to iodine.

DILOXANIDE FUROATE

Diloxanide furoate is a dichloroacetamide derivative. It is an effective luminal amebicide but is not active against tissue trophozoites. In the gut, diloxanide furoate is split into diloxanide and furoic acid; about 90% of the diloxanide is rapidly absorbed and then conjugated to form the glucuronide, which is promptly excreted in the urine. The unabsorbed diloxanide is the active antiamebic substance. The mechanism of action of diloxanide furoate is unknown.

Diloxanide furoate is considered by many the drug of choice for asymptomatic luminal infections. It is not available commercially in the USA, but can be obtained from some compounding pharmacies. It is used with a tissue amebicide, usually metronidazole, to treat serious intestinal and extraintestinal infections. Diloxanide furoate does not produce serious adverse effects. Flatulence is common, but nausea and abdominal cramps are infrequent and rashes are rare. The drug is not recommended in pregnancy.

PAROMOMYCIN SULFATE

Paromomycin sulfate is an aminoglycoside antibiotic (see also Chapter 45) that is not significantly absorbed from the gastrointestinal tract. It is used only as a luminal amebicide and has no effect against extraintestinal amebic infections. The small amount absorbed is slowly excreted unchanged, mainly by glomerular filtration. However, the drug may accumulate with renal insufficiency and contribute to renal toxicity. Paromomycin is an effective luminal amebicide that appears to have similar efficacy and probably less toxicity than other agents; in a recent study, it was superior to diloxanide furoate in clearing asymptomatic infections. Adverse effects include occasional abdominal distress and diarrhea. Parenteral paromomycin is now used to treat visceral leishmaniasis and is discussed separately in the text that follows.

EMETINE & DEHYDROEMETINE

Emetine, an alkaloid derived from ipecac, and dehydroemetine, a synthetic analog, are effective against tissue trophozoites of *E histolytica,* but because of major toxicity concerns their use is limited to unusual circumstances in which severe amebiasis requires effective therapy and metronidazole cannot be used. Dehydroemetine is preferred because of its somewhat better toxicity profile. The drugs should be used for the minimum period needed to relieve severe symptoms (usually 3–5 days) and should be administered subcutaneously (preferred) or intramuscularly in a supervised setting. Emetine and dehydroemetine should not be used intravenously. Adverse effects, which are generally mild with use for 3–5 days, increase over time and include pain, tenderness, and sterile abscesses at the injection site; diarrhea, nausea, and vomiting; muscle weakness and discomfort; and minor electrocardiographic changes. Serious toxicities include cardiac arrhythmias, heart failure, and hypotension. The drugs should not be used in patients with cardiac or renal disease, in young children, or in pregnancy unless absolutely necessary.

OTHER ANTIPROTOZOAL DRUGS

The primary drugs used to treat African trypanosomiasis are set forth in Table 52–6, and those for other protozoal infections are listed in Table 52–7. Important drugs that are not covered elsewhere in this or other chapters are discussed below.

PENTAMIDINE

Pentamidine has activity against trypanosomatid protozoans and against *P jiroveci,* but toxicity is significant.

Chemistry & Pharmacokinetics

Pentamidine is an aromatic diamidine (Figure 52–3) formulated as an isethionate salt. Pentamidine is only administered parenterally. The drug leaves the circulation rapidly, with an initial half-life of about 6 hours, but it is bound avidly by tissues. Pentamidine thus accumulates and is eliminated very slowly, with a terminal elimination half-life of about 12 days. The drug can be detected in urine 6 or more weeks after treatment. Only trace amounts of pentamidine appear in the central nervous system, so it is not

TABLE 52–6 Treatment of African trypanosomiasis.

Disease	Stage	First-Line Drugs	Alternative Drugs
West African	Early	Pentamidine	Suramin, eflornithine
	CNS involvement	Eflornithine	Melarsoprol,[1] eflornithine-nifurtimox[1]
East African	Early	Suramin[1]	Pentamidine
	CNS involvement	Melarsoprol[1]	

[1]Available in the USA from the Drug Service, CDC, Atlanta, Georgia (phone: 404-639-3670; http://www.cdc.gov/laboratory/drugservice/index.html).

TABLE 52–7 Treatment of other protozoal infections. Not all preparations are available in the USA.[1]

Organism or Clinical Setting	Drugs of Choice[2]	Alternative Drugs
Babesia species	Clindamycin, 600 mg 3 times daily for 7 days *plus* Quinine, 650 mg for 7 days	Atovaquone *or* azithromycin
Balantidium coli	Tetracycline, 500 mg 4 times daily for 10 days	Metronidazole, 750 mg 3 times daily for 5 days
Cryptosporidium species	Paromomycin, 500–750 mg 3 or 4 times daily for 10 days	Azithromycin, 500 mg daily for 21 days
Cyclospora cayetanensis	Trimethoprim-sulfamethoxazole, one double-strength tablet 4 times daily for 7–14 days	
Dientamoeba fragilis	Iodoquinol, 650 mg 3 times daily for 20 days	Tetracycline, 500 mg 4 times daily for 10 days *or* Paromomycin, 500 mg 3 times daily for 7 days
Giardia lamblia	Metronidazole, 250 mg 3 times daily for 5 days *or* Tinidazole, 2 g once	Furazolidone, 100 mg 4 times daily for 7 days *or* Albendazole, 400 mg daily for 5 days
Isospora belli	Trimethoprim-sulfamethoxazole, one double-strength tablet 4 times daily for 10 days, then twice daily for 21 days	Pyrimethamine, 75 mg daily for 14 days *plus* Folinic acid, 10 mg daily for 14 days
Microsporidia	Albendazole, 400 mg twice daily for 20–30 days	
Leishmaniasis		
Visceral *(L donovani, L chagasi, L infantum)* or mucosal *(L braziliensis)*	Sodium stibogluconate, 20 mg/kg/d IV or IM for 28 days	Meglumine antimoniate *or* Pentamidine *or* Amphotericin *or* Miltefosine *or* Paromomycin
Cutaneous *(L major, L tropica, L mexicana, L braziliensis)*	Sodium stibogluconate, 20 mg/kg/d IV or IM for 20 days	Meglumine antimoniate *or* Amphotericin *or* Pentamidine *or* Topical or intralesional therapies
Pneumocystis jiroveci, P carinii[3]	Trimethoprim-sulfamethoxazole, 15–20 mg trimethoprim component/kg/d IV, or two double-strength tablets every 8 hours for 21 days	Pentamidine *or* Trimethoprim-dapsone *or* Clindamycin *plus* primaquine *or* Atovaquone
Toxoplasma gondii		

(*continued*)

TABLE 52–7 Treatment of other protozoal infections. Not all preparations are available in the USA.[1] (Continued)

Organism or Clinical Setting	Drugs of Choice[2]	Alternative Drugs
Acute, congenital, immunocompromised	Pyrimethamine *plus* clindamycin *plus* folinic acid	Pyrimethamine *plus* sulfadiazine *plus* folinic acid
Pregnancy	Spiramycin, 3 g daily until delivery	
Trichomonas vaginalis	Metronidazole, 2 g once or 250 mg 3 times daily for 7 days	
	or	
	Tinidazole, 2 g once	
Trypanosoma cruzi	Nifurtimox	
	or	
	Benznidazole	

[1]Additional information may be obtained from the Parasitic Disease Drug Service, Parasitic Diseases Branch, CDC, Atlanta, Georgia (phone: 404-639-3670; http://www.cdc.gov/laboratory/drugservice/index.html).

[2]Established, relatively simple dosing regimens are provided. Route is oral unless otherwise indicated. See text for additional information, toxicities, cautions, and discussions of dosing for the more rarely used drugs, many of which are highly toxic.

[3]*P jiroveci* (*carinii* in animals) has traditionally been considered a protozoan because of its morphology and drug sensitivity, but recent molecular analyses have shown it to be most closely related to fungi.

effective against central nervous system African trypanosomiasis. Pentamidine can also be inhaled as a nebulized powder for the prevention of pneumocystosis. Absorption into the systemic circulation after inhalation appears to be minimal. The mechanism of action of pentamidine is unknown.

Clinical Uses

A. Pneumocystosis

Pentamidine is a well-established alternative therapy for pulmonary and extrapulmonary disease caused by *P jiroveci.* The drug has somewhat lower efficacy and greater toxicity than trimethoprim-sulfamethoxazole. The standard dosage is 3 mg/kg/d intravenously for 21 days. Significant adverse reactions are common, and with multiple regimens now available to treat *P jiroveci* infection, pentamidine is best reserved for patients with severe disease who cannot tolerate or fail other drugs.

Pentamidine is also an alternative agent for primary or secondary prophylaxis against pneumocystosis in immunocompromised individuals, including patients with advanced AIDS. For this indication, pentamidine is administered as an inhaled aerosol (300 mg inhaled monthly). The drug is well tolerated in this form. Its efficacy is very good but clearly less than that of daily trimethoprim-sulfamethoxazole. Because of its cost and ineffectiveness against nonpulmonary disease, it is best reserved for patients who cannot tolerate oral chemoprophylaxis with other drugs.

B. African Trypanosomiasis (Sleeping Sickness)

Pentamidine has been used since 1940 and is the drug of choice to treat the early hemolymphatic stage of disease caused by *Trypanosoma brucei gambiense* (West African sleeping sickness). The drug is inferior to suramin for the treatment of early East African sleeping sickness. Pentamidine should not be used to treat late trypanosomiasis with central nervous system involvement. A number of dosing regimens have been described, generally providing 2–4 mg/kg daily or on alternate days for a total of 10–15 doses. Pentamidine has also been used for chemoprophylaxis against African trypanosomiasis, with dosing of 4 mg/kg every 3–6 months.

C. Leishmaniasis

Pentamidine is an alternative to sodium stibogluconate in the treatment of visceral leishmaniasis, with similar efficacy, although resistance has been reported. The drug has been successful in some cases that have failed therapy with antimonials. The dosage is 2–4 mg/kg intramuscularly daily or every other day for up to 15 doses, and a second course may be necessary. Pentamidine has also shown success against cutaneous leishmaniasis, but it is not routinely used for this purpose.

Adverse Effects & Cautions

Pentamidine is a highly toxic drug, with adverse effects noted in about 50% of patients receiving 4 mg/kg/d. Rapid intravenous administration can lead to severe hypotension, tachycardia, dizziness, and dyspnea, so the drug should be administered slowly (over 2 hours), and patients should be recumbent and monitored closely during treatment. With intramuscular administration, pain at the injection site is common, and sterile abscesses may develop.

Pancreatic toxicity is common. Hypoglycemia due to inappropriate insulin release often appears 5–7 days after onset of treatment, can persist for days to several weeks, and may be followed by hyperglycemia. Reversible renal insufficiency is also common. Other adverse effects include rash, metallic taste, fever, gastrointestinal symptoms, abnormal liver function tests, acute pancreatitis, hypocalcemia, thrombocytopenia, hallucinations, and cardiac arrhythmias. Inhaled pentamidine is generally well tolerated but may cause cough, dyspnea, and bronchospasm.

SODIUM STIBOGLUCONATE

Pentavalent antimonials, including sodium stibogluconate (pentostam; Figure 52–3) and meglumine antimoniate, are generally considered first-line agents for cutaneous and visceral leishmaniasis except in parts of India, where the efficacy of these drugs has diminished greatly. The drugs are rapidly absorbed and distributed after intravenous (preferred) or intramuscular administration and eliminated in two phases, with short initial (about 2-hour) half-life and much longer terminal (> 24-hour) half-life. Treatment is given once daily at a dosage of 20 mg/kg/d intravenously or intramuscularly for 20 days in cutaneous leishmaniasis and 28 days in visceral and mucocutaneous disease.

The mechanism of action of the antimonials is unknown. Their efficacy against different species may vary, possibly based on local drug resistance patterns. Cure rates are generally quite good, but resistance to sodium stibogluconate is increasing in some endemic areas, notably in India where other agents (eg, amphotericin or miltefosine) are generally recommended.

Few adverse effects occur initially, but the toxicity of stibogluconate increases over the course of therapy. Most common are gastrointestinal symptoms, fever, headache, myalgias, arthralgias, and rash. Intramuscular injections can be very painful and lead to sterile abscesses. Electrocardiographic changes may occur, most commonly T-wave changes and QT prolongation. These changes are generally reversible, but continued therapy may lead to dangerous arrhythmias. Thus, the electrocardiogram should be monitored during therapy. Hemolytic anemia and serious liver, renal, and cardiac effects are rare.

NITAZOXANIDE

Nitazoxanide is a nitrothiazolyl-salicylamide prodrug. Nitazoxanide was recently approved in the USA for use against *Giardia lamblia* and *Cryptosporidium parvum.* It is rapidly absorbed and converted to tizoxanide and tizoxanide conjugates, which are subsequently excreted in both urine and feces. The active metabolite, tizoxanide, inhibits the pyruvate-ferredoxin oxidoreductase pathway. Nitazoxanide appears to have activity against metronidazole-resistant protozoal strains and is well tolerated. Unlike metronidazole, nitazoxanide and its metabolites appear to be free of mutagenic effects. Other organisms that may be susceptible to nitazoxanide include *E histolytica, Helicobacter pylori, Ascaris lumbricoides,* several tapeworms, and *Fasciola hepatica.* The recommended adult dosage is 500 mg twice daily for 3 days.

OTHER DRUGS FOR TRYPANOSOMIASIS & LEISHMANIASIS

Available therapies for all forms of trypanosomiasis are seriously deficient in efficacy, safety, or both. Availability of these therapies is also a concern, since they are supplied mainly through donation or nonprofit production by pharmaceutical companies. For visceral leishmaniasis, three new promising therapies are liposomal amphotericin, miltefosine, and paromomycin.

A. Suramin

Suramin is a sulfated naphthylamine that was introduced in the 1920s. It is the first-line therapy for early hemolymphatic East African trypanosomiasis (*T brucei rhodesiense* infection), but because it does not enter the central nervous system, it is not effective against advanced disease. Suramin is less effective than pentamidine for early West African trypanosomiasis. The drug's mechanism of action is unknown. It is administered intravenously and displays complex pharmacokinetics with very tight protein binding. Suramin has a short initial half-life but a terminal elimination half-life of about 50 days. The drug is slowly cleared by renal excretion.

Suramin is administered after a 200-mg intravenous test dose. Regimens that have been used include 1 g on days 1, 3, 7, 14, and 21 or 1 g each week for 5 weeks. Combination therapy with pentamidine may improve efficacy. Suramin can also be used for chemoprophylaxis against African trypanosomiasis. Adverse effects are common. Immediate reactions can include fatigue, nausea, vomiting, and, more rarely, seizures, shock, and death. Later reactions include fever, rash, headache, paresthesias, neuropathies, renal abnormalities including proteinuria, chronic diarrhea, hemolytic anemia, and agranulocytosis.

B. Melarsoprol

Melarsoprol is a trivalent arsenical that has been available since 1949 and is first-line therapy for advanced central nervous system East African trypanosomiasis, and second-line therapy (after eflornithine) for advanced West African trypanosomiasis. After intravenous administration it is excreted rapidly, but clinically relevant concentrations accumulate in the central nervous system within 4 days. Melarsoprol is administered in propylene glycol by slow intravenous infusion at a dosage of 3.6 mg/kg/d for 3–4 days, with repeated courses at weekly intervals, if needed. A new regimen of 2.2 mg/kg daily for 10 days had efficacy and toxicity similar to what was observed with three courses over 26 days. Melarsoprol is extremely toxic. The use of such a toxic drug is justified only by the severity of advanced trypanosomiasis and the lack of available alternatives. Immediate adverse effects include fever, vomiting, abdominal pain, and arthralgias. The most important toxicity is a reactive encephalopathy that generally appears within the first week of therapy (in 5–10% of patients) and is probably due to disruption of trypanosomes in the central nervous system. Common consequences of the encephalopathy include cerebral edema, seizures, coma, and death. Other serious toxicities include renal and cardiac disease and hypersensitivity reactions. Failure rates with melarsoprol appear to have increased recently in parts of Africa, suggesting the possibility of drug resistance.

C. Eflornithine

Eflornithine (difluoromethylornithine), an inhibitor of ornithine decarboxylase, is the only new drug registered to treat African trypanosomiasis in the last half-century. It is now the first-line drug for advanced West African trypanosomiasis, but is not effective for East African disease. Eflornithine is less toxic than melarsoprol but not as widely available. The drug had very limited

availability until recently, when it was developed for use as a topical depilatory cream, leading to donation of the drug for the treatment of trypanosomiasis. Eflornithine is administered intravenously, and good central nervous system drug levels are achieved. The elimination half-life is about 3 hours. The usual regimen is 100 mg/kg intravenously every 6 hours for 7–14 days (14 days was superior for a newly diagnosed infection). Eflornithine appears to be as effective as melarsoprol against advanced *T brucei gambiense* infection, but its efficacy against *T brucei rhodesiense* is limited by drug resistance. Toxicity from eflornithine is significant, but considerably less than that from melarsoprol. Adverse effects include diarrhea, vomiting, anemia, thrombocytopenia, leukopenia, and seizures. These effects are generally reversible. Increased experience with eflornithine and increased availability of the compound in endemic areas may lead to its replacement of suramin, pentamidine, and melarsoprol in the treatment of *T brucei gambiense* infection.

D. Nifurtimox

Nifurtimox, a nitrofuran, is the most commonly used drug for American trypanosomiasis (Chagas' disease). Nifurtimox is also under study in the treatment of African trypanosomiasis, particularly in combination with eflornithine. Nifurtimox is well absorbed after oral administration and eliminated with a plasma half-life of about 3 hours. The drug is administered at a dosage of 8–10 mg/kg/d (divided into three to four doses) orally for 3–4 months in the treatment of acute Chagas' disease. Nifurtimox decreases the severity of acute disease and usually eliminates detectable parasites, but it is often ineffective in fully eradicating infection. Thus, it often fails to prevent progression to the gastrointestinal and cardiac syndromes associated with chronic infection that are the most important clinical consequences of *Trypanosoma cruzi* infection. Efficacy may vary in different parts of South America, possibly related to drug resistance in some areas. Nifurtimox has not been proved effective in the treatment of chronic Chagas' disease. Toxicity related to nifurtimox is common. Adverse effects include nausea, vomiting, abdominal pain, fever, rash, restlessness, insomnia, neuropathies, and seizures. These effects are generally reversible but often lead to cessation of therapy before completion of a standard course.

E. Benznidazole

Benznidazole is an orally administered nitroimidazole that appears to have efficacy similar to that of nifurtimox in the treatment of acute Chagas' disease. Availability of the drug is currently limited. Important toxicities include peripheral neuropathy, rash, gastrointestinal symptoms, and myelosuppression.

F. Amphotericin

This important antifungal drug (see Chapter 48) is an alternative therapy for visceral leishmaniasis, especially in parts of India with high-level resistance to sodium stibogluconate. Liposomal amphotericin has shown excellent efficacy at a dosage of 3 mg/kg/d intravenously on days 1–5, 14, and 21. Nonliposomal amphotericin (1 mg/kg intravenously every other day for 30 days) is much less expensive, also efficacious, and widely used in India. Amphotericin is also used for cutaneous leishmaniasis in some areas. The use of amphotericin, and especially liposomal preparations, is limited in developing countries by difficulty of administration, cost, and toxicity.

G. Miltefosine

Miltefosine is an alkylphosphocholine analog that is the first effective oral drug for visceral leishmaniasis. It has recently shown excellent efficacy in the treatment of visceral leishmaniasis in India, where it is administered orally (2.5 mg/kg/d with varied dosing schedules) for 28 days. It was also recently shown to be effective in regimens including a single dose of liposomal amphotericin followed by 7–14 days of miltefosine. A 28-day course of miltefosine (2.5 mg/kg/d) was also effective for the treatment of New World cutaneous leishmaniasis. Vomiting and diarrhea are common but generally short-lived toxicities. Transient elevations in liver enzymes and nephrotoxicity are also seen. The drug should be avoided in pregnancy (or in women who may become pregnant within 2 months of treatment) because of its teratogenic effects. Miltefosine is registered for the treatment of visceral leishmaniasis in India and some other countries, and—considering the serious limitations of other drugs, including parenteral administration, toxicity, and resistance—it may become the treatment of choice for that disease. Resistance to miltefosine develops readily in vitro. To circumvent this problem, various drug combinations, including miltefosine with antimonials, amphotericin, or paromomycin, are under study.

H. Paromomycin

Paromomycin sulfate is an aminoglycoside antibiotic that until recently was used in parasitology only for oral therapy of intestinal parasitic infections (see previous text). It has recently been developed for the treatment of visceral leishmaniasis. A phase 3 trial in India showed excellent efficacy for this disease, with a daily intramuscular dosage of 11 mg/kg for 21 days yielding a 95% cure rate, and noninferiority compared with amphotericin. The drug was registered for the treatment of visceral leishmaniasis in India in 2006. However, a recent trial showed poorer efficacy in Africa, with the cure rate for paromomycin significantly inferior to that with sodium stibogluconate. In initial studies, paromomycin was well tolerated, with common mild injection pain, uncommon ototoxicity and reversible liver enzyme elevations, and no nephrotoxicity. Paromomycin is much less expensive than liposomal amphotericin or miltefosine, the other promising new therapies for visceral leishmaniasis.

PREPARATIONS AVAILABLE

Albendazole (Albenza)
Oral: 200 mg tablets

Artemether/lumefantrine (Coartem)
Oral: 20 mg artemether/120 mg lumefantrine tablets

Artesunate*

Atovaquone (Mepron)
Oral: 750 mg/5 mL suspension

Atovaquone-proguanil (Malarone)
Oral: 250 mg atovaquone + 100 mg proguanil tablets; pediatric 62.5 mg atovaquone + 25 mg proguanil tablets

Chloroquine (generic, Aralen)
Oral: 250, 500 mg tablets (equivalent to 150, 300 mg base, respectively)
Parenteral: 50 mg/mL (equivalent to 40 mg/mL base) for injection

Clindamycin (generic, Cleocin)
Oral: 75, 150, 300 mg capsules; 75 mg/5 mL suspension
Parenteral: 150 mg/mL for injection

Doxycycline (generic, Vibramycin)
Oral: 20, 50, 100 mg capsules; 50, 100 mg tablets; 25 mg/5 mL suspension; 50 mg/5 mL syrup
Parenteral: 100, 200 mg for injection

Eflornithine (Ornidyl)
Parenteral: 200 mg/mL for injection

Iodoquinol (Yodoxin)
Oral: 210, 650 mg tablets

Mefloquine (generic, Lariam)
Oral: 250 mg tablets

Melarsoprol (Mel B)*

Metronidazole (generic, Flagyl)
Oral: 250, 500 mg tablets; 375 mg capsules; extended-release 750 mg tablets
Parenteral: 5 mg/mL

Nifurtimox*

Nitazoxanide (Alinia)
Oral: 500 mg tablets, powder for 100 mg/5 mL oral solution

Paromomycin (Humatin)
Oral: 250 mg capsules

Pentamidine (Pentam 300, Pentacarinat, pentamidine isethionate)
Parenteral: 300 mg powder for injection
Aerosol (Nebupent): 300 mg powder

Primaquine (generic)
Oral: 26.3 mg (equivalent to 15 mg base) tablet

Pyrimethamine (Daraprim)
Oral: 25 mg tablets

Quinidine gluconate (generic)
Parenteral: 80 mg/mL (equivalent to 50 mg/mL base) for injection

Quinine (generic)
Oral: 260 mg tablets; 200, 260, 325 mg capsules

Sodium stibogluconate*

Sulfadoxine and pyrimethamine (Fansidar)
Oral: 500 mg sulfadoxine plus 25 mg pyrimethamine tablets

Suramin*

Tinidazole (Tindamax)
Oral: 250, 500 mg tablets

*Available in the USA only from the Drug Service, CDC, Atlanta, Georgia (phone: 404-639-3670; http://www.cdc.gov/laboratory/drugservice/index.html).

REFERENCES

General

Drugs for parasitic infections. Med Lett Drugs Ther 2010;Supplement.

Malaria

Baird JK: Effectiveness of antimalarial drugs. N Engl J Med 2005;352:1565.

Baird JK: Resistance to therapies for infection by *Plasmodium vivax*. Clin Microbiol Rev 2009;22:508.

Barnes KI et al: Efficacy of rectal artesunate compared with parenteral quinine in initial treatment of moderately severe malaria in African children and adults: A randomised study. Lancet 2004;363:1598.

Boggild AK et al: Atovaquone-proguanil: Report from the CDC expert meeting on malaria chemoprophylaxis (II). Am J Trop Med Hyg 2007;76:208.

Dondorp AM et al: Artemisinin resistance in *Plasmodium falciparum* malaria. N Engl J Med 2009;361:455.

Dondorp A et al: Artesunate versus quinine for treatment of severe falciparum malaria: A randomised trial. Lancet 2005;366:717.

Dondorp AM et al: Artesunate versus quinine in the treatment of severe falciparum malaria in African children (AQUAMAT): An open-label, randomised trial. Lancet 2010;376:1647.

Dorsey G et al: Combination therapy for uncomplicated falciparum malaria in Ugandan children: A randomized trial. JAMA 2007;297:2210.

Efferth T, Kaina B: Toxicity of the antimalarial artemisinin and its derivatives. Crit Rev Toxicol 2010;40:405.

Freedman DO: Malaria prevention in short-term travelers. N Engl J Med 2008;359:603.

Greenwood BM et al: Malaria. Lancet 2005;365:1487.

Hill DR et al: Primaquine: Report from CDC expert meeting on malaria chemoprophylaxis I. Am J Trop Med Hyg 2006;75:402.

Nosten F, White NJ: Artemisinin-based combination treatment of falciparum malaria. Am J Trop Med Hyg 2007;77(Suppl 6):181.

Nosten F et al: Antimalarial drugs in pregnancy: A review. Curr Drug Saf 2006;1:1.

Rosenthal PJ: Artesunate for the treatment of severe falciparum malaria. N Engl J Med 2008;358:1829.

Stepniewska K, White NJ: Pharmacokinetic determinants of the window of selection for antimalarial drug resistance. Antimicrob Agents Chemother 2008;52:1589.

Taylor WR, White NJ: Antimalarial drug toxicity: A review. Drug Saf 2004;27:25.

White NJ: Cardiotoxicity of antimalarial drugs. Lancet Infect Dis 2007;7:549.

White NJ: Qinghaosu (artemisinin): The price of success. Science 2008;320:330.

Whitty CJ, et al: Malaria: An update on treatment of adults in non-endemic countries. Br Med J 2006;333:241.

World Health Organization: Guidelines for the treatment of malaria. Geneva. 2010. http://www.who.int/malaria/publications/atoz/9789241547925/en/index.html

Intestinal Protozoal Infections

Blessmann J et al: Treatment of amoebic liver abscess with metronidazole alone or in combination with ultrasound-guided needle aspiration: A comparative, prospective and randomized study. Trop Med Int Health 2003;8:1030.

Fox LM, Saravolatz LD: Nitazoxanide: A new thiazolide antiparasitic agent. Clin Infect Dis 2005;40:1173.

Haque R et al: Amebiasis. N Engl J Med 2003;348:1565.

Petri WA: Therapy of intestinal protozoa. Trends Parasitol 2003;19:523.

Pierce KK et al: Update on human infections caused by intestinal protozoa. Curr Opin Gastroenterol 2009;25:12.

Pritt BS, Clark DG: Amebiasis. Mayo Clin Proc 2008;83:1154.

Rossignol JF: *Cryptosporidium* and *Giardia*: Treatment options and prospects for new drugs. Exp Parasitol 2010;124:45.

Other Protozoal Infections

Amato VS et al: Treatment of mucosal leishmaniasis in Latin America: Systematic review. Am J Trop Med Hyg 2007;77:266.

Aronson NE et al: A randomized controlled trial of local heat therapy versus intravenous sodium stibogluconate for the treatment of cutaneous Leishmania major infection. PLoS Negl Trop Dis 2010;4:e628.

Bhattacharya SK et al: Phase 4 trial of miltefosine for the treatment of Indian visceral leishmaniasis. J Infect Dis 2007;196:591.

Bisser S et al: Equivalence trial of melarsoprol and nifurtimox monotherapy and combination therapy for the treatment of second-stage *Trypanosoma brucei gambiense* sleeping sickness. J Infect Dis 2007;195:322.

Brun R et al: Human African trypanosomiasis. Lancet 2010;375:148.

Chappuis F et al: Visceral leishmaniasis: What are the needs for diagnosis, treatment and control? Nat Rev Microbiol 2007;5:873.

Croft SL, Barrett MP, Urbina JA: Chemotherapy of trypanosomiases and leishmaniasis. Trends Parasitol 2005;21:508.

Hailu A et al: Geographical variation in the response of visceral leishmaniasis to paromomycin in East Africa: A multicentre, open-label, randomized trial. PLoS Negl Trop Dis 2010;4:e709.

Jackson Y et al: Tolerance and safety of nifurtimox in patients with chronic Chagas disease. Clin Infect Dis 2010;51:e69.

Lescure FX et al: Chagas disease: Changes in knowledge and management. Lancet Infect Dis 2010;10:556.

Murray HW et al: Advances in leishmaniasis. Lancet 2005;366:1561.

Priotto G et al: Nifurtimox-eflornithine combination therapy for second-stage African *Trypanosoma brucei gambiense* trypanosomiasis: A multicentre, randomised, phase III, non-inferiority trial. Lancet 2009;374:56.

Rassi A et al: Chagas disease. Lancet. 2010;375:1388.

Reithinger R et al: Cutaneous leishmaniasis. Lancet Infect Dis 2007;7:581.

Schmid C et al: Effectiveness of a 10-day melarsoprol schedule for the treatment of late-stage human African trypanosomiasis: Confirmation from a multinational study (IMPAMEL II). J Infect Dis 2005;191:1922.

Soto J et al: Efficacy of miltefosine for Bolivian cutaneous leishmaniasis. Am J Trop Med Hyg 2008;78:210.

Sundar S et al: Injectable paromomycin for visceral leishmaniasis in India. N Engl J Med 2007;356:2571.

Sundar S et al: New treatment approach in Indian visceral leishmaniasis: Single-dose liposomal amphotericin B followed by short-course oral miltefosine. Clin Infect Dis 2008;47:1000.

Sundar S et al: Oral miltefosine for Indian visceral leishmaniasis. N Engl J Med 2002;347:1739.

Tuon FF et al: Treatment of New World cutaneous leishmaniasis—a systematic review with a meta-analysis. Int J Dermatol 2008;47:109.

van Griensven J, et al: Combination therapy for visceral leishmaniasis. Lancet Infect Dis 2010;10:184.

Vélez I et al: Efficacy of miltefosine for the treatment of American cutaneous leishmaniasis. Am J Trop Med Hyg 2010;83:351.

Wortmann G et al: Liposomal amphotericin B for treatment of cutaneous leishmaniasis. Am J Trop Med Hyg 2010;83:1028.

CASE STUDY ANSWER

This child has acute falciparum malaria, and her lethargy and abnormal laboratory tests are consistent with progression to severe disease. She should be hospitalized and treated urgently with intravenous artesunate or, if this is unavailable, intravenous quinine or quinidine. She should be followed closely for progression of severe malaria, in particular neurologic, renal, or pulmonary complications, and if treated with quinine or quinidine should have cardiac monitoring for potential toxicities.

CHAPTER 53

Clinical Pharmacology of the Antihelminthic Drugs

Philip J. Rosenthal, MD

CASE STUDY

A 29-year-old Peruvian man presents with the incidental finding of a 10 by 8 by 8 cm liver cyst on an abdominal computed tomography (CT) scan. The patient had noted 2 days of abdominal pain and fever, and his clinical evaluation and CT scan were consistent with appendicitis. His clinical findings resolved after laparoscopic appendectomy. Ten years ago, the patient emigrated to the United States from a rural area of Peru where his family trades in sheepskins. His father and sister have undergone resection of abdominal masses, but details of their diagnoses are unavailable. What is your differential diagnosis? What are your diagnostic and therapeutic plans?

CHEMOTHERAPY OF HELMINTHIC INFECTIONS

Helminths (worms) are multicellular organisms that infect very large numbers of humans and cause a broad range of diseases. Over 1 billion people are infected with intestinal nematodes, and many millions are infected with filarial nematodes, flukes, and tapeworms. They are an even greater problem in domestic animals. Many drugs, which are directed against a number of different targets, are available to treat helminthic infections. In many cases, especially in the developing world, the goal is control of infection, with elimination of most parasites controlling disease symptoms and decreasing the transmission of infection. In other cases, complete elimination of parasites is the goal of therapy, although this goal can be challenging with certain helminthic infections, because of both limited efficacy of drugs and frequent reinfection after therapy in endemic areas.

Table 53–1 lists the major helminthic infections and provides a guide to the drug of choice and alternative drugs for each infection. In the text that follows, these drugs are arranged alphabetically. In general, parasites should be identified before treatment is started.

ALBENDAZOLE

Albendazole, a broad-spectrum oral antihelminthic, is the drug of choice and is approved in the USA for treatment of hydatid disease and cysticercosis. It is also used in the treatment of pinworm and hookworm infections, ascariasis, trichuriasis, and strongyloidiasis.

Basic Pharmacology

Albendazole is a benzimidazole carbamate. After oral administration, it is erratically absorbed (increased with a fatty meal) and then rapidly undergoes first-pass metabolism in the liver to the active metabolite albendazole sulfoxide. It reaches variable maximum plasma concentrations about 3 hours after a 400-mg oral dose, and its plasma half-life is 8–12 hours. The sulfoxide is mostly protein-bound, distributes well to tissues, and enters bile, cerebrospinal fluid, and hydatid cysts. Albendazole metabolites are excreted in the urine.

Benzimidazoles are thought to act against nematodes by inhibiting microtubule synthesis. Albendazole also has larvicidal effects in hydatid disease, cysticercosis, ascariasis, and hookworm infection and ovicidal effects in ascariasis, ancylostomiasis, and trichuriasis.

TABLE 53–1 Drugs for the treatment of helminthic infections.[1]

Infecting Organism	Drug of Choice	Alternative Drugs
Roundworms (nematodes)		
Ascaris lumbricoides (roundworm)	Albendazole or pyrantel pamoate or mebendazole	Ivermectin, piperazine
Trichuris trichiura (whipworm)	Mebendazole or albendazole	Ivermectin
Necator americanus (hookworm); *Ancylostoma duodenale* (hookworm)	Albendazole or mebendazole or pyrantel pamoate	
Strongyloides stercoralis (threadworm)	Ivermectin	Albendazole or thiabendazole
Enterobius vermicularis (pinworm)	Mebendazole or pyrantel pamoate	Albendazole
Trichinella spiralis (trichinosis)	Mebendazole or albendazole; add corticosteroids for severe infection	
Trichostrongylus species	Pyrantel pamoate or mebendazole	Albendazole
Cutaneous larva migrans (creeping eruption)	Albendazole or ivermectin	Thiabendazole (topical)
Visceral larva migrans	Albendazole	Mebendazole
Angiostrongylus cantonensis	Albendazole or mebendazole	
Wuchereria bancrofti (filariasis); *Brugia malayi* (filariasis); tropical eosinophilia; *Loa loa* (loiasis)	Diethylcarbamazine	Ivermectin
Onchocerca volvulus (onchocerciasis)	Ivermectin	
Dracunculus medinensis (guinea worm)	Metronidazole	Thiabendazole or mebendazole
Capillaria philippinensis (intestinal capillariasis)	Albendazole	Mebendazole
Flukes (trematodes)		
Schistosoma haematobium (bilharziasis)	Praziquantel	Metrifonate
Schistosoma mansoni	Praziquantel	Oxamniquine
Schistosoma japonicum	Praziquantel	
Clonorchis sinensis (liver fluke); *Opisthorchis* species	Praziquantel	Albendazole
Paragonimus westermani (lung fluke)	Praziquantel	Bithionol
Fasciola hepatica (sheep liver fluke)	Bithionol or triclabendazole	
Fasciolopsis buski (large intestinal fluke)	Praziquantel or niclosamide	
Heterophyes heterophyes; Metagonimus yokogawai (small intestinal flukes)	Praziquantel or niclosamide	
Tapeworms (cestodes)		
Taenia saginata (beef tapeworm)	Praziquantel or niclosamide	Mebendazole
Diphyllobothrium latum (fish tapeworm)	Praziquantel or niclosamide	
Taenia solium (pork tapeworm)	Praziquantel or niclosamide	
Cysticercosis (pork tapeworm larval stage)	Albendazole	Praziquantel
Hymenolepis nana (dwarf tapeworm)	Praziquantel	Niclosamide, nitazoxanide
Echinococcus granulosus (hydatid disease); *Echinococcus multilocularis*	Albendazole	

[1]Additional information may be obtained from the Parasitic Disease Drug Service, Parasitic Diseases Branch, Centers for Disease Control and Prevention, Atlanta, Georgia, 30333. Telephone: (404) 639-3670. Some of the drugs listed are not generally available in the USA.

Clinical Uses

Albendazole is administered on an empty stomach when used against intraluminal parasites but with a fatty meal when used against tissue parasites.

A. Ascariasis, Trichuriasis, and Hookworm and Pinworm Infections

For adults and children older than 2 years of age with ascariasis and hookworm infections, the treatment is a single dose of 400 mg

orally (repeated for 2–3 days for heavy ascaris infections and in 2 weeks for pinworm infections). These treatments typically achieve good cure rates and marked reduction in egg counts in those not cured. For trichuriasis, three daily 400-mg oral doses of albendazole are now recommended. A recent meta-analysis showed albendazole to be superior to mebendazole or pyrantel pamoate for treatment of hookworm infection; other studies showed that three doses of mebendazole and albendazole increased stool clearance of eggs compared with single treatments, with albendazole superior to mebendazole. Cure rates for trichuriasis with single-dose albendazole or mebendazole were less than 30%, which suggests that the three-dose regimen just noted, or other drugs (eg, ivermectin), might be superior.

B. Hydatid Disease

Albendazole is the treatment of choice for medical therapy and is a useful adjunct to surgical removal or aspiration of cysts. It is more active against *Echinococcus granulosus* than against *E multilocularis*. Dosing is 400 mg twice daily with meals for 1 month or longer. Daily therapy for up to 6 months has been well tolerated. One reported therapeutic strategy is to treat with albendazole and praziquantel, to assess response after 1 month or more, and, depending on the response, to then manage the patient with continued chemotherapy or combined surgical and drug therapy.

C. Neurocysticercosis

Indications for medical therapy for neurocysticercosis are controversial, since antihelminthic therapy is not clearly superior to therapy with corticosteroids alone and may exacerbate neurologic disease. Therapy is probably most appropriate for symptomatic parenchymal or intraventricular cysts. Corticosteroids are usually given with the antihelminthic drug to decrease inflammation caused by dying organisms. Albendazole is now generally considered the drug of choice over praziquantel because of its shorter course, lower cost, improved penetration into the subarachnoid space, and increased drug levels (as opposed to decreased levels of praziquantel) when administered with corticosteroids. Albendazole is given in a dosage of 400 mg twice daily for up to 21 days.

D. Other Infections

Albendazole is the drug of choice in the treatment of cutaneous larva migrans (400 mg daily for 3 days), visceral larva migrans (400 mg twice daily for 5 days), intestinal capillariasis (400 mg daily for 10 days), microsporidial infections (400 mg twice daily for 2 weeks or longer), and gnathostomiasis (400 mg twice daily for 3 weeks). It also has activity against trichinosis (400 mg twice daily for 1–2 weeks) and clonorchiasis (400 mg twice daily for 1 week). There have been reports of some effectiveness in treatment of opisthorchiasis, toxocariasis, and loiasis, and conflicting reports of effectiveness in giardiasis and taeniasis. Albendazole is included in programs to control lymphatic filariasis, but it appears to be less active than diethylcarbamazine or ivermectin for this purpose. Albendazole has been recommended as empiric therapy to treat those who return from the tropics with persistent unexplained eosinophilia.

Adverse Reactions, Contraindications, & Cautions

When used for 1–3 days, albendazole is nearly free of significant adverse effects. Mild and transient epigastric distress, diarrhea, headache, nausea, dizziness, lassitude, and insomnia can occur. In long-term use for hydatid disease, albendazole is well tolerated, but it can cause abdominal distress, headaches, fever, fatigue, alopecia, increases in liver enzymes, and pancytopenia.

Blood counts and liver function studies should be monitored during long-term therapy. The drug should not be given to patients with known hypersensitivity to other benzimidazole drugs or to those with cirrhosis. The safety of albendazole in pregnancy and in children younger than 2 years of age has not been established.

BITHIONOL

Bithionol is an alternative to triclabendazole for the treatment of fascioliasis (sheep liver fluke). Bithionol is also an alternative drug in the treatment of pulmonary paragonimiasis.

Basic Pharmacology

After ingestion, bithionol reaches peak blood levels in 4–8 hours. Excretion appears to be mainly via the kidney.

Clinical Uses

For treatment of paragonimiasis and fascioliasis, the dosage of bithionol is 30–50 mg/kg in two or three divided doses, given orally after meals on alternate days for 10–15 doses. For pulmonary paragonimiasis, cure rates are over 90%. For cerebral paragonimiasis, repeat courses of therapy may be necessary.

Adverse Reactions, Contraindications, & Cautions

Adverse effects, which occur in up to 40% of patients, are generally mild and transient, but occasionally their severity requires interruption of therapy. These problems include diarrhea, abdominal cramps, anorexia, nausea, vomiting, dizziness, and headache. Skin rashes may occur after a week or more of therapy, suggesting a reaction to antigens released from dying worms.

Bithionol should be used with caution in children younger than 8 years of age because there has been limited experience in this age group.

DIETHYLCARBAMAZINE CITRATE

Diethylcarbamazine is a drug of choice in the treatment of filariasis, loiasis, and tropical eosinophilia. It has been replaced by ivermectin for the treatment of onchocerciasis.

Basic Pharmacology

Diethylcarbamazine, a synthetic piperazine derivative, is marketed as a citrate salt. It is rapidly absorbed from the gastrointestinal

tract; after a 0.5 mg/kg dose, peak plasma levels are reached within 1–2 hours. The plasma half-life is 2–3 hours in the presence of acidic urine but about 10 hours if the urine is alkaline, a Henderson-Hasselbalch trapping effect (see Chapter 1). The drug rapidly equilibrates with all tissues except fat. It is excreted, principally in the urine, as unchanged drug and the N-oxide metabolite. Dosage may have to be reduced in patients with persistent urinary alkalosis or renal impairment.

Diethylcarbamazine immobilizes microfilariae and alters their surface structure, displacing them from tissues and making them more susceptible to destruction by host defense mechanisms. The mode of action against adult worms is unknown.

Clinical Uses

The drug should be taken after meals.

A. *Wuchereria bancrofti, Brugia malayi, Brugia timori,* and *Loa loa*

Diethylcarbamazine is the drug of choice for treatment of infections with these parasites because of its efficacy and lack of serious toxicity. Microfilariae of all species are rapidly killed; adult parasites are killed more slowly, often requiring several courses of treatment. The drug is highly effective against adult *L loa*. The extent to which *W bancrofti* and *B malayi* adults are killed is not known, but after appropriate therapy microfilariae do not reappear in the majority of patients.

These infections are treated for 2 or (for *L loa*) 3 weeks, with initial low doses to reduce the incidence of allergic reactions to dying microfilariae. This regimen is 50 mg (1 mg/kg in children) on day 1, three 50 mg doses on day 2, three 100 mg doses (2 mg/kg in children) on day 3, and then 2 mg/kg three times daily to complete the 2–3 week course.

Antihistamines may be given for the first few days of therapy to limit allergic reactions, and corticosteroids should be started and doses of diethylcarbamazine lowered or interrupted if severe reactions occur. Cures may require several courses of treatment. For patients with high *L loa* worm burdens (more than 2500 circulating parasites/mL), strategies to decrease risks of severe toxicity include apheresis, if available, to remove microfilariae before treatment with diethylcarbamazine or therapy with albendazole, which is slower acting and better tolerated, before therapy with diethylcarbamazine or ivermectin.

Diethylcarbamazine may also be used for chemoprophylaxis (300 mg weekly or 300 mg on 3 successive days each month for loiasis; 50 mg monthly for bancroftian and Malayan filariasis).

B. Other Uses

For tropical eosinophilia, diethylcarbamazine is given orally at a dosage of 2 mg/kg three times daily for 7 days. Diethylcarbamazine is effective in *Mansonella streptocerca* infections, since it kills both adults and microfilariae. Limited information suggests that the drug is not effective, however, against adult *M ozzardi* or *M perstans* and that it has limited activity against microfilariae of these parasites. An important application of diethylcarbamazine has been mass treatment to reduce the prevalence of *W bancrofti* infection, generally in combination with ivermectin or albendazole. This strategy has led to excellent progress in disease control in a number of countries.

Adverse Reactions, Contraindications, & Cautions

Reactions to diethylcarbamazine, which are generally mild and transient, include headache, malaise, anorexia, weakness, nausea, vomiting, and dizziness. Adverse effects also occur as a result of the release of proteins from dying microfilariae or adult worms. Reactions are particularly severe with onchocerciasis, but diethylcarbamazine is no longer commonly used for this infection, because ivermectin is equally efficacious and less toxic. Reactions to dying microfilariae are usually mild in *W bancrofti*, more intense in *B malayi*, and occasionally severe in *L loa* infections. Reactions include fever, malaise, papular rash, headache, gastrointestinal symptoms, cough, chest pain, and muscle or joint pain. Leukocytosis is common. Eosinophilia may increase with treatment. Proteinuria may also occur. Symptoms are most likely to occur in patients with heavy loads of microfilariae. Retinal hemorrhages and, rarely, encephalopathy have been described.

Between the third and twelfth days of treatment, local reactions may occur in the vicinity of dying adult or immature worms. These include lymphangitis with localized swellings in *W bancrofti* and *B malayi*, small wheals in the skin in *L loa*, and flat papules in *M streptocerca* infections. Patients with attacks of lymphangitis due to *W bancrofti* or *B malayi* should be treated during a quiescent period between attacks.

Caution is advised when using diethylcarbamazine in patients with hypertension or renal disease.

DOXYCYCLINE

This tetracycline antibiotic is described in more detail in Chapter 44. Doxycycline has recently been shown to have significant macrofilaricidal activity against *W bancrofti*, suggesting better activity than any other available drug against adult worms. Activity is also seen against onchocerciasis. Doxycycline acts indirectly, by killing *Wolbachia,* an intracellular bacterial symbiont of filarial parasites. It may prove to be an important drug for filariasis, both for treatment of active disease and in mass chemotherapy campaigns.

IVERMECTIN

Ivermectin is the drug of choice in strongyloidiasis and onchocerciasis. It is also an alternative drug for a number of other helminthic infections.

Basic Pharmacology

Ivermectin, a semisynthetic macrocyclic lactone, is a mixture of avermectin B_{1a} and B_{1b}. It is derived from the soil actinomycete *Streptomyces avermitilis.*

Ivermectin is used only orally in humans. The drug is rapidly absorbed, reaching maximum plasma concentrations 4 hours after a

12 mg dose. The drug has a wide tissue distribution and a volume of distribution of about 50 L. Its half-life is about 16 hours. Excretion of the drug and its metabolites is almost exclusively in the feces.

Ivermectin appears to paralyze nematodes and arthropods by intensifying γ-aminobutyric acid (GABA)–mediated transmission of signals in peripheral nerves. In onchocerciasis, ivermectin is microfilaricidal. It does not effectively kill adult worms but blocks the release of microfilariae for some months after therapy. After a single standard dose, microfilariae in the skin diminish rapidly within 2–3 days, remain low for months, and then gradually increase; microfilariae in the anterior chamber of the eye decrease slowly over months, eventually clear, and then gradually return. With repeated doses of ivermectin, the drug appears to have a low-level macrofilaricidal action and to permanently reduce microfilarial production.

Clinical Uses

A. Onchocerciasis

Treatment is with a single oral dose of ivermectin, 150 mcg/kg, with water on an empty stomach. Doses are repeated; regimens vary from monthly to less frequent (every 6–12 months) dosing schedules. After acute therapy, treatment is repeated at 12-month intervals until the adult worms die, which may take 10 years or longer. With the first treatment only, patients with microfilariae in the cornea or anterior chamber may be treated with corticosteroids to avoid inflammatory eye reactions.

Ivermectin also now plays a key role in onchocerciasis control. Annual mass treatments have led to major reductions in disease transmission. However, evidence of diminished responsiveness after mass administration of ivermectin has raised concern regarding selection of drug-resistant parasites.

B. Strongyloidiasis

Treatment consists of two daily doses of 200 mcg/kg. In immunosuppressed patients with disseminated infection, repeated treatment is often needed, and cure may not be possible. In this case, suppressive therapy—ie, once monthly—may be helpful.

C. Other Parasites

Ivermectin reduces microfilariae in *B malayi* and *M ozzardi* infections but not in *M perstans* infections. It has been used with diethylcarbamazine and albendazole for the control of *W bancrofti*, but it does not kill adult worms. In loiasis, although the drug reduces microfilaria concentrations, it can occasionally induce severe reactions and appears to be more dangerous in this regard than diethylcarbamazine. Ivermectin is also effective in controlling scabies, lice, and cutaneous larva migrans and in eliminating a large proportion of ascarid worms.

Adverse Reactions, Contraindications, & Cautions

In strongyloidiasis treatment, infrequent adverse effects include fatigue, dizziness, nausea, vomiting, abdominal pain, and rashes. In onchocerciasis treatment, adverse effects are principally from the killing of microfilariae and can include fever, headache, dizziness, somnolence, weakness, rash, increased pruritus, diarrhea, joint and muscle pains, hypotension, tachycardia, lymphadenitis, lymphangitis, and peripheral edema. This reaction starts on the first day and peaks on the second day after treatment. This reaction occurs in 5–30% of persons and is generally mild, but it may be more frequent and more severe in individuals who are not long-term residents of onchocerciasis-endemic areas. A more intense reaction occurs in 1–3% of persons and a severe reaction in 0.1%, including high fever, hypotension, and bronchospasm. Corticosteroids are indicated in these cases, at times for several days. Toxicity diminishes with repeated dosing. Swellings and abscesses occasionally occur at 1–3 weeks, presumably at sites of adult worms.

Some patients develop corneal opacities and other eye lesions several days after treatment. These are rarely severe and generally resolve without corticosteroid treatment.

It is best to avoid concomitant use of ivermectin with other drugs that enhance GABA activity, eg, barbiturates, benzodiazepines, and valproic acid. Ivermectin should not be used during pregnancy. Safety in children younger than 5 years has not been established.

MEBENDAZOLE

Mebendazole is a synthetic benzimidazole that has a wide spectrum of antihelminthic activity and a low incidence of adverse effects.

Basic Pharmacology

Less than 10% of orally administered mebendazole is absorbed. The absorbed drug is protein-bound (> 90%), is rapidly converted to inactive metabolites (primarily during its first pass in the liver), and has a half-life of 2–6 hours. It is excreted mostly in the urine, principally as decarboxylated derivatives. In addition, a portion of absorbed drug and its derivatives are excreted in the bile. Absorption is increased if the drug is ingested with a fatty meal.

Mebendazole probably acts by inhibiting microtubule synthesis; the parent drug appears to be the active form. Efficacy of the drug varies with gastrointestinal transit time, with intensity of infection, and perhaps with the strain of parasite. The drug kills hookworm, ascaris, and trichuris eggs.

Clinical Uses

Mebendazole is indicated for use in ascariasis, trichuriasis, hookworm and pinworm infections, and certain other helminthic infections. It can be taken before or after meals; the tablets should be chewed before swallowing. For pinworm infection, the dose is 100 mg once, repeated at 2 weeks. For ascariasis, trichuriasis, hookworm, and trichostrongylus infections, a dosage of 100 mg twice daily for 3 days is used for adults and for children older than 2 years of age. Cure rates are good for pinworm infections and ascariasis, but have been disappointing in recent studies of trichuriasis. Cure rates are also lower for hookworm infections, but a

marked reduction in the worm burden occurs in those not cured. For intestinal capillariasis, mebendazole is used at a dosage of 200 mg twice daily for 21 or more days. In trichinosis, limited reports suggest efficacy against adult worms in the intestinal tract and tissue larvae. Treatment is three times daily, with fatty foods, at 200–400 mg per dose for 3 days and then 400–500 mg per dose for 10 days; corticosteroids should be coadministered for severe infections.

Adverse Reactions, Contraindications, & Cautions

Short-term mebendazole therapy for intestinal nematodes is nearly free of adverse effects. Mild nausea, vomiting, diarrhea, and abdominal pain have been reported infrequently. Rare side effects, usually with high-dose therapy, are hypersensitivity reactions (rash, urticaria), agranulocytosis, alopecia, and elevation of liver enzymes.

Mebendazole is teratogenic in animals and therefore contraindicated in pregnancy. It should be used with caution in children younger than 2 years of age because of limited experience and rare reports of convulsions in this age group. Plasma levels may be decreased by concomitant use of carbamazepine or phenytoin and increased by cimetidine. Mebendazole should be used with caution in patients with cirrhosis.

METRIFONATE (TRICHLORFON)

Metrifonate is a safe, low-cost alternative drug for the treatment of *Schistosoma haematobium* infections. It is not active against *S mansoni or S japonicum*. It is not available in the USA.

Basic Pharmacology

Metrifonate, an organophosphate compound, is rapidly absorbed after oral administration. After the standard oral dose, peak blood levels are reached in 1–2 hours; the half-life is about 1.5 hours. Clearance appears to be through nonenzymatic transformation to dichlorvos, its active metabolite. Metrifonate and dichlorvos are well distributed to the tissues and are completely eliminated in 24–48 hours.

The mode of action is thought to be related to cholinesterase inhibition. This inhibition temporarily paralyzes the adult worms, resulting in their shift from the bladder venous plexus to small arterioles of the lungs, where they are trapped, encased by the immune system, and die. The drug is not effective against *S haematobium* eggs; live eggs continue to pass in the urine for several months after all adult worms have been killed.

Clinical Uses

In the treatment of *S haematobium*, an oral dose of 7.5–10 mg/kg is given three times at 14-day intervals. Cure rates on this schedule are 44–93%, with marked reductions in egg counts in those not cured. Metrifonate was also effective as a prophylactic agent when given monthly to children in a highly endemic area, and it has been used in mass treatment programs. In mixed infections with *S haematobium* and *S mansoni*, metrifonate has been successfully combined with oxamniquine.

Adverse Reactions, Contraindications, & Cautions

Some studies note mild and transient cholinergic symptoms, including nausea and vomiting, diarrhea, abdominal pain, bronchospasm, headache, sweating, fatigue, weakness, dizziness, and vertigo. These symptoms may begin within 30 minutes and persist up to 12 hours.

Metrifonate should not be used after recent exposure to insecticides or drugs that might potentiate cholinesterase inhibition. Metrifonate is contraindicated in pregnancy.

NICLOSAMIDE

Niclosamide is a second-line drug for the treatment of most tapeworm infections, but it is not available in the USA.

Basic Pharmacology

Niclosamide is a salicylamide derivative. It appears to be minimally absorbed from the gastrointestinal tract—neither the drug nor its metabolites have been recovered from the blood or urine.

Adult worms (but not ova) are rapidly killed, presumably due to inhibition of oxidative phosphorylation or stimulation of ATPase activity.

Clinical Uses

The adult dose of niclosamide is 2 g once, given in the morning on an empty stomach. The tablets must be chewed thoroughly and then swallowed with water.

A. *Taenia saginata* (Beef Tapeworm), *T solium* (Pork Tapeworm), and *Diphyllobothrium latum* (Fish Tapeworm)

A single 2 g dose of niclosamide results in cure rates of over 85% for *D latum* and about 95% for *T saginata*. It is probably equally effective against *T solium*. Cysticercosis can theoretically occur after treatment of *T solium* infections, because viable ova are released into the gut lumen after digestion of segments, but no such cases have been reported.

B. Other Tapeworms

Most patients treated with niclosamide for *Hymenolepsis diminuta* and *Dipylidium caninum* infections are cured with a 7-day course of treatment; a few require a second course. Praziquantel is superior for *Hymenolepis nana* (dwarf tapeworm) infection. Niclosamide is not effective against cysticercosis or hydatid disease.

C. Intestinal Fluke Infections

Niclosamide can be used as an alternative drug in the treatment of *Fasciolopsis buski*, *Heterophyes heterophyes*, and *Metagonimus yokogawai* infections. The standard dose is given every other day for three doses.

Adverse Reactions, Contraindications, & Cautions

Infrequent, mild, and transitory adverse events include nausea, vomiting, diarrhea, and abdominal discomfort. The consumption of alcohol should be avoided on the day of treatment and for 1 day afterward. The safety of the drug has not been established in pregnancy or for children younger than 2 years of age.

OXAMNIQUINE

Oxamniquine is an alternative to praziquantel for the treatment of *S mansoni* infections. It has also been used extensively for mass treatment. It is not effective against *S haematobium* or *S japonicum*. It is not available in the USA.

Basic Pharmacology

Oxamniquine, a semisynthetic tetrahydroquinoline, is readily absorbed orally; it should be taken with food. Its plasma half-life is about 2.5 hours. The drug is extensively metabolized to inactive metabolites and excreted in the urine—up to 75% in the first 24 hours. Intersubject variations in serum concentration have been noted, which may explain some treatment failures.

Oxamniquine is active against both mature and immature stages of *S mansoni* but does not appear to be cercaricidal. The mechanism of action is unknown. Contraction and paralysis of the worms results in detachment from terminal venules in the mesentery and transit to the liver, where many die; surviving females return to the mesenteric vessels but cease to lay eggs. Strains of *S mansoni* in different parts of the world vary in susceptibility. Oxamniquine has been effective in instances of praziquantel resistance.

Clinical Uses

Oxamniquine is safe and effective in all stages of *S mansoni* disease, including advanced hepatosplenomegaly. In the acute (Katayama) syndrome, treatment results in disappearance of acute symptoms and clearance of the infection. The drug is generally less effective in children, who require higher doses than adults. It is better tolerated with food.

Optimal dosage schedules vary for different regions of the world. In the western hemisphere and western Africa, the adult oxamniquine dosage is 12–15 mg/kg given once. In northern and southern Africa, standard schedules are 15 mg/kg twice daily for 2 days. In eastern Africa and the Arabian peninsula, standard dosage is 15–20 mg/kg twice in 1 day. Cure rates are 70–95%, with marked reduction in egg excretion in those not cured. In mixed schistosome infections, oxamniquine has been successfully used in combination with metrifonate.

Adverse Reactions, Contraindications, & Cautions

Mild symptoms, starting about 3 hours after a dose and lasting for several hours, occur in more than one third of patients. Central nervous system symptoms (dizziness, headache, drowsiness) are most common; nausea and vomiting, diarrhea, colic, pruritus, and urticaria also occur. Infrequent adverse effects are low-grade fever, an orange to red discoloration of the urine, proteinuria, microscopic hematuria, and a transient decrease in leukocytes. Seizures have been reported rarely.

Since the drug makes many patients dizzy or drowsy, it should be used with caution in patients whose work or activity requires mental alertness (eg, no driving for 24 hours). It should be used with caution in those with a history of epilepsy. Oxamniquine is contraindicated in pregnancy.

PIPERAZINE

Piperazine is an alternative for the treatment of ascariasis, with cure rates over 90% when taken for 2 days, but it is not recommended for other helminth infections. Piperazine is available as the hexahydrate and as a variety of salts. It is readily absorbed, and maximum plasma levels are reached in 2–4 hours. Most of the drug is excreted unchanged in the urine in 2–6 hours, and excretion is complete within 24 hours.

Piperazine causes paralysis of ascaris by blocking acetylcholine at the myoneural junction; unable to maintain their position in the host, live worms are expelled by normal peristalsis.

For ascariasis, the dosage of piperazine (as the hexahydrate) is 75 mg/kg (maximum dose, 3.5 g) orally once daily for 2 days. For heavy infections, treatment should be continued for 3–4 days or repeated after 1 week.

Occasional mild adverse effects include nausea, vomiting, diarrhea, abdominal pain, dizziness, and headache. Neurotoxicity and allergic reactions are rare. Piperazine compounds should not be given to women during pregnancy, to patients with impaired renal or hepatic function, or to those with a history of epilepsy or chronic neurologic disease.

PRAZIQUANTEL

Praziquantel is effective in the treatment of schistosome infections of all species and most other trematode and cestode infections, including cysticercosis. The drug's safety and effectiveness as a single oral dose have also made it useful in mass treatment of several infections.

Basic Pharmacology

Praziquantel is a synthetic isoquinoline-pyrazine derivative. It is rapidly absorbed, with a bioavailability of about 80% after oral administration. Peak serum concentrations are reached 1–3 hours after a therapeutic dose. Cerebrospinal fluid concentrations of praziquantel reach 14–20% of the drug's plasma concentration. About 80% of the drug is bound to plasma proteins. Most of the drug is rapidly metabolized to inactive mono- and polyhydroxylated products after a first pass in the liver. The half-life is 0.8–1.5 hours. Excretion is mainly via the kidneys (60–80%) and bile (15–35%). Plasma concentrations of praziquantel increase when the drug is

taken with a high-carbohydrate meal or with cimetidine; bioavailability is markedly reduced with some antiepileptics (phenytoin, carbamazepine) or with corticosteroids.

Praziquantel appears to increase the permeability of trematode and cestode cell membranes to calcium, resulting in paralysis, dislodgement, and death. In schistosome infections of experimental animals, praziquantel is effective against adult worms and immature stages, and it has a prophylactic effect against cercarial infection.

Clinical Uses

Praziquantel tablets are taken with liquid after a meal; they should be swallowed without chewing because their bitter taste can induce retching and vomiting.

A. Schistosomiasis

Praziquantel is the drug of choice for all forms of schistosomiasis. The dosage is 20 mg/kg per dose for two (*S mansoni* and *S haematobium*) or three (*S japonicum* and *S mekongi*) doses at intervals of 4–6 hours. High cure rates (75–95%) are achieved when patients are evaluated at 3–6 months; there is marked reduction in egg counts in those not cured. The drug is effective in adults and children and is generally well tolerated by patients in the hepatosplenic stage of advanced disease. There is no standard regimen for acute schistosomiasis (Katayama syndrome), but standard doses as described above, often with corticosteroids to limit inflammation from the acute immune response and dying worms, are recommended. Increasing evidence indicates rare *S mansoni* drug resistance, which may be countered with extended courses of therapy (eg, 3–6 days at standard dosing) or treatment with oxamniquine. Effectiveness of praziquantel for chemoprophylaxis has not been established.

B. Clonorchiasis, Opisthorchiasis, and Paragonimiasis

Standard dosing is 25 mg/kg three times daily for 2 days for each of these fluke infections.

C. Taeniasis and Diphyllobothriasis

A single dose of praziquantel, 5–10 mg/kg, results in nearly 100% cure rates for *T saginata*, *T solium*, and *D latum* infections. Because praziquantel does not kill eggs, it is theoretically possible that larvae of *T solium* released from eggs in the large bowel could penetrate the intestinal wall and give rise to cysticercosis, but this hazard is probably minimal.

D. Neurocysticercosis

Albendazole is now the preferred drug, but when it is not appropriate or available, praziquantel has similar efficacy. Indications for praziquantel are similar to those for albendazole. The praziquantel dosage is 100 mg/kg/d in three divided doses for 1 day, then 50 mg/kg/d to complete a 2- to 4-week course. Clinical responses to therapy vary from dramatic improvements of seizures and other neurologic findings to no response and even progression of the disease. Praziquantel—but not albendazole—has diminished bioavailability when taken concurrently with a corticosteroid. Recommendations on use of both antihelminthics and corticosteroids in neurocysticercosis vary.

E. *Hymenolepis nana*

Praziquantel is the drug of choice for *H nana* infections and the first drug to be highly effective. A single dose of 25 mg/kg is taken initially and repeated in 1 week.

F. Hydatid Disease

In hydatid disease, praziquantel kills protoscoleces but does not affect the germinal membrane. Praziquantel is being evaluated as an adjunct with albendazole pre- and postsurgery. In addition to its direct action, praziquantel enhances the plasma concentration of albendazole.

G. Other Parasites

Limited trials at a dosage of 25 mg/kg three times daily for 1–2 days indicate effectiveness of praziquantel against fasciolopsiasis, metagonimiasis, and other forms of heterophyiasis. Praziquantel was not effective for fascioliasis, however, even at dosages as high as 25 mg/kg three times daily for 3–7 days.

Adverse Reactions, Contraindications, & Cautions

Mild and transient adverse effects are common. They begin within several hours after ingestion of praziquantel and may persist for about 1 day. Most common are headache, dizziness, drowsiness, and lassitude; others include nausea, vomiting, abdominal pain, loose stools, pruritus, urticaria, arthralgia, myalgia, and low-grade fever. Mild and transient elevations of liver enzymes have been reported. Several days after starting praziquantel, low-grade fever, pruritus, and skin rashes (macular and urticarial), sometimes associated with worsened eosinophilia, may occur, probably due to the release of proteins from dying worms rather than direct drug toxicity. The intensity and frequency of adverse effects increase with dosage such that they occur in up to 50% of patients who receive 25 mg/kg three times in 1 day.

In neurocysticercosis, neurologic abnormalities may be exacerbated by inflammatory reactions around dying parasites. Common findings in patients who do not receive corticosteroids, usually presenting during or shortly after therapy, are headache, meningismus, nausea, vomiting, mental changes, and seizures (often accompanied by increased cerebrospinal fluid pleocytosis). More serious findings, including arachnoiditis, hyperthermia, and intracranial hypertension, may also occur. Corticosteroids are commonly used with praziquantel in the treatment of neurocysticercosis to decrease the inflammatory reaction, but this is controversial and complicated by knowledge that corticosteroids decrease the plasma level of praziquantel up to 50%. Praziquantel is contraindicated in ocular cysticercosis, because parasite destruction in the eye may cause irreparable damage. Some workers also caution against use of the drug in spinal neurocysticercosis.

The safety of praziquantel in children younger than age 4 years is not established, but no specific problems in young children have been documented. Indeed, the drug appears to be better tolerated in children than in adults. Praziquantel increased abortion rates in rats and therefore should be avoided in pregnancy if possible. Because the drug induces dizziness and drowsiness, patients should not drive during therapy and should be warned regarding activities requiring particular physical coordination or alertness.

PYRANTEL PAMOATE

Pyrantel pamoate is a broad-spectrum antihelminthic highly effective for the treatment of pinworm, ascaris, and *Trichostrongylus orientalis* infections. It is moderately effective against both species of hookworm. It is not effective in trichuriasis or strongyloidiasis. Oxantel pamoate, an analog of pyrantel not available in the USA, has been used successfully in the treatment of trichuriasis; the two drugs have been combined for their broad-spectrum antihelminthic activity.

Basic Pharmacology

Pyrantel pamoate is a tetrahydropyrimidine derivative. It is poorly absorbed from the gastrointestinal tract and active mainly against luminal organisms. Peak plasma levels are reached in 1–3 hours. Over half of the administered dose is recovered unchanged in the feces.

Pyrantel is effective against mature and immature forms of susceptible helminths within the intestinal tract but not against migratory stages in the tissues or against ova. The drug is a neuromuscular blocking agent that causes release of acetylcholine and inhibition of cholinesterase; this results in paralysis of worms, which is followed by expulsion.

Clinical Uses

The standard dose is 11 mg (base)/kg (maximum, 1 g), given orally once with or without food. For pinworm, the dose is repeated in 2 weeks, and cure rates are greater than 95%. The drug is available in the USA without prescription for this indication.

For ascariasis, a single dose yields cure rates of 85–100%. Treatment should be repeated if eggs are found 2 weeks after treatment. For hookworm infections, a single dose is effective against light infections; but for heavy infections, especially with *Necator americanus*, a 3-day course is necessary to reach 90% cure rates. A course of treatment can be repeated in 2 weeks.

Adverse Reactions, Contraindications, & Cautions

Adverse effects are infrequent, mild, and transient. They include nausea, vomiting, diarrhea, abdominal cramps, dizziness, drowsiness, headache, insomnia, rash, fever, and weakness. Pyrantel should be used with caution in patients with liver dysfunction, because low, transient aminotransferase elevations have been noted in a small number of patients. Experience with the drug in pregnant women and children younger than 2 years of age is limited.

THIABENDAZOLE

Thiabendazole is an alternative to ivermectin or albendazole for the treatment of strongyloidiasis and cutaneous larva migrans.

Basic Pharmacology

Thiabendazole is a benzimidazole compound. Although it is a chelating agent that forms stable complexes with a number of metals, including iron, it does not bind calcium.

Thiabendazole is rapidly absorbed after ingestion. With a standard dose, drug concentrations in plasma peak within 1–2 hours; the half-life is 1.2 hours. The drug is almost completely metabolized in the liver to the 5-hydroxy form; 90% is excreted in the urine in 48 hours, largely as the glucuronide or sulfonate conjugate. Thiabendazole can also be absorbed from the skin.

The mechanism of action of thiabendazole is probably the same as that of other benzimidazoles (see above). The drug has ovicidal effects against some parasites.

Clinical Uses

The standard dosage, 25 mg/kg (maximum 1.5 g) twice daily, should be given after meals. Tablets should be chewed. For strongyloides infection, treatment is for 2 days. Cure rates are reportedly 93%. A course can be repeated in 1 week if indicated. In patients with hyperinfection syndrome, the standard dose is continued twice daily for 5–7 days. For cutaneous larva migrans, thiabendazole cream can be applied topically, or the oral drug can be given for 2 days (although albendazole is less toxic and therefore preferred).

Adverse Reactions, Contraindications, & Cautions

Thiabendazole is much more toxic than other benzimidazoles and more toxic than ivermectin, so other agents are now preferred for most indications. Common adverse effects include dizziness, anorexia, nausea, and vomiting. Less common problems are epigastric pain, abdominal cramps, diarrhea, pruritus, headache, drowsiness, and neuropsychiatric symptoms. Irreversible liver failure and fatal Stevens-Johnson syndrome have been reported.

Experience with thiabendazole is limited in children weighing less than 15 kg. The drug should not be used in pregnancy or in the presence of hepatic or renal disease

PREPARATIONS AVAILABLE[1]

Albendazole (Albenza)
Oral: 200 mg tablets; 100 mg/5 mL suspension
Note: Albendazole is approved in the USA for the treatment of cysticercosis and hydatid disease.

Bithionol (Bitin)[1]

Diethylcarbamazine (Hetrazan)
Oral: 50 mg tablets

Ivermectin (Mectizan, Stromectol)
Oral: 3, 6 mg tablets
Note: Ivermectin is approved for use in the USA for the treatment of onchocerciasis and strongyloidiasis. See Chapter 65 for comment on the unlabeled use of drugs.

Mebendazole (generic, Vermox)
Oral: 100 mg chewable tablets; outside the USA, 100 mg/5 mL suspension

Metrifonate (trichlorfon, Bilarcil)[1]

Niclosamide (Niclocide)[1]

Oxamniquine (Vansil, Mansil)[1]

Oxantel pamoate (Quantrel); oxantel/pyrantel pamoate (Telopar)
Oral: tablets containing 100 mg (base) of each drug; suspensions containing 20 or 50 mg (base) per mL
Note: Oxantel pamoate and oxantel/pyrantel pamoate are not available in the USA.

Piperazine (generic, Vermizine)[1]

Praziquantel (Biltricide; others outside the USA)
Oral: 600 mg tablets (other strengths outside the USA)

Pyrantel pamoate (Antiminth, Combantrin, Pin-rid, Pin-X)
Oral: 50 mg (base)/mL suspension; 180 mg; 62.5 mg (base) capsules (available without prescription in the USA)

Suramin (Bayer 205, others)[1]

Thiabendazole (Mintezol)
Oral: 500 mg chewable tablets; suspension, 500 mg/mL

[1]Additional information may be obtained from the Parasitic Disease Drug Service, Parasitic Diseases Branch, Centers for Disease Control and Prevention, Atlanta, Georgia, 30333. Telephone: (404) 639-3670.

REFERENCES

Bagheri H et al: Adverse drug reactions to anthelmintics. Ann Pharmacother 2004;38:383.

Basáñez MG et al: Effect of single-dose ivermectin on *Onchocerca volvulus*: A systematic review and meta-analysis. Lancet Infect Dis 2008;8:310.

Bethony J et al: Soil-transmitted helminth infections: Ascariasis, trichuriasis, and hookworm. Lancet 2006;367:1521.

Bockarie MJ et al: Efficacy of single-dose diethylcarbamazine compared with diethylcarbamazine combined with albendazole against *Wuchereria bancrofti* infection in Papua New Guinea. Am J Trop Med Hyg 2007;76:62.

Bockarie MJ et al: Mass treatment to eliminate filariasis in Papua New Guinea. N Engl J Med 2002;347:1841.

Craig P, Ito A: Intestinal cestodes. Curr Opin Infect Dis 2007;20:524.

Danso-Appiah A et al: Drugs for treating urinary schistosomiasis. Cochrane Database Syst Rev 2008:CD000053

Dayan AD: Albendazole, mebendazole and praziquantel. Review of non-clinical toxicity and pharmacokinetics. Acta Trop 2003;86:141.

Drugs for parasitic infections. Med Lett Drugs Ther 2007;(Suppl 1).

Flohr C et al: Low efficacy of mebendazole against hookworm in Vietnam: Two randomized controlled trials. Am J Trop Med Hyg 2007;76:732.

Fox LM: Ivermectin: Uses and impact 20 years on. Curr Opin Infect Dis 2006;19:588.

Garcia HH et al: Current consensus guidelines for treatment of neurocysticercosis. Clin Microbiol Rev 2002;15:747.

Garcia HH et al: A trial of antiparasitic treatment to reduce the rate of seizures due to cerebral cysticercosis. N Engl J Med 2004;350:249.

Horton J: Albendazole: A broad spectrum anthelminthic for treatment of individuals and populations. Curr Opin Infect Dis 2002;15:599.

Keiser J, Utzinger J: Efficacy of current drugs against soil-transmitted helminth infections: Systematic review and meta-analysis. JAMA 2008;299:1937.

Matthaiou DK et al: Albendazole versus praziquantel in the treatment of neurocysticercosis: A meta-analysis of comparative trials. PLoS Negl Trop Dis 2008;2:e194.

Meltzer E et al: Eosinophilia among returning travelers: A practical approach. Am J Trop Med Hyg 2008;78:702.

Osei-Atweneboana MY: Prevalence and intensity of *Onchocerca volvulus* infection and efficacy of ivermectin in endemic communities in Ghana: A two-phase epidemiological study. Lancet 2007;369:2021.

Ramzy RM et al: Effect of yearly mass drug administration with diethylcarbamazine and albendazole on bancroftian filariasis in Egypt: A comprehensive assessment. Lancet 2006;367:992.

Reddy M et al: Oral drug therapy for multiple neglected tropical diseases: A systematic review. JAMA 2007;298:1911.

Smego RA Jr, Sebanego P: Treatment options for hepatic cystic echinococcosis. Int J Infect Dis 2005;9:69.

Supali T et al: Doxycycline treatment of *Brugia malayi*-infected persons reduces microfilaremia and adverse reactions after diethylcarbamazine and albendazole treatment. Clin Infect Dis 2008;46:1385.

Taylor MJ et al: Macrofilaricidal activity after doxycycline treatment of *Wuchereria bancrofti*: A double-blind, randomised placebo-controlled trial. Lancet 2005;365:2116.

Tisch DJ, Michael E, Kazura JW: Mass chemotherapy options to control lymphatic filariasis: A systematic review. Lancet Infect Dis 2005;5:514.

Udall DN: Recent updates on onchocerciasis: Diagnosis and treatment. Clin Infect Dis 2007;44:53.

CASE STUDY ANSWER

The presentation is highly suggestive of cystic hydatid disease (infection with *Echinococcus granulosis*), which is transmitted by eggs from the feces of dogs in contact with livestock. Other causes of liver fluid collections include amebic and pyogenic abscesses, but these are usually not cystic in appearance. For echinococcosis, a typical cystic lesion and positive serology support the diagnosis, and treatment generally entails albendazole in conjunction with cautious surgery or percutaneous aspiration. One approach entails treatment with albendazole followed by aspiration to confirm the diagnosis and, if it is confirmed, to remove most of the infecting worms.

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CHAPTER 54

Cancer Chemotherapy

Edward Chu, MD, &
Alan C. Sartorelli, PhD

CASE STUDY

A 55-year-old man presents with increasing fatigue, 15-pound weight loss, and a microcytic anemia. Colonoscopy identifies a mass in the ascending colon, and biopsy specimens reveal well-differentiated colorectal cancer (CRC). He undergoes surgical resection and is found to have high-risk stage III CRC with five positive lymph nodes. After surgery, he feels entirely well with no symptoms. Of note, he has no other comorbid illnesses. What is this patient's prognosis? Should he receive adjuvant chemotherapy? The patient receives a combination of 5-fluorouracil (5-FU), leucovorin, and oxaliplatin as adjuvant therapy. One week after receiving the first cycle of therapy, he experiences significant toxicity in the form of myelosuppression, diarrhea, and altered mental status. What is the most likely explanation for this increased toxicity? Is there any role for genetic testing to determine the etiology of this level of toxicity?

Cancer continues to be the second leading cause of mortality from disease in the USA, accounting for nearly 500,000 deaths in 2008. Cancer is a disease characterized by a loss in the normal control mechanisms that govern cell survival, proliferation, and differentiation. Cells that have undergone neoplastic transformation usually express cell surface antigens that may be of normal fetal type, may display other signs of apparent immaturity, and may exhibit qualitative or quantitative chromosomal abnormalities, including various translocations and the appearance of amplified gene sequences. It is now well established that a small subpopulation of cells, referred to as tumor stem cells, reside within a tumor mass. They retain the ability to undergo repeated cycles of proliferation as well as to migrate to distant sites in the body to colonize various organs in the process called metastasis. Such tumor stem cells thus can express clonogenic (colony-forming) capability, and they are characterized by chromosome abnormalities reflecting their genetic instability, which leads to progressive selection of subclones that can survive more readily in the multicellular environment of the host. This genetic instability also allows them to become resistant to chemotherapy and radiotherapy. The invasive and metastatic processes as well as a series of metabolic abnormalities associated with the cancer result in tumor-related symptoms and eventual death of the patient unless the neoplasm can be eradicated with treatment.

CAUSES OF CANCER

The incidence, geographic distribution, and behavior of specific types of cancer are related to multiple factors, including sex, age, race, genetic predisposition, and exposure to environmental carcinogens. Of these factors, **environmental exposure** is probably most important. Exposure to ionizing radiation has been well documented as a significant risk factor for a number of cancers, including acute leukemias, thyroid cancer, breast cancer, lung cancer, soft tissue sarcoma, and basal cell and squamous cell skin cancers. Chemical carcinogens (particularly those in tobacco smoke) as well as azo dyes, aflatoxins, asbestos, benzene, and radon have all been well documented as leading to a wide range of human cancers.

Several **viruses** have been implicated in the etiology of various human cancers. For example, hepatitis B and hepatitis C are associated with the development of hepatocellular cancer; HIV is associated with Hodgkin's and non-Hodgkin's lymphomas; human papillomavirus is associated with cervical cancer and head and neck cancer; and Ebstein-Barr virus is associated with nasopharyngeal cancer. Expression of virus-induced neoplasia may also depend on additional host and environmental factors that modulate the transformation process. Cellular genes are known that are homologous to the transforming genes of the retroviruses, a family

ACRONYMS

ABVD	Doxorubicin (Adriamycin, hydroxydaunorubicin), bleomycin, vinblastine, dacarbazine
CHOP	Cyclophosphamide, doxorubicin (hydroxydaunorubicin, Adriamycin), vincristine (Oncovin), prednisone
CMF	Cyclophosphamide, methotrexate, fluorouracil
COP	Cyclophosphamide, vincristine (Oncovin), prednisone
FAC	5-Fluorouracil, doxorubicin (Adriamycin, hydroxydaunorubicin), cyclophosphamide
FEC	5-Fluorouracil, epirubicin, cyclophosphamide
5-FU	5-Fluorouracil
FOLFIRI	5-Fluorouracil, leucovorin, irinotecan
FOLFOX	5-Fluorouracil, leucovorin, oxaliplatin
MP	Melphalan, prednisone
6-MP	6-Mercaptopurine
MOPP	Mechlorethamine, vincristine (Oncovin), procarbazine, prednisone
MTX	Methotrexate
PCV	Procarbazine, lomustine, vincristine
PEB	Cisplatin (platinum), etoposide, bleomycin
6-TG	6-Thioguanine
VAD	Vincristine, doxorubicin (Adriamycin), dexamethasone
XELOX	Capecitabine, oxaliplatin

of RNA viruses, and induce oncogenic transformation. These mammalian cellular genes, known as **oncogenes,** have been shown to code for specific growth factors and their corresponding receptors. These genes may be amplified (increased number of gene copies) or mutated, both of which can lead to constitutive overexpression in malignant cells. The *bcl*-2 family of genes represents a series of pro-survival genes that promotes survival by directly inhibiting apoptosis, a key pathway of programmed cell death.

Another class of genes, known as **tumor suppressor genes,** may be deleted or mutated, which gives rise to the neoplastic phenotype. The *p53* gene is the best-established tumor suppressor gene identified to date, and the normal wild-type gene appears to play an important role in suppressing neoplastic transformation. Of note, *p53* is mutated in up to 50% of all human solid tumors, including liver, breast, colon, lung, cervix, bladder, prostate, and skin.

CANCER TREATMENT MODALITIES

With present methods of treatment, about one third of patients are cured with local treatment strategies, such as surgery or radiotherapy, when the tumor remains localized at the time of diagnosis. Earlier diagnosis might lead to increased cure rates with such local treatment. In the remaining cases, however, early micrometastasis is a characteristic feature, indicating that a systemic approach with chemotherapy is required for effective cancer management. In patients with locally advanced disease, chemotherapy is often combined with radiotherapy to allow for surgical resection to take place, and such a combined modality approach has led to improved clinical outcomes. At present, about 50% of patients who are initially diagnosed with cancer can be cured. In contrast, chemotherapy alone is able to cure less than 10% of all cancer patients when the tumor is diagnosed at an advanced stage.

Chemotherapy is presently used in three main clinical settings: (1) primary induction treatment for advanced disease or for cancers for which there are no other effective treatment approaches, (2) neoadjuvant treatment for patients who present with localized disease, for whom local forms of therapy such as surgery or radiation, or both, are inadequate by themselves, (3) adjuvant treatment to local methods of treatment, including surgery, radiation therapy, or both.

Primary induction chemotherapy refers to chemotherapy administered as the primary treatment in patients who present with advanced cancer for which no alternative treatment exists. This has been the main approach in treating patients with advanced metastatic disease, and in most cases, the goals of therapy are to relieve tumor-related symptoms, improve overall quality of life, and prolong time to tumor progression. Studies in a wide range of solid tumors have shown that chemotherapy in patients with advanced disease confers survival benefit when compared with supportive care, providing sound rationale for the early initiation of drug treatment. However, cancer chemotherapy can be curative in only a small subset of patients who present with advanced disease. In adults, these curable cancers include Hodgkin's and non-Hodgkin's lymphoma, acute myelogenous leukemia, germ cell cancer, and choriocarcinoma, while the curable childhood cancers include acute lymphoblastic leukemia, Burkitt's lymphoma, Wilms' tumor, and embryonal rhabdomyosarcoma.

Neoadjuvant chemotherapy refers to the use of chemotherapy in patients who present with localized cancer for which alternative local therapies, such as surgery, exist but which are less than completely effective. At present, neoadjuvant therapy is most often administered in the treatment of anal cancer, bladder cancer, breast cancer, esophageal cancer, laryngeal cancer, locally advanced non-small cell lung cancer, and osteogenic sarcoma. For some of these diseases, such as anal cancer, gastroesophageal cancer, laryngeal cancer, and non-small cell lung cancer, optimal clinical benefit is derived when chemotherapy is administered with radiation therapy either concurrently or sequentially.

One of the most important roles for cancer chemotherapy is as an adjuvant to local treatment modalities such as surgery or radiation therapy, and this has been termed **adjuvant chemotherapy.** The goal of chemotherapy in this setting is to reduce the incidence of both local and systemic recurrence and to improve the overall survival of patients. In general, chemotherapy regimens with clinical activity against advanced disease may have curative potential following surgical resection of the primary tumor, provided the appropriate dose and schedule are administered. Adjuvant chemotherapy is effective in prolonging both disease-free survival (DFS) and overall survival (OS) in patients with breast cancer, colon cancer, gastric cancer, non-small cell lung cancer, Wilms' tumor, anaplastic astrocytoma, and osteogenic sarcoma. Patients with primary malignant melanoma at high risk of local recurrence

or systemic metastases derive clinical benefit from adjuvant treatment with the biologic agent α-interferon, although this treatment must be given for 1 year's duration for maximal clinical efficacy. Finally, the antihormonal agents tamoxifen, anastrozole, and letrozole are effective in the adjuvant therapy of postmenopausal women with early-stage breast cancer whose breast tumors express the estrogen receptor (see Chapter 40 for additional detail). However, because these agents are cytostatic rather than cytocidal, they must be administered on a long-term basis, with the standard recommendation being 5 years' duration.

ROLE OF CELL CYCLE KINETICS & ANTICANCER EFFECT

The key principles of cell cycle kinetics were initially developed using the murine L1210 leukemia as the experimental model system (Figure 54–1). However, drug treatment of human cancers requires a clear understanding of the differences between the characteristics of this rodent leukemia and of human cancers, as well as an understanding of the differences in growth rates of normal target tissues between mice and humans. For example, L1210 is a rapidly growing leukemia with a high percentage of cells synthesizing DNA, as measured by the uptake of tritiated thymidine (the labeling index). Because L1210 leukemia has a growth fraction of 100% (ie, all its cells are actively progressing through the cell cycle), its life cycle is consistent and predictable. Based on the murine L1210 model, the cytotoxic effects of anticancer drugs follow log cell-kill kinetics. As such, a given agent would be predicted to kill a constant fraction of cells as opposed to a constant number.

Thus, if a particular dose of an individual drug leads to a 3 log kill of cancer cells and reduces the tumor burden from 10^{10} to 10^{7} cells, the same dose used at a tumor burden of 10^{5} cells reduces the tumor mass to 10^{2} cells. Cell kill is, therefore, proportional, regardless of tumor burden. The cardinal rule of chemotherapy—the invariable inverse relation between cell number and curability—was established with this model, and this relationship is applicable to other hematologic malignancies.

Although growth of murine leukemias simulates exponential cell kinetics, mathematical modeling data suggest that most human solid tumors do not grow in such an exponential manner. Taken together, the experimental data in human solid cancers support a Gompertzian model of tumor growth and regression. The critical distinction between Gompertzian and exponential growth is that the growth fraction of the tumor is not constant with Gompertzian kinetics but instead decreases exponentially with time (exponential growth is matched by exponential retardation of growth, due to blood supply limitations and other factors). The growth fraction peaks when the tumor is approximately one third its maximum size. Under the Gompertzian model, when a patient with advanced cancer is treated, the tumor mass is larger, its growth fraction is low, and the fraction of cells killed is, therefore, small. An important feature of Gompertzian growth is that response to chemotherapy in drug-sensitive tumors depends, in large measure, on where the tumor is in its particular growth curve.

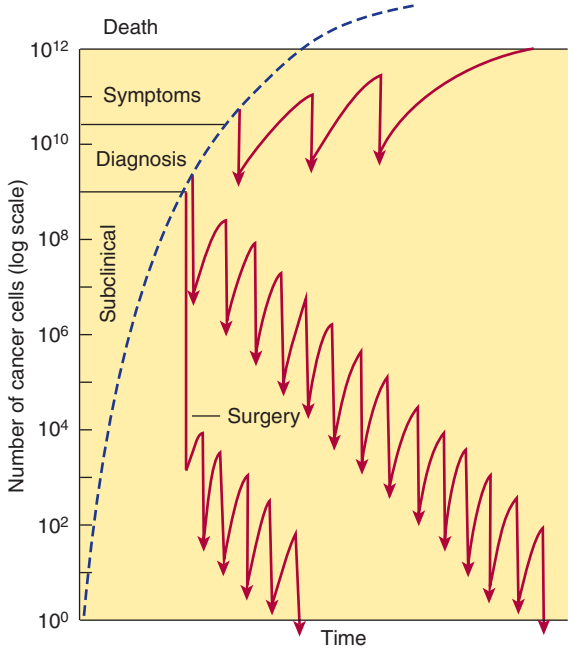


FIGURE 54–1 The log-kill hypothesis. Relationship of tumor cell number to time of diagnosis, symptoms, treatment, and survival. Three alternative approaches to drug treatment are shown for comparison with the course of tumor growth when no treatment is given *(dashed line)*. In the protocol diagrammed at top, treatment (indicated by the arrows) is given infrequently, and the result is manifested as prolongation of survival but with recurrence of symptoms between courses of treatment and eventual death of the patient. The combination chemotherapy treatment diagrammed in the middle section is begun earlier and is more intensive. Tumor cell kill exceeds regrowth, drug resistance does not develop, and "cure" results. In this example, treatment has been continued long after all clinical evidence of cancer has disappeared (1–3 years). This approach has been established as effective in the treatment of childhood acute leukemia, testicular cancers, and Hodgkin's lymphoma. In the treatment diagrammed near the bottom of the graph, early surgery has been employed to remove the primary tumor and intensive adjuvant chemotherapy has been administered long enough (up to 1 year) to eradicate the remaining tumor cells that comprise the occult micrometastases.

Information on cell and population kinetics of cancer cells explains, in part, the limited effectiveness of most available anticancer drugs. A schematic summary of cell cycle kinetics is presented in Figure 54–2. This information is relevant to the mode of action, indications, and scheduling of cell cycle-specific (CCS) and cell cycle-nonspecific (CCNS) drugs. Agents falling into these two major classes are summarized in Table 54–1.

The Role of Drug Combinations

With rare exceptions (eg, choriocarcinoma and Burkitt's lymphoma), single drugs at clinically tolerable doses have been unable to cure cancer. In the 1960s and early 1970s, drug combination regimens were developed based on the known biochemical actions

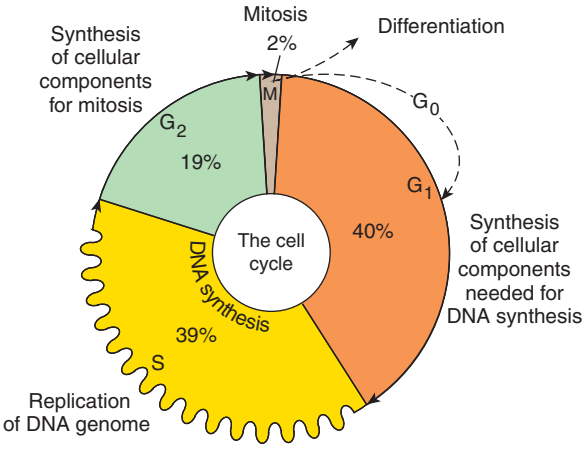


FIGURE 54–2 The cell cycle and cancer. A conceptual depiction of the cell cycle phases that all cells—normal and neoplastic—must traverse before and during cell division. The percentages given represent the approximate percentage of time spent in each phase by a typical malignant cell; the duration of G_1, however, can vary markedly. Many of the effective anticancer drugs exert their action on cells traversing the cell cycle and are called cell cycle-specific (CCS) drugs (see Table 54–1). A second group of agents called cell cycle-nonspecific (CCNS) drugs can sterilize tumor cells whether they are cycling or resting in the G_0 compartment. CCNS drugs can kill both G_0 and cycling cells (although cycling cells are more sensitive).

of available anticancer drugs rather than on their clinical efficacy. Such regimens were, however, largely ineffective. The era of effective combination chemotherapy began when a number of active drugs from different classes became available for use in combination in the treatment of the acute leukemias and lymphomas. Following this initial success with hematologic malignancies, combination chemotherapy was extended to the treatment of solid tumors.

The use of combination chemotherapy is important for several reasons. First, it provides maximal cell kill within the range of toxicity tolerated by the host for each drug as long as dosing is not compromised. Second, it provides a broader range of interaction between drugs and tumor cells with different genetic abnormalities in a heterogeneous tumor population. Finally, it may prevent or slow the subsequent development of cellular drug resistance. The same principles apply to the therapy of chronic infections, such as HIV and tuberculosis.

Certain principles have guided the selection of drugs in the most effective drug combinations, and they provide a paradigm for the development of new drug therapeutic programs.

1. **Efficacy:** Only drugs known to be somewhat effective when used alone against a given tumor should be selected for use in combination. If available, drugs that produce complete remission in some fraction of patients are preferred to those that produce only partial responses.
2. **Toxicity:** When several drugs of a given class are available and are equally effective, a drug should be selected on the basis of toxicity that does not overlap with the toxicity of other drugs in the combination. Although such selection leads to a wider range of adverse effects, it minimizes the risk of a lethal effect caused by multiple insults to the same organ system by different drugs and allows dose intensity to be maximized.
3. **Optimum scheduling:** Drugs should be used in their optimal dose and schedule, and drug combinations should be given at consistent intervals. Because long intervals between cycles negatively affect dose intensity, the treatment-free interval between cycles should be the shortest time necessary for recovery of the most sensitive normal target tissue, which is usually the bone marrow.
4. **Mechanism of interaction:** There should be a clear understanding of the biochemical, molecular, and pharmacokinetic mechanisms of interaction between the individual drugs in a given combination, to allow for maximal effect. Omission of a drug from a combination may allow overgrowth by a tumor clone sensitive to that drug alone and resistant to other drugs in the combination.

TABLE 54–1 Cell cycle effects of major classes of anticancer drugs.

Cell Cycle-Specific (CCS) Agents	Cell Cycle-Nonspecific (CCNS) Agents
Antimetabolites (S phase)	**Alkylating agents**
Capecitabine	Altretamine
Cladribine	Bendamustine
Clofarabine	Busulfan
Cytarabine (ara-C)	Carmustine
Fludarabine	Chlorambucil
5-Fluorouracil (5-FU)	Cyclophosphamide
Gemcitabine	Dacarbazine
6-Mercaptopurine (6-MP)	Lomustine
Methotrexate (MTX)	Mechlorethamine
Nelarabine	Melphalan
Pralatrexate	Temozolomide
6-Thioguanine (6-TG)	Thiotepa
Epipodophyllotoxin (topoisomerase II inhibitor) (G_1–S phase)	**Antitumor antibiotics**
Etoposide	Dactinomycin
Taxanes (M phase)	Mitomycin
Albumin-bound paclitaxel	**Camptothecins (topoisomerase I inhibitors)**
Cabazitaxel	Irinotecan
Paclitaxel	Topotecan
Vinca alkaloids (M phase)	**Platinum analogs**
Vinblastine	Carboplatin
Vincristine	Cisplatin
Vinorelbine	Oxaliplatin
Antimicrotubule inhibitor (M phase)	**Anthracyclines**
Ixabepilone	Daunorubicin
Antitumor antibiotics (G_2–M phase)	Doxorubicin
Bleomycin	Epirubicin
	Idarubicin
	Mitoxantrone

5. **Avoidance of arbitrary dose changes:** An arbitrary reduction in the dose of an effective drug in order to add other less effective drugs may reduce the dose of the most effective agent below the threshold of effectiveness and destroy the ability of the combination to cure disease in a given patient.

Dosage Factors

Dose intensity is one of the main factors limiting the ability of chemotherapy or radiation therapy to achieve cure. The dose-response curve in biologic systems is usually sigmoidal in shape, with a threshold, a linear phase, and a plateau phase. For chemotherapy, therapeutic selectivity is dependent on the difference between the dose-response curves of normal and tumor tissues. In experimental animal models, the dose-response curve is usually steep in the linear phase, and a reduction in dose when the tumor is in the linear phase of the dose-response curve almost always results in a loss in the capacity to cure the tumor effectively before a reduction in the antitumor activity is observed. Although complete remissions continue to be observed with dose reduction as low as 20%, residual tumor cells may not be entirely eliminated, thereby allowing for eventual relapse. Because anticancer drugs are associated with toxicity, it is often appealing for clinicians to avoid acute toxicity by simply reducing the dose or by increasing the time interval between each cycle of treatment. However, such empiric modifications in dose represent a major cause of treatment failure in patients with drug-sensitive tumors.

A positive relationship between dose intensity and clinical efficacy has been documented in several solid tumors, including advanced ovarian, breast, lung, and colon cancers, as well as in hematologic malignancies, such as the lymphomas. At present, there are three main approaches to dose-intense delivery of chemotherapy. The first approach, **dose escalation,** involves increasing the doses of the respective anticancer agents. The second strategy is administration of anticancer agents in a dose-intense manner by **reducing the interval** between treatment cycles, while the third approach involves **sequential scheduling** of either single agents or of combination regimens. Each of these strategies is presently being applied to a wide range of solid cancers, including breast, colorectal, and non-small cell lung, and in general, such dose-intense regimens have significantly improved clinical outcomes.

DRUG RESISTANCE

A fundamental issue in cancer chemotherapy is the development of cellular drug resistance. Some tumor types, eg, malignant melanoma, renal cell cancer, and brain cancer, exhibit *primary* resistance, ie, absence of response on the first exposure, to currently available agents. The presence of inherent drug resistance was first proposed by Goldie and Coleman in the early 1980s and was thought to result from the genomic instability associated with the development of most cancers. For example, mutations in the *p53* tumor suppressor gene occur in up to 50% of all human tumors. Preclinical and clinical studies have shown that loss of *p53* function leads to resistance to radiation therapy as well as resistance to a wide range of anticancer agents. Defects in the mismatch repair enzyme family, which are tightly linked to the development of familial and sporadic colorectal cancer, lead to resistance to several unrelated anticancer agents, including the fluoropyrimidines, the thiopurines, and cisplatin/carboplatin. In contrast to *primary* resistance, *acquired* resistance develops in response to exposure to a given anticancer agent. Experimentally, drug resistance can be highly specific to a single drug and is usually based on a specific change in the genetic machinery of a given tumor cell with amplification or increased expression of one or more genes. In other instances, a multidrug-resistant phenotype occurs, associated with increased expression of the *MDR1* gene, which encodes a cell surface transporter glycoprotein (P-glycoprotein, see Chapter 1). This form of drug resistance leads to enhanced drug efflux and reduced intracellular accumulation of a broad range of structurally unrelated anticancer agents, including the anthracyclines, vinca alkaloids, taxanes, camptothecins, epipodophyllotoxins, and even small molecule inhibitors, such as imatinib.

BASIC PHARMACOLOGY OF CANCER CHEMOTHERAPEUTIC DRUGS

ALKYLATING AGENTS

The major clinically useful alkylating agents (Figure 54–3) have a structure containing a bis(chloroethyl)amine, ethyleneimine, or nitrosourea moiety, and they are classified in several different groups. Among the bis(chloroethyl)amines, cyclophosphamide, mechlorethamine, melphalan, and chlorambucil are the most useful. Ifosfamide is closely related to cyclophosphamide but has a somewhat different spectrum of activity and toxicity. Thiotepa and busulfan are used to treat breast and ovarian cancer, and chronic myeloid leukemia, respectively. The major nitrosoureas are carmustine (BCNU) and lomustine (CCNU).

Mechanism of Action

As a class, the alkylating agents exert their cytotoxic effects via transfer of their alkyl groups to various cellular constituents. Alkylations of DNA within the nucleus probably represent the major interactions that lead to cell death. However, these drugs react chemically with sulfhydryl, amino, hydroxyl, carboxyl, and phosphate groups of other cellular nucleophiles as well. The general mechanism of action of these drugs involves intramolecular cyclization to form an ethyleneimonium ion that may directly or through formation of a carbonium ion transfer an alkyl group to a cellular constituent (Figure 54–4). In addition to alkylation, a secondary mechanism that occurs with nitrosoureas involves carbamoylation of lysine residues of proteins through formation of isocyanates.

The major site of alkylation within DNA is the N7 position of guanine; however, other bases are also alkylated albeit to lesser degrees, including N1 and N3 of adenine, N3 of cytosine, and O6 of guanine, as well as phosphate atoms and proteins associated with DNA. These interactions can occur on a single strand or on

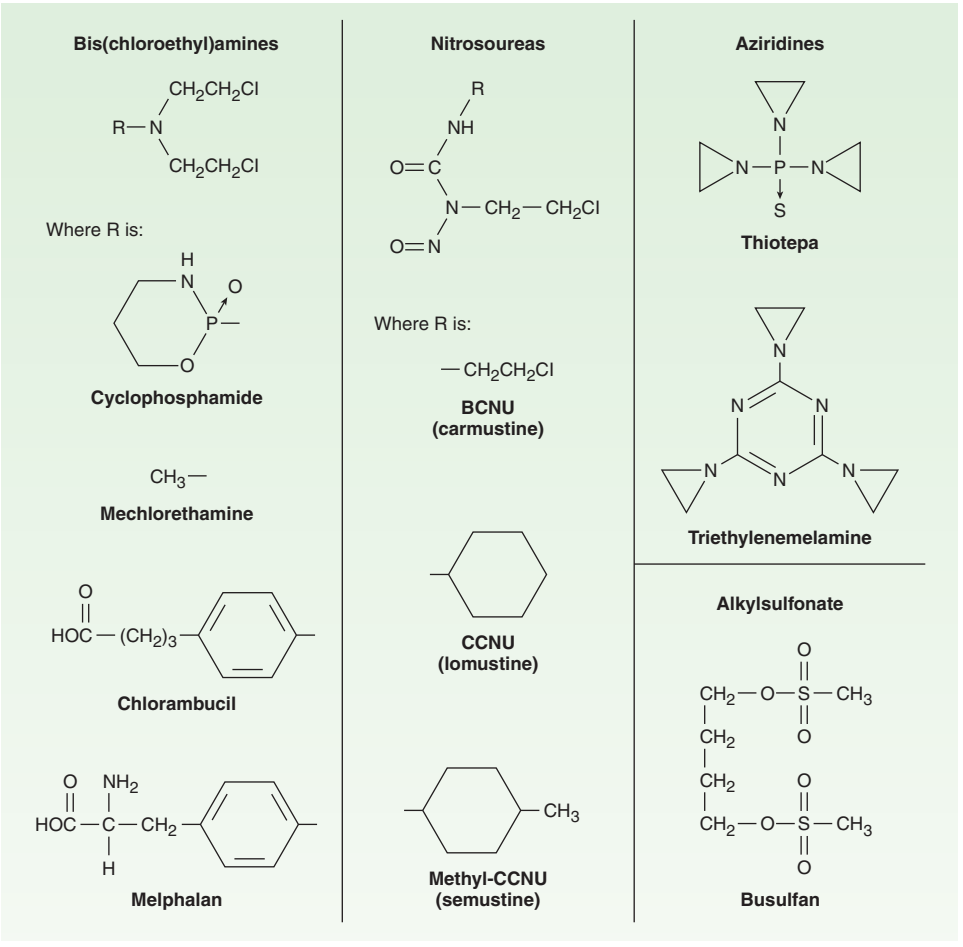


FIGURE 54–3 Structures of major classes of alkylating agents.

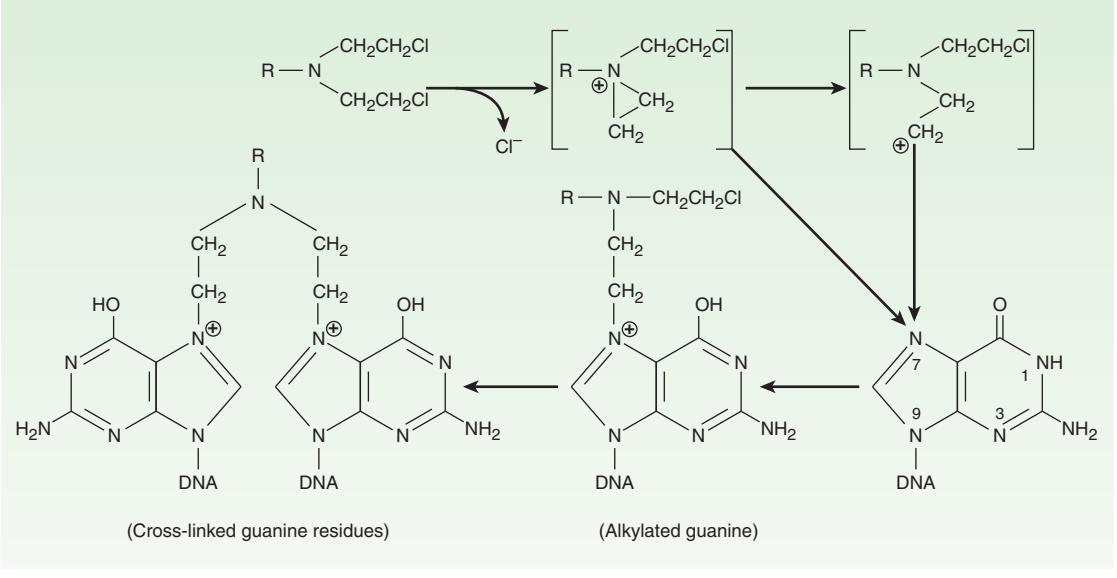


FIGURE 54–4 Mechanism of alkylation of DNA guanine. A bis(chloroethyl)amine forms an ethyleneimonium ion that reacts with a base such as N7 of guanine in DNA, producing an alkylated purine. Alkylation of a second guanine residue, through the illustrated mechanism, results in cross-linking of DNA strands.

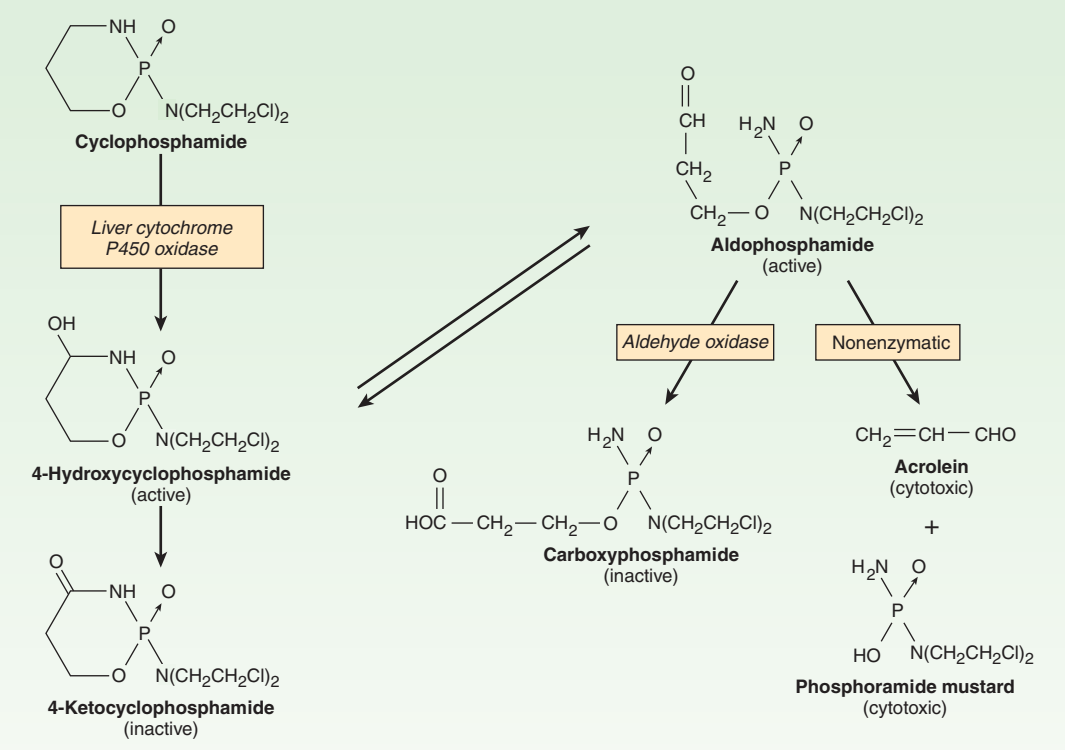


FIGURE 54–5 Cyclophosphamide metabolism.

both strands of DNA through cross-linking, as most major alkylating agents are bifunctional, with two reactive groups. Alkylation of guanine can result in miscoding through abnormal base pairing with thymine or in depurination by excision of guanine residues. The latter effect leads to DNA strand breakage through scission of the sugar-phosphate backbone of DNA. Cross-linking of DNA appears to be of major importance to the cytotoxic action of alkylating agents, and replicating cells are most susceptible to these drugs. Thus, although alkylating agents are not cell cycle specific, cells are most susceptible to alkylation in late G_1 and S phases of the cell cycle.

Resistance

The mechanism of acquired resistance to alkylating agents may involve increased capability to repair DNA lesions, decreased transport of the alkylating drug into the cell, and increased expression or activity of glutathione and glutathione-associated proteins, which are needed to conjugate the alkylating agent, or increased glutathione *S*-transferase activity, which catalyzes the conjugation.

Adverse Effects

The adverse effects usually associated with alkylating agents are generally dose-related and occur primarily in rapidly growing tissues such as bone marrow, gastrointestinal tract, and reproductive system. Nausea and vomiting can be a serious issue with a number of these agents. In addition, they are potent vesicants and can damage tissues at the site of administration as well as produce systemic toxicity. As a class, alkylating agents are carcinogenic in nature, and there is an increased risk of secondary malignancies, especially acute myelogenous leukemia.

Cyclophosphamide is one of the most widely used alkylating agents. One of the potential advantages of this compound relates to its high oral bioavailability. As a result, it can be administered via the oral and intravenous routes with equal clinical efficacy. It is inactive in its parent form, and must be activated to cytotoxic forms by liver microsomal enzymes (Figure 54–5). The cytochrome P450 mixed-function oxidase system converts cyclophosphamide to 4-hydroxycyclophosphamide, which is in equilibrium with aldophosphamide. These active metabolites are delivered to both tumor and normal tissue, where nonenzymatic cleavage of aldophosphamide to the cytotoxic forms—phosphoramide mustard and acrolein—occurs. The liver appears to be protected through the enzymatic formation of the inactive metabolites 4-ketocyclophosphamide and carboxyphosphamide.

The major toxicities of the individual alkylating agents are outlined in Table 54–2 and discussed below.

NITROSOUREAS

These drugs appear to be non-cross-resistant with other alkylating agents; all require biotransformation, which occurs by nonenzymatic decomposition, to metabolites with both alkylating and carbamoylating activities. The nitrosoureas are highly lipid-soluble and are able to cross the blood-brain barrier, making them effective

TABLE 54–2 Alkylating agents and platinum analogs: Clinical activity and toxicities.

Alkylating Agent	Mechanism of Action	Clinical Applications	Acute Toxicity	Delayed Toxicity
Mechlorethamine	Forms DNA cross-links, resulting in inhibition of DNA synthesis and function	Hodgkin's and non-Hodgkin's lymphoma	Nausea and vomiting	Moderate depression of peripheral blood count; excessive doses produce severe bone marrow depression with leukopenia, thrombocytopenia, and bleeding; alopecia and hemorrhagic cystitis occasionally occur with cyclophosphamide; cystitis can be prevented with adequate hydration; busulfan is associated with skin pigmentation, pulmonary fibrosis, and adrenal insufficiency
Chlorambucil	Same as above	CLL and non-Hodgkin's lymphoma	Nausea and vomiting	
Cyclophosphamide	Same as above	Breast cancer, ovarian cancer, non-Hodgkin's lymphoma, CLL, soft tissue sarcoma, neuroblastoma, Wilms' tumor, rhabdomyosarcoma	Nausea and vomiting	
Bendamustine	Same as above	CLL, non-Hodgkin's lymphoma	Nausea and vomiting	
Melphalan	Same as above	Multiple myeloma, breast cancer, ovarian cancer	Nausea and vomiting	
Thiotepa	Same as above	Breast cancer, ovarian cancer, superficial bladder cancer	Nausea and vomiting	
Busulfan	Same as above	CML	Nausea and vomiting	
Carmustine	Same as above	Brain cancer, Hodgkin's and non-Hodgkin's lymphoma	Nausea and vomiting	Myelosuppression; rarely interstitial lung disease and interstitial nephritis
Lomustine	Same as above	Brain cancer	Nausea and vomiting	
Altretamine	Same as above	Ovarian cancer	Nausea and vomiting	Myelosuppression, peripheral neuropathy, flu-like syndrome
Temozolomide	Methylates DNA and inhibits DNA synthesis and function	Brain cancer, melanoma	Nausea and vomiting, headache and fatigue	Myelosuppression, mild elevation in liver function tests, photosensitivity
Procarbazine	Methylates DNA and inhibits DNA synthesis and function	Hodgkin's and non-Hodgkin's lymphoma, brain tumors	Central nervous system depression	Myelosuppression, hypersensitivity reactions
Dacarbazine	Methylates DNA and inhibits DNA synthesis and function	Hodgkin's lymphoma, melanoma, soft tissue sarcoma	Nausea and vomiting	Myelosuppression, central nervous system toxicity with neuropathy, ataxia, lethargy, and confusion
Cisplatin	Forms intrastrand and interstrand DNA cross-links; binding to nuclear and cytoplasmic proteins	Non-small cell and small cell lung cancer, breast cancer, bladder cancer, cholangiocarcinoma, gastroesophageal cancer, head and neck cancer, ovarian cancer, germ cell cancer	Nausea and vomiting	Nephrotoxicity, peripheral sensory neuropathy, ototoxicity, nerve dysfunction
Carboplatin	Same as cisplatin	Non-small cell and small cell lung cancer, breast cancer, bladder cancer, head and neck cancer, ovarian cancer	Nausea and vomiting	Myelosuppression; rarely peripheral neuropathy, renal toxicity, hepatic dysfunction
Oxaliplatin	Same as cisplatin	Colorectal cancer, gastroesophageal cancer, pancreatic cancer	Nausea and vomiting, laryngopharyngeal dysesthesias	Myelosuppression, peripheral sensory neuropathy, diarrhea

CLL, chronic lymphocytic leukemia; CML, chronic myelogenous leukemia.

in the treatment of brain tumors. Although the majority of alkylations by the nitrosoureas are on the N7 position of guanine in DNA, the critical alkylation responsible for cytotoxicity appears to be on the O6 position of guanine, which leads to G-C crosslinks in DNA. After oral administration of lomustine, peak plasma levels of metabolites appear within 1–4 hours; central nervous system concentrations reach 30–40% of the activity present in the plasma. Urinary excretion appears to be the major route of elimination from the body. One naturally occurring sugar-containing nitrosourea, streptozocin, is interesting because it has minimal bone marrow toxicity. This agent has activity in the treatment of insulin-secreting islet cell carcinoma of the pancreas.

NONCLASSIC ALKYLATING AGENTS

Several other compounds have mechanisms of action that involve DNA alkylation as their cytotoxic mechanism of action. These agents include procarbazine, dacarbazine, and bendamustine. Their respective clinical activities and associated toxicities are listed in Table 54–2.

Procarbazine

Procarbazine is an orally active methylhydrazine derivative, and in the clinical setting, it is used in combination regimens for Hodgkin's and non-Hodgkin's lymphoma as well as brain tumors.

The precise mechanism of action of procarbazine is uncertain; however, it inhibits DNA, RNA, and protein biosynthesis; prolongs interphase; and produces chromosome breaks. Oxidative metabolism of this drug by microsomal enzymes generates azoprocarbazine and H_2O_2, which may be responsible for DNA strand scission. A variety of other drug metabolites are formed that may be cytotoxic. One metabolite is a weak monoamine oxidase (MAO) inhibitor, and adverse events can occur when procarbazine is given with other MAO inhibitors as well as with sympathomimetic agents, tricyclic antidepressants, antihistamines, central nervous system depressants, antidiabetic agents, alcohol, and tyramine-containing foods.

There is an increased risk of secondary cancers in the form of acute leukemia, and its carcinogenic potential is thought to be higher than that of most other alkylating agents.

Dacarbazine

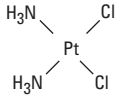
Dacarbazine is a synthetic compound that functions as an alkylating agent following metabolic activation in the liver by oxidative *N*-demethylation to the monomethyl derivative. This metabolite spontaneously decomposes to diazomethane, which generates a methyl carbonium ion that is believed to be the key cytotoxic species. Dacarbazine is administered parenterally and is used in the treatment of malignant melanoma, Hodgkin's lymphoma, soft tissue sarcomas, and neuroblastoma. In terms of safety profile, the main dose-limiting toxicity is myelosuppression, but nausea and vomiting can be severe in some cases. This agent is a potent vesicant, and care must be taken to avoid extravasation during drug administration.

Bendamustine

Bendamustine is a bifunctional alkylating agent consisting of a purine benzimidazole ring and a nitrogen mustard moiety. As with other alkylating agents, it forms cross-links with DNA resulting in single- and double-stranded breaks, leading to inhibition of DNA synthesis and function. This molecule also inhibits mitotic checkpoints and induces mitotic catastrophe, which leads to cell death. Of note, the cross-resistance between bendamustine and other alkylating agents is only partial, thereby providing a rationale for its clinical activity despite the development of resistance to other alkylating agents. This agent is approved for use in chronic lymphocytic leukemia, with activity also observed in Hodgkin's and non-Hodgkin's lymphoma, multiple myeloma, and breast cancer. The main dose-limiting toxicities include myelosuppression and mild nausea and vomiting. Hypersensitivity infusion reactions, skin rash, and other skin reactions occur rarely.

PLATINUM ANALOGS

Three platinum analogs are currently used in clinical practice: cisplatin, carboplatin, and oxaliplatin. Cisplatin (cis-diamminedichloroplatinum [II]) is an inorganic metal complex that was initially discovered through a serendipitous observation that neutral platinum complexes inhibited division and filamentous growth of *Escherichia coli*. Several platinum analogs were subsequently synthesized. Although the precise mechanism of action of the platinum analogs is unclear, they are thought to exert their cytotoxic effects in the same manner as alkylating agents. As such, they kill tumor cells in all stages of the cell cycle and bind DNA through the formation of intrastrand and interstrand cross-links, thereby leading to inhibition of DNA synthesis and function. The primary binding site is the N7 position of guanine, but covalent interaction with the N3 position of adenine and O6 position of cytosine can also occur. In addition to targeting DNA, the platinum analogs have been shown to bind to both cytoplasmic and nuclear proteins, which may also contribute to their cytotoxic and antitumor effects. The platinum complexes appear to synergize with certain other anticancer drugs, including alkylating agents, fluoropyrimidines, and taxanes.



Cisplatin

Cisplatin has major antitumor activity in a broad range of solid tumors, including non-small cell and small cell lung cancer, esophageal and gastric cancer, cholangiocarcinoma, head and neck cancer, and genitourinary cancers, particularly testicular, ovarian, and bladder cancer. When used in combination regimens, cisplatin-based therapy has led to the cure of nonseminomatous testicular cancer. Cisplatin and the other platinum analogs are extensively cleared by the kidneys and excreted in the urine. As a result, dose modification is required in patients with renal dysfunction.

Carboplatin is a second-generation platinum analog whose mechanisms of cytotoxic action, mechanisms of resistance, and clinical pharmacology are identical to those described for cisplatin.

As with cisplatin, carboplatin has broad-spectrum activity against a wide range of solid tumors. However, in contrast to cisplatin, it exhibits significantly less renal toxicity and gastrointestinal toxicity. Its main dose-limiting toxicity is myelosuppression. It has therefore been widely used in transplant regimens to treat refractory hematologic malignancies. Moreover, since vigorous intravenous hydration is not required for carboplatin therapy, carboplatin is viewed as an easier agent to administer to patients, and as such, it has replaced cisplatin in various combination chemotherapy regimens.

Oxaliplatin is a third-generation diaminocyclohexane platinum analog. Its mechanism of action and clinical pharmacology are identical to those of cisplatin and carboplatin. However, tumors that are resistant to cisplatin or carboplatin on the basis of mismatch repair defects are not cross-resistant to oxaliplatin, and this finding may explain the activity of this platinum compound in colorectal cancer. Oxaliplatin was initially approved for use as second-line therapy in combination with the fluoropyrimidine 5-fluorouracil (5-FU) and leucovorin, termed the FOLFOX regimen, for metastatic colorectal cancer. The FOLFOX regimen was subsequently (2005) approved for the first-line treatment of metastatic colorectal cancer. At this time, oxaliplatin-based chemotherapy has also been approved in the adjuvant therapy of high-risk stage II and stage III colon cancer. Clinical activity has been observed in other gastrointestinal cancers, such as pancreatic, gastroesophageal, and hepatocellular cancer. In the side effect profile, neurotoxicity is the main dose-limiting toxicity, and is manifested by a peripheral sensory neuropathy. There are two forms of neurotoxicity, an acute form that is often triggered and worsened by exposure to cold, and a chronic form that is dose-dependent. Although this chronic form is dependent on the cumulative dose of drug administered, it tends to be reversible, in contrast to cisplatin-induced neurotoxicity.

The major toxicities of the individual platinum analogs are outlined in Table 54–2.

ANTIMETABOLITES

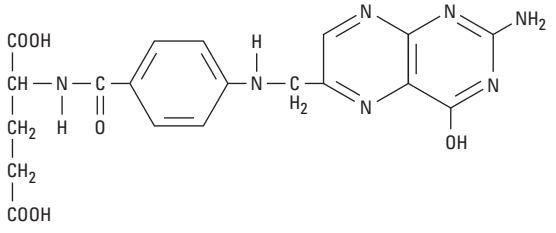
The development of drugs with actions on intermediary metabolism of proliferating cells has been important both conceptually and clinically. While biochemical properties unique to all cancer cells have yet to be discovered, there are a number of quantitative differences in metabolism between cancer cells and normal cells that render cancer cells more sensitive to the antimetabolites. Many of these agents have been rationally designed and synthesized based on knowledge of critical cellular processes involved in DNA biosynthesis.

The individual antimetabolites and their respective clinical spectrum and toxicities are presented in Table 54–3 and are discussed below.

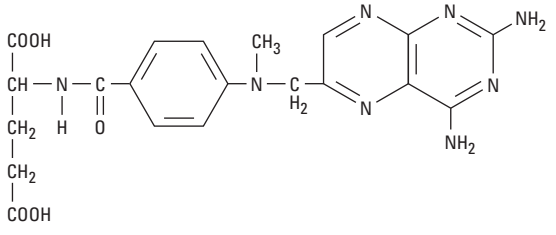
ANTIFOLATES

Methotrexate

Methotrexate (MTX) is a folic acid analog that binds with high affinity to the active catalytic site of dihydrofolate reductase (DHFR). This results in inhibition of the synthesis of tetrahydrofolate (THF), the key one-carbon carrier for enzymatic processes involved in de novo synthesis of thymidylate, purine nucleotides, and the amino acids serine and methionine. Inhibition of these various metabolic processes thereby interferes with the formation of DNA, RNA, and key cellular proteins (see Figure 33–3). Intracellular formation of polyglutamate metabolites, with the addition of up to 5–7 glutamate residues, is critically important for the therapeutic action of MTX, and this process is catalyzed by the enzyme folylpolyglutamate synthase (FPGS). MTX polyglutamates are selectively retained within cancer cells, and they display increased inhibitory effects on enzymes involved in de novo purine nucleotide and thymidylate biosynthesis, making them important determinants of MTX's cytotoxic action.



Folic acid



Methotrexate

Resistance to MTX has been attributed to (1) decreased drug transport via the reduced folate carrier or folate receptor protein, (2) decreased formation of cytotoxic MTX polyglutamates, (3) increased levels of the target enzyme DHFR through gene amplification and other genetic mechanisms, and (4) altered DHFR protein with reduced affinity for MTX. Recent studies have suggested that decreased accumulation of drug through activation of the multidrug resistance transporter P170 glycoprotein may also result in drug resistance.

MTX is administered by the intravenous, intrathecal, or oral route. However, oral bioavailability is saturable and erratic at doses greater than 25 mg/m^2. Renal excretion is the main route of elimination and is mediated by glomerular filtration and tubular secretion. As a result, dose modification is required in the setting of renal dysfunction. Care must also be taken when MTX is used in the presence of drugs such as aspirin, nonsteroidal anti-inflammatory agents, penicillin, and cephalosporins, as these agents inhibit the renal excretion of MTX. The biologic effects of MTX can be reversed by administration of the reduced folate leucovorin (5-formyltetrahydrofolate) or by L-leucovorin, which is the active enantiomer. Leucovorin rescue is used in conjunction with high-dose MTX therapy to rescue normal cells from undue toxicity, and it has also been used in cases of accidental drug overdose. The main adverse effects are listed in Table 54–3.

TABLE 54–3 Antimetabolites: Clinical activity and toxicities.

Drug	Mechanism of Action	Clinical Applications	Toxicity
Capecitabine	Inhibits TS; incorporation of FUTP into RNA resulting in alteration in RNA processing; incorporation of FdUTP into DNA resulting in inhibition of DNA synthesis and function	Breast cancer, colorectal cancer, gastroesophageal cancer, hepatocellular cancer, pancreatic cancer	Diarrhea, hand-foot syndrome, myelosuppression, nausea and vomiting
5-Fluorouracil	Inhibits TS; incorporation of FUTP into RNA resulting in alteration in RNA processing; incorporation of FdUTP into DNA resulting in inhibition of DNA synthesis and function	Colorectal cancer, anal cancer, breast cancer, gastroesophageal cancer, head and neck cancer, hepatocellular cancer	Nausea, mucositis, diarrhea, bone marrow depression, neurotoxicity
Methotrexate	Inhibits DHFR; inhibits TS; inhibits de novo purine nucleotide synthesis	Breast cancer, head and neck cancer, osteogenic sarcoma, primary central nervous system lymphoma, non-Hodgkin's lymphoma, bladder cancer, choriocarcinoma	Mucositis, diarrhea, myelosuppression with neutropenia and thrombocytopenia
Pemetrexed	Inhibits TS, DHFR, and purine nucleotide synthesis	Mesothelioma, non-small cell lung cancer	Myelosuppression, skin rash, mucositis, diarrhea, fatigue, hand-foot syndrome
Cytarabine	Inhibits DNA chain elongation, DNA synthesis and repair; inhibits ribonucleotide reductase with reduced formation of dNTPs; incorporation of cytarabine triphosphate into DNA	AML, ALL, CML in blast crisis	Nausea and vomiting, myelosuppression with neutropenia and thrombocytopenia, cerebellar ataxia
Gemcitabine	Inhibits DNA synthesis and repair; inhibits ribonucleotide reductase with reduced formation of dNTPs; incorporation of gemcitabine triphosphate into DNA resulting in inhibition of DNA synthesis and function	Pancreatic cancer, bladder cancer, breast cancer, non-small cell lung cancer, ovarian cancer, non-Hodgkin's lymphoma, soft tissue sarcoma	Nausea, vomiting, diarrhea, myelosuppression
Fludarabine	Inhibits DNA synthesis and repair; inhibits ribonucleotide reductase; incorporation of fludarabine triphosphate into DNA; induction of apoptosis	Non-Hodgkin's lymphoma, CLL	Myelosuppression, immunosuppression, fever, myalgias, arthralgias
Cladribine	Inhibits DNA synthesis and repair; inhibits ribonucleotide reductase; incorporation of cladribine triphosphate into DNA; induction of apoptosis	Hairy cell leukemia, CLL, non-Hodgkin's lymphoma	Myelosuppression, nausea and vomiting, and immunosuppression
6-Mercaptopurine (6-MP)	Inhibits de novo purine nucleotide synthesis; incorporation of triphosphate into RNA; incorporation of triphosphate into DNA	AML	Myelosuppression, immunosuppression, and hepatotoxicity
6-Thioguanine	Same as 6-MP	ALL, AML	Same as above

ALL, acute lymphoblastic leukemia; AML, acute myelogenous leukemia; CLL, chronic lymphocytic leukemia; CML, chronic myelogenous leukemia; DHFR, dihydrofolate reductase; dNTP, deoxyribonucleotide triphosphate; FdUTP, 5-fluorodeoxyuridine-5′-triphosphate; FUTP, 5-fluorouridine-5′-triphosphate; TS, thymidine synthase.

Pemetrexed

Pemetrexed is a pyrrolopyrimidine antifolate analog with activity in the S phase of the cell cycle. As in the case of MTX, it is transported into the cell via the reduced folate carrier and requires activation by FPGS to yield higher polyglutamate forms. While this agent targets DHFR and enzymes involved in de novo purine nucleotide biosynthesis, its main mechanism of action is inhibition of thymidylate synthase. At present, this antifolate is approved for use in combination with cisplatin in the treatment of mesothelioma, as a single agent in the second-line therapy of non-small cell lung cancer, and in combination with cisplatin for the first-line treatment of non-small cell lung cancer. As with MTX, pemetrexed is mainly excreted in the urine, and dose modification is required in the setting of renal dysfunction. The main adverse effects include myelosuppression, skin rash, mucositis, diarrhea, fatigue, and hand-foot syndrome. Of note, vitamin supplementation with folic acid and vitamin B_{12} appear to reduce the toxicities associated with pemetrexed, while not interfering with clinical efficacy. The hand-foot syndrome is manifested by painful erythema and swelling of the hands and feet, and dexamethasone treatment has been shown to be effective in reducing the incidence and severity of this toxicity.

Pralatrexate

Pralatrexate is a 10-deaza-aminopterin antifolate analog, and as in the case of MTX, it is transported into the cell via the reduced folate carrier (RFC) and requires activation by FPGS to yield higher polyglutamate forms. However, this molecule was designed to be a more potent substrate for the RFC-1 carrier protein as well as an improved substrate for FPGS. It inhibits DHFR, inhibits enzymes involved in de novo purine nucleotide biosynthesis, and also inhibits thymidylate synthase. Although pralatrexate was

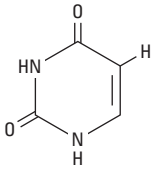
originally developed for non-small lung cancer, it is presently approved for use in the treatment of relapsed or refractory peripheral T-cell lymphoma. As with the other antifolate analogs, pralatrexate is mainly excreted in the urine, and dose modification is required in the setting of renal dysfunction. The main adverse effects include myelosuppression, skin rash, mucositis, diarrhea, and fatigue. Vitamin supplementation with folic acid and vitamin B_{12} appear to reduce the toxicities associated with pralatrexate, while not interfering with clinical efficacy.

FLUOROPYRIMIDINES

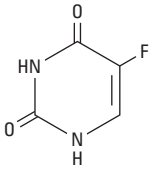
5-Fluorouracil

5-Fluorouracil (5-FU) is inactive in its parent form and requires activation via a complex series of enzymatic reactions to ribosyl and deoxyribosyl nucleotide metabolites. One of these metabolites, 5-fluoro-2′-deoxyuridine-5′-monophosphate (FdUMP), forms a covalently bound ternary complex with the enzyme thymidylate synthase and the reduced folate 5,10-methylenetetrahydrofolate, a reaction critical for the de novo synthesis of thymidylate. This results in inhibition of DNA synthesis through "thymineless death." 5-FU is converted to 5-fluorouridine-5′-triphosphate (FUTP), which is then incorporated into RNA, where it interferes with RNA processing and mRNA translation. 5-FU is also converted to 5-fluorodeoxyuridine-5′-triphosphate (FdUTP), which can be incorporated into cellular DNA, resulting in inhibition of DNA synthesis and function. Thus, the cytotoxicity of 5-FU is thought to be the result of combined effects on both DNA- and RNA-mediated events.

5-FU is administered intravenously, and the clinical activity of this drug is highly schedule-dependent. Because of its extremely short half-life, on the order of 10–15 minutes, infusional schedules of administration have been generally favored over bolus schedules. Up to 80–85% of an administered dose of 5-FU is catabolized by the enzyme dihydropyrimidine dehydrogenase (DPD). Of note, a pharmacogenetic syndrome involving partial or complete deficiency of the DPD enzyme is seen in up to 5% of cancer patients; in this setting, severe toxicity in the form of myelosuppression, diarrhea, nausea and vomiting, and neurotoxicity is observed.



Uracil



5-FU

5-FU remains the most widely used agent in the treatment of colorectal cancer, both as adjuvant therapy and for advanced disease. It also has activity against a wide variety of solid tumors, including cancers of the breast, stomach, pancreas, esophagus, liver, head and neck, and anus. Major toxicities include myelosuppression, gastrointestinal toxicity in the form of mucositis and diarrhea, skin toxicity manifested by the hand-foot syndrome, and neurotoxicity.

Capecitabine

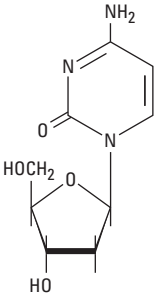
Capecitabine is a fluoropyrimidine carbamate prodrug with 70–80% oral bioavailability. It undergoes extensive metabolism in the liver by the enzyme carboxylesterase to an intermediate, 5′-deoxy-5-fluorocytidine. This metabolite is then converted to 5′-deoxy-5-fluorouridine by the enzyme cytidine deaminase. These two initial steps occur mainly in the liver. The 5′-deoxy-5-fluorouridine metabolite is finally hydrolyzed by thymidine phosphorylase to 5-FU directly in the tumor. The expression of thymidine phosphorylase has been shown to be significantly higher in a broad range of solid tumors than in corresponding normal tissue, particularly in breast cancer and colorectal cancer.

This oral fluoropyrimidine is used in the treatment of metastatic breast cancer either as a single agent or in combination with other anticancer agents, including docetaxel, paclitaxel, lapatinib, ixabepilone, and trastuzumab. It is also approved for use in the adjuvant therapy of stage III and high-risk stage II colon cancer as well as for treatment of metastatic colorectal cancer as monotherapy. At this time, significant efforts are directed at combining this agent with other active cytotoxic agents, including irinotecan and oxaliplatin. In Europe and Asia, the capecitabine/oxaliplatin (XELOX) regimen is approved for the first-line treatment of metastatic colorectal cancer, and this regimen is now widely used in the USA. The main toxicities of capecitabine include diarrhea and the hand-foot syndrome. While myelosuppression, nausea and vomiting, and mucositis are also observed with this agent, their incidence is significantly less than that observed with intravenous 5-FU.

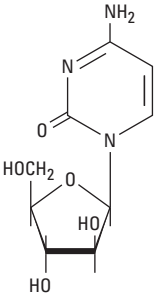
DEOXYCYTIDINE ANALOGS

Cytarabine

Cytarabine (ara-C) is an S phase-specific antimetabolite that is converted by deoxycytidine kinase to the 5'-mononucleotide (ara-CMP). Ara-CMP is further metabolized to the diphosphate and triphosphate metabolites, and the ara-CTP triphosphate is felt to be the main cytotoxic metabolite. Ara-CTP competitively inhibits DNA polymerase-α and DNA polymerase-β, thereby resulting in blockade of DNA synthesis and DNA repair, respectively. This metabolite is also incorporated into RNA and DNA. Incorporation into DNA leads to interference with chain elongation and defective ligation of fragments of newly synthesized DNA. The cellular retention of ara-CTP appears to correlate with its lethality to malignant cells.



Cytosine deoxyriboside



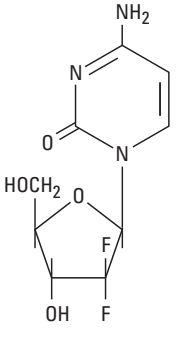
Cytosine arabinoside (cytarabine)

After intravenous administration, the drug is cleared rapidly, with most of an administered dose being deaminated to inactive forms. The stoichiometric balance between the level of activation and catabolism of cytarabine is important in determining its eventual cytotoxicity.

The clinical activity of cytarabine is highly schedule-dependent and because of its rapid degradation, it is usually administered via continuous infusion over a 5–7 day period. Its activity is limited exclusively to hematologic malignancies, including acute myelogenous leukemia and non-Hodgkin's lymphoma. This agent has absolutely no activity in solid tumors. The main adverse effects associated with cytarabine therapy include myelosuppression, mucositis, nausea and vomiting, and neurotoxicity when high-dose therapy is administered.

Gemcitabine

Gemcitabine is a fluorine-substituted deoxycytidine analog that is phosphorylated initially by the enzyme deoxycytidine kinase to the monophosphate form and then by other nucleoside kinases to the diphosphate and triphosphate nucleotide forms. The antitumor effect is considered to result from several mechanisms: inhibition of ribonucleotide reductase by gemcitabine diphosphate, which reduces the level of deoxyribonucleoside triphosphates required for DNA synthesis; inhibition by gemcitabine triphosphate of DNA polymerase-α and DNA polymerase-β, thereby resulting in blockade of DNA synthesis and DNA repair; and incorporation of gemcitabine triphosphate into DNA, leading to inhibition of DNA synthesis and function. Following incorporation of the gemcitabine triphosphate into DNA, only one additional nucleotide can be added to the growing DNA strand, resulting in chain termination.



Gemcitabine

This nucleoside analog was initially approved for use in advanced pancreatic cancer but is now widely used to treat a broad range of malignancies, including non-small cell lung cancer, bladder cancer, ovarian cancer, soft tissue sarcoma, and non-Hodgkin's lymphoma. Myelosuppression in the form of neutropenia is the principal dose-limiting toxicity. Nausea and vomiting occur in 70% of patients and a flu-like syndrome has also been observed. In rare cases, renal microangiopathy syndromes, including hemolytic-uremic syndrome and thrombotic thrombocytopenic purpura have been reported.

PURINE ANTAGONISTS

6-Thiopurines

6-Mercaptopurine (6-MP) was the first of the thiopurine analogs found to be effective in cancer therapy. This agent is used primarily in the treatment of childhood acute leukemia, and a closely related analog, azathioprine, is used as an immunosuppressive agent (see Chapter 55). As with other thiopurines, 6-MP is inactive in its parent form and must be metabolized by hypoxanthine-guanine phosphoribosyl transferase (HGPRT) to form the monophosphate nucleotide 6-thioinosinic acid, which in turn inhibits several enzymes of de novo purine nucleotide synthesis (Figure 54–6). The monophosphate form is eventually metabolized to the triphosphate form, which can then be incorporated into both RNA and DNA. Significant levels of thioguanylic acid and 6-methylmercaptopurine ribotide (MMPR) are also formed from 6-MP. These metabolites may contribute to its cytotoxic action.

6-Thioguanine (6-TG) also inhibits several enzymes in the de novo purine nucleotide biosynthetic pathway (Figure 54–6). Various metabolic lesions result, including inhibition of purine nucleotide interconversion; decrease in intracellular levels of guanine nucleotides, which leads to inhibition of glycoprotein synthesis; interference with the formation of DNA and RNA; and incorporation of thiopurine nucleotides into both DNA and RNA. 6-TG has a synergistic action when used together with cytarabine in the treatment of adult acute leukemia.

6-MP is converted to an inactive metabolite (6-thiouric acid) by an oxidation reaction catalyzed by xanthine oxidase, whereas 6-TG undergoes deamination. This is an important issue because the purine analog allopurinol, a potent xanthine oxidase inhibitor, is frequently used as a supportive care measure in the treatment of acute leukemias to prevent the development of hyperuricemia that often occurs with tumor cell lysis. Because allopurinol inhibits xanthine oxidase, simultaneous therapy with allopurinol and 6-MP would result in increased levels of 6-MP, thereby leading to excessive

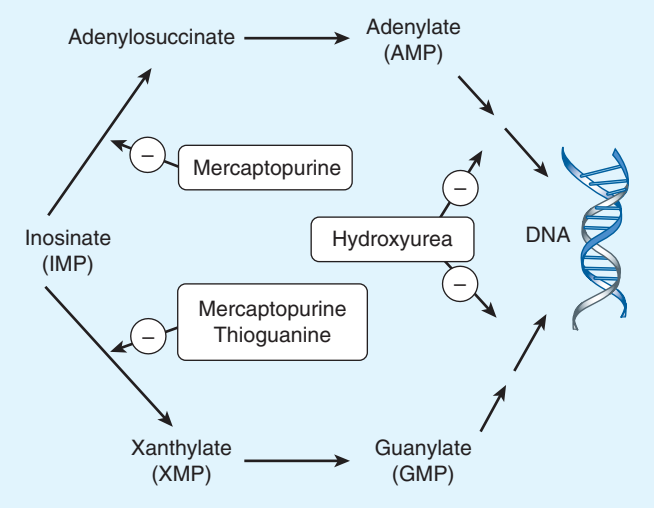
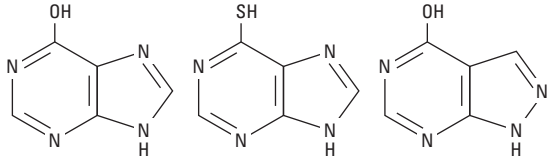
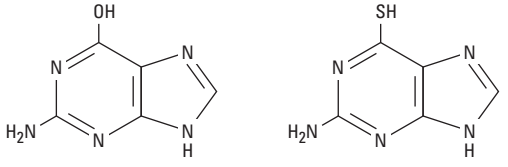


FIGURE 54–6 Mechanism of action of 6-mercaptopurine and 6-thioguanine.

toxicity. In this setting, the dose of mercaptopurine must be reduced by 50–75%. In contrast, such an interaction does not occur with 6-TG, which can be used in full doses with allopurinol.





The thiopurines are also metabolized by the enzyme thiopurine methyltransferase (TPMT), in which a methyl group is attached to the thiopurine ring. Patients who have a pharmacogenetic syndrome involving partial or complete deficiency of this enzyme are at increased risk for developing severe toxicities in the form of myelosuppression and gastrointestinal toxicity with mucositis and diarrhea.

Fludarabine

Fludarabine phosphate is rapidly dephosphorylated to 2-fluoro-arabinofuranosyladenosine and then phosphorylated intracellularly by deoxycytidine kinase to the triphosphate. The triphosphate metabolite interferes with the processes of DNA synthesis and DNA repair through inhibition of DNA polymerase-α and DNA polymerase-β. The triphosphate form can also be directly incorporated into DNA, resulting in inhibition of DNA synthesis and function. The diphosphate metabolite of fludarabine inhibits ribonucleotide reductase, leading to inhibition of essential deoxyribonucleotide triphosphates. Finally, fludarabine induces apoptosis in susceptible cells through as yet undetermined mechanisms. This purine nucleotide analog is used mainly in the treatment of low-grade non-Hodgkin's lymphoma and chronic lymphocytic leukemia (CLL). It is given parenterally, and up to 25–30% of parent drug is excreted in the urine. The main dose-limiting toxicity is myelosuppression. This agent is a potent immunosuppressant with inhibitory effects on CD4 and CD8 T cells. Patients are at increased risk for opportunistic infections, including fungi, herpes, and *Pneumocystis jiroveci* pneumonia (PCP). Patients should receive PCP prophylaxis with trimethoprim-sulfamethoxazole (double strength) at least three times a week, and this should continue for up to 1 year after stopping fludarabine therapy.

Cladribine

Cladribine (2-chlorodeoxyadenosine) is a purine nucleoside analog with high specificity for lymphoid cells. Inactive in its parent form, it is initially phosphorylated by deoxycytidine kinase to the monophosphate form and eventually metabolized to the triphosphate form, which can then be incorporated into DNA. The triphosphate metabolite can also interfere with DNA synthesis and DNA repair by inhibiting DNA polymerase-α and DNA polymerase-β, respectively. Cladribine is indicated for the treatment of hairy cell leukemia, with activity in other low-grade lymphoid malignancies such as CLL and low-grade non-Hodgkin's lymphoma. It is normally administered as a single continuous 7-day infusion; under these conditions, it has a very manageable safety profile with the main toxicity consisting of transient myelosuppression. As with other purine nucleoside analogs, it has immunosuppressive effects, and a decrease in CD4 and CD8 T cells, lasting for over 1 year, is observed in patients.

NATURAL PRODUCT CANCER CHEMOTHERAPY DRUGS

VINCA ALKALOIDS

Vinblastine

Vinblastine is an alkaloid derived from the periwinkle plant *Vinca rosea*. Its mechanism of action involves inhibition of tubulin polymerization, which disrupts assembly of microtubules, an important part of the cytoskeleton and the mitotic spindle. This inhibitory effect results in mitotic arrest in metaphase, bringing cell division to a halt, which then leads to cell death. Vinblastine and other vinca alkaloids are metabolized by the liver P450 system, and the majority of the drug is excreted in feces via the hepatobiliary system. As such, dose modification is required in the setting of liver dysfunction. The main adverse effects are outlined in Table 54–4, and they include nausea and vomiting, bone marrow suppression, and alopecia. This agent is also a potent vesicant, and care must be taken in its administration. It has clinical activity in the treatment of Hodgkin's and non-Hodgkin's lymphomas, breast cancer, and germ cell cancer.

Vincristine

Vincristine is another alkaloid derivative of *V rosea* and is closely related in structure to vinblastine. Its mechanism of action, mechanism of resistance, and clinical pharmacology are identical to those of vinblastine. Despite these similarities to vinblastine, vincristine has a strikingly different spectrum of clinical activity and safety profile.

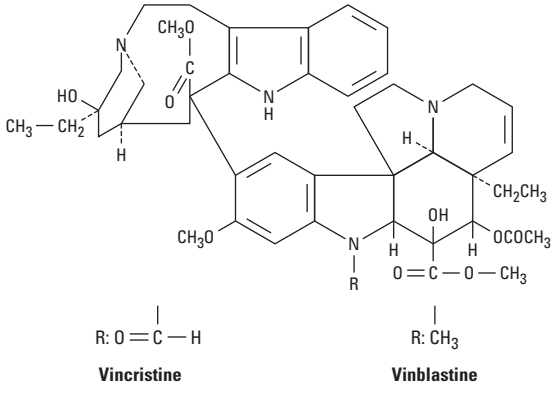


TABLE 54–4 Natural product cancer chemotherapy drugs: Clinical activity and toxicities.

Drug	Mechanism of Action	Clinical Applications[1]	Acute Toxicity	Delayed Toxicity
Bleomycin	Oxygen free radicals bind to DNA causing single- and double-strand DNA breaks	Hodgkin's and non-Hodgkin's lymphoma, germ cell cancer, head and neck cancer	Allergic reactions, fever, hypotension	Skin toxicity, pulmonary fibrosis, mucositis, alopecia
Daunorubicin	Oxygen free radicals bind to DNA causing single- and double-strand DNA breaks; inhibits topoisomerase II; intercalates into DNA	AML, ALL	Nausea, fever, red urine (not hematuria)	Cardiotoxicity (see text), alopecia, myelosuppression
Docetaxel	Inhibits mitosis	Breast cancer, non-small cell lung cancer, prostate cancer, gastric cancer, head and neck cancer, ovarian cancer, bladder cancer	Hypersensitivity	Neurotoxicity, fluid retention, myelosuppression with neutropenia
Doxorubicin	Oxygen free radicals bind to DNA causing single- and double-strand DNA breaks; inhibits topoisomerase II; intercalates into DNA	Breast cancer, Hodgkin's and non-Hodgkin's lymphoma, soft tissue sarcoma, ovarian cancer, non-small cell and small cell lung cancer, thyroid cancer, Wilms' tumor, neuroblastoma	Nausea, red urine (not hematuria)	Cardiotoxicity (see text), alopecia, myelosuppression, stomatitis
Etoposide	Inhibits topoisomerase II	Non-small cell and small cell lung cancer; non-Hodgkin's lymphoma, gastric cancer	Nausea, vomiting, hypotension	Alopecia, myelosuppression
Idarubicin	Oxygen free radicals bind to DNA causing single- and double-strand DNA breaks; inhibits topoisomerase II; intercalates into DNA	AML, ALL, CML in blast crisis	Nausea and vomiting	Myelosuppression, mucositis, cardiotoxicity
Irinotecan	Inhibits topoisomerase I	Colorectal cancer, gastroesophageal cancer, non-small cell and small cell lung cancer	Diarrhea, nausea, vomiting	Diarrhea, myelosuppression, nausea and vomiting
Mitomycin	Acts as an alkylating agent and forms cross-links with DNA; formation of oxygen free radicals, which target DNA	Superficial bladder cancer, gastric cancer, breast cancer, non-small cell lung cancer, head and neck cancer (in combination with radiotherapy)	Nausea and vomiting	Myelosuppression, mucositis, anorexia and fatigue, hemolytic-uremic syndrome
Paclitaxel	Inhibits mitosis	Breast cancer, non-small cell and small cell lung cancer, ovarian cancer, gastroesophageal cancer, prostate cancer, bladder cancer, head and neck cancer	Nausea, vomiting, hypotension, arrhythmias, hypersensitivity	Myelosuppression, peripheral sensory neuropathy
Topotecan	Inhibits topoisomerase I	Small cell lung cancer, ovarian cancer	Nausea and vomiting	Myelosuppression
Vinblastine	Inhibits mitosis	Hodgkin's and non-Hodgkin's lymphoma, germ cell cancer, breast cancer, Kaposi's sarcoma	Nausea and vomiting	Myelosuppression, mucositis, alopecia, syndrome of inappropriate secretion of antidiuretic hormone (SIADH), vascular events
Vincristine	Inhibits mitosis	ALL, Hodgkin's and non-Hodgkin's lymphoma, rhabdomyosarcoma, neuroblastoma, Wilms' tumor	None	Neurotoxicity with peripheral neuropathy, paralytic ileus, myelosuppression, alopecia, SIADH
Vinorelbine	Inhibits mitosis	Non-small cell lung cancer, breast cancer, ovarian cancer	Nausea and vomiting	Myelosuppression, constipation, SIADH

[1]See Table 54–3 for acronyms.

Vincristine has been effectively combined with prednisone for remission induction in acute lymphoblastic leukemia in children. It is also active in various hematologic malignancies such as Hodgkin's and non-Hodgkin's lymphomas, and multiple myeloma, and in several pediatric tumors including rhabdomyosarcoma, neuroblastoma, Ewing's sarcoma, and Wilms' tumor.

The main dose-limiting toxicity is neurotoxicity, usually expressed as a peripheral sensory neuropathy, although autonomic nervous system dysfunction with orthostatic hypotension, urinary retention, and paralytic ileus or constipation, cranial nerve palsies, ataxia, seizures, and coma have been observed. While myelosuppression occurs, it is generally milder and much less significant than with vinblastine.

The other adverse effect that may develop is the syndrome of inappropriate secretion of antidiuretic hormone (SIADH).

Vinorelbine

Vinorelbine is a semisynthetic derivative of vinblastine whose mechanism of action is identical to that of vinblastine and vincristine, ie, inhibition of mitosis of cells in the M phase through inhibition of tubulin polymerization. This agent has activity in non-small cell lung cancer, breast cancer, and ovarian cancer. Myelosuppression with neutropenia is the dose-limiting toxicity, but other adverse effects include nausea and vomiting, transient elevations in liver function tests, neurotoxicity, and SIADH.

TAXANES & RELATED DRUGS

Paclitaxel is an alkaloid ester derived from the Pacific yew (*Taxus brevifolia*) and the European yew (*Taxus baccata*). The drug functions as a mitotic spindle poison through high-affinity binding to microtubules with *enhancement* of tubulin polymerization. This promotion of microtubule assembly by paclitaxel occurs in the absence of microtubule-associated proteins and guanosine triphosphate and results in inhibition of mitosis and cell division.

Paclitaxel has significant activity in a broad range of solid tumors, including ovarian, advanced breast, non-small cell and small cell lung, head and neck, esophageal, prostate, and bladder cancers and AIDS-related Kaposi's sarcoma. It is metabolized extensively by the liver P450 system, and nearly 80% of the drug is excreted in feces via the hepatobiliary route. Dose reduction is required in patients with liver dysfunction. The primary dose-limiting toxicities are listed in Table 54–4. Hypersensitivity reactions may be observed in up to 5% of patients, but the incidence is significantly reduced by premedication with dexamethasone, diphenhydramine, and an H_2 blocker.

A novel albumin-bound paclitaxel formulation (Abraxane) is approved for use in metastatic breast cancer. In contrast to paclitaxel, this formulation is not associated with hypersensitivity reactions, and premedication to prevent such reactions is not required. Moreover, this agent has significantly reduced myelosuppressive effects compared with paclitaxel, and the neurotoxicity that results appears to be more readily reversible than is typically observed with paclitaxel.

Docetaxel is a semisynthetic taxane derived from the European yew tree. Its mechanism of action, metabolism, and elimination are identical to those of paclitaxel. It is approved for use as second-line therapy in advanced breast cancer and non-small cell lung cancer, and it also has major activity in head and neck cancer, small cell lung cancer, gastric cancer, advanced platinum-refractory ovarian cancer, and bladder cancer. Its major toxicities are listed in Table 54–4.

Cabazitaxel is a semisynthetic taxane produced from a precursor extracted from the yew tree. Its mechanism of action, metabolism, and elimination are identical to those of the other taxanes. However, unlike other taxanes, cabazitaxel is a poor substrate for the multidrug resistance P-glycoprotein efflux pump and may therefore be useful for treating multidrug-resistant tumors. It is approved for use in combination with prednisone in the second-line therapy of hormone-refractory metastatic prostate cancer previously treated with a docetaxel-containing regimen. Its major toxicities include myelosuppression, neurotoxicity, and allergic reactions.

Although not strictly a taxane, **ixabepilone** is a semisynthetic epothilone B analog that functions as a microtubule inhibitor and binds directly to β-tubulin subunits on microtubules, leading to inhibition of normal microtubule dynamics. As such, it is active in the M phase of the cell cycle. This agent is presently approved for metastatic breast cancer in combination with the oral fluoropyrimidine capecitabine or as monotherapy. Of note, this agent continues to have activity in drug-resistant tumors that overexpress P-glycoprotein or tubulin mutations. The main adverse effects include myelosuppression, hypersensitivity reactions, and neurotoxicity in the form of peripheral sensory neuropathy.

EPIPODOPHYLLOTOXINS

Etoposide is a semisynthetic derivative of podophyllotoxin, which is extracted from the mayapple root (*Podophyllum peltatum*). Intravenous and oral formulations of etoposide are approved for clinical use in the USA. The oral bioavailability is about 50%, requiring the oral dose to be twice that of an intravenous dose. Up to 30–50% of drug is excreted in the urine, and dose reduction is required in the setting of renal dysfunction. The main site of action is inhibition of the DNA enzyme topoisomerase II. Etoposide has clinical activity in germ cell cancer, small cell and non-small cell lung cancer, Hodgkin's and non-Hodgkin's lymphomas, and gastric cancer. In addition, it is effective in high-dose regimens in the transplant setting for breast cancer and lymphomas. Major toxicities are listed in Table 54–4.

CAMPTOTHECINS

The camptothecins are natural products derived from the *Camptotheca acuminata* tree originally found in China; they inhibit the activity of topoisomerase I, the key enzyme responsible for cutting and religating single DNA strands. Inhibition of this enzyme results in DNA damage. **Topotecan** and **irinotecan** are the two camptothecin analogs used in clinical practice in the USA. Although they both inhibit the same molecular target, their spectrum of clinical activity is quite different. Topotecan is indicated in the treatment of advanced ovarian cancer as second-line therapy following initial treatment with platinum-based chemotherapy. It is also approved as second-line therapy of small cell lung cancer. The main route of elimination is renal excretion, and dosage must be adjusted in patients with renal impairment.

Irinotecan is a prodrug that is converted mainly in the liver by the carboxylesterase enzyme to the SN-38 metabolite, which is 1000-fold more potent as an inhibitor of topoisomerase I than the parent compound. In contrast to topotecan, irinotecan and SN-38 are mainly eliminated in bile and feces, and dose reduction is required in the setting of liver dysfunction. Irinotecan was originally approved as second-line monotherapy in patients with metastatic

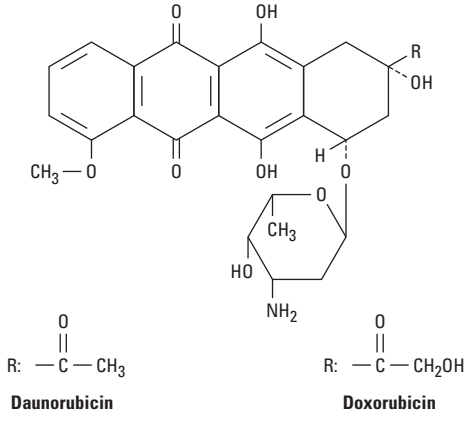
colorectal cancer who had failed fluorouracil-based therapy. It is now approved as first-line therapy when used in combination with 5-FU and leucovorin. Myelosuppression and diarrhea are the two most common adverse events (Table 54–4). There are two forms of diarrhea: an early form that occurs within 24 hours after administration and is thought to be a cholinergic event effectively treated with atropine, and a late form that usually occurs 2–10 days after treatment. The late diarrhea can be severe, leading to significant electrolyte imbalance and dehydration in some cases.

ANTITUMOR ANTIBIOTICS

Screening of microbial products has led to the discovery of a number of growth-inhibiting compounds that have proved to be clinically useful in cancer chemotherapy. Many of these antibiotics bind to DNA through intercalation between specific bases and block the synthesis of RNA, DNA, or both; cause DNA strand scission; and interfere with cell replication. All of the anticancer antibiotics now being used in clinical practice are products of various strains of the soil microbe *Streptomyces*. These include the anthracyclines, bleomycin, and mitomycin.

ANTHRACYCLINES

The anthracycline antibiotics, isolated from *Streptomyces peucetius* var *caesius*, are among the most widely used cytotoxic anticancer drugs. The structures of two congeners, doxorubicin and daunorubicin, are shown below. Several other anthracycline analogs have entered clinical practice, including idarubicin, epirubicin, and mitoxantrone. The anthracyclines exert their cytotoxic action through four major mechanisms: (1) inhibition of topoisomerase II; (2) high-affinity binding to DNA through intercalation, with consequent blockade of the synthesis of DNA and RNA, and DNA strand scission; (3) generation of semiquinone free radicals and oxygen free radicals through an iron-dependent, enzyme-mediated reductive process; and (4) binding to cellular membranes to alter fluidity and ion transport. While the precise mechanisms by which the anthracyclines exert their cytotoxic effects remain to be defined (and may depend upon the specific tumor type), it is now well-established that the free radical mechanism is the cause of the cardiotoxicity associated with the anthracyclines (Table 54–4).



Daunorubicin **Doxorubicin**

In the clinical setting, anthracyclines are administered via the intravenous route. The anthracyclines are metabolized extensively in the liver, with reduction and hydrolysis of the ring substituents. The hydroxylated metabolite is an active species, whereas the aglycone is inactive. Up to 50% of drug is eliminated in the feces via biliary excretion, and dose reduction is required in the setting of liver dysfunction. Although anthracyclines are usually administered on an every-3-week schedule, alternative schedules such as low-dose weekly or 72- to 96-hour continuous infusions have been shown to yield equivalent clinical efficacy with reduced toxicity.

Doxorubicin is one of the most important anticancer drugs in clinical practice, with major clinical activity in cancers of the breast, endometrium, ovary, testicle, thyroid, stomach, bladder, liver, and lung; in soft tissue sarcomas; and in several childhood cancers, including neuroblastoma, Ewing's sarcoma, osteosarcoma, and rhabdomyosarcoma. It also has clinical activity in hematologic malignancies, including acute lymphoblastic leukemia, multiple myeloma, and Hodgkin's and non-Hodgkin's lymphomas. It is generally used in combination with other anticancer agents (eg, cyclophosphamide, cisplatin, and 5-FU), and clinical activity is improved with combination regimens as opposed to single-agent therapy.

Daunorubicin was the first agent in this class to be isolated, and it is still used in the treatment of acute myeloid leukemia. In contrast to doxorubicin, its efficacy in solid tumors is limited.

Idarubicin is a semisynthetic anthracycline glycoside analog of daunorubicin, and it is approved for use in combination with cytarabine for induction therapy of acute myeloid leukemia. When combined with cytarabine, idarubicin appears to be more active than daunorubicin in producing complete remissions and in improving survival in patients with acute myelogenous leukemia.

Epirubicin is an anthracycline analog whose mechanism of action and clinical pharmacology are identical to those of all other anthracyclines. It was initially approved for use as a component of adjuvant therapy in early-stage, node-positive breast cancer but is also used in the treatment of metastatic breast cancer and gastroesophageal cancer.

Mitoxantrone (dihydroxyanthracenedione) is an anthracene compound whose structure resembles the anthracycline ring. It binds to DNA to produce strand breakage and inhibits both DNA and RNA synthesis. It is currently used in the treatment of advanced, hormone-refractory prostate cancer and low-grade non-Hodgkin's lymphoma. It is also indicated in breast cancer and in pediatric and adult acute myeloid leukemias. Myelosuppression with leukopenia is the dose-limiting toxicity, and mild nausea and vomiting, mucositis, and alopecia also occur. Although the drug is thought to be less cardiotoxic than doxorubicin, both acute and chronic cardiac toxicity are reported. A blue discoloration of the fingernails, sclera, and urine is observed 1–2 days after drug administration.

The main dose-limiting toxicity of all anthracyclines is myelosuppression, with neutropenia more commonly observed than thrombocytopenia. In some cases, mucositis is dose-limiting. Two forms of cardiotoxicity are observed. The acute form occurs within the first 2–3 days and presents as arrhythmias and conduction abnormalities, other electrocardiographic changes, pericarditis, and myocarditis. This form is usually transient and in most cases

is asymptomatic. The chronic form results in a dose-dependent, dilated cardiomyopathy associated with heart failure. The chronic cardiac toxicity appears to result from increased production of free radicals within the myocardium. This effect is rarely seen at total doxorubicin dosages below 500–550 mg/m^2. Use of lower weekly doses or continuous infusions of doxorubicin appear to reduce the incidence of cardiac toxicity. In addition, treatment with the iron-chelating agent **dexrazoxane** (ICRF-187) is currently approved to prevent or reduce anthracycline-induced cardiotoxicity in women with metastatic breast cancer who have received a total cumulative dose of doxorubicin of 300 mg/m^2. The anthracyclines can also produce a "radiation recall reaction," with erythema and desquamation of the skin observed at sites of prior radiation therapy.

MITOMYCIN

Mitomycin (mitomycin C) is an antibiotic isolated from *Streptomyces caespitosus*. It undergoes metabolic activation through an enzyme-mediated reduction to generate an alkylating agent that cross-links DNA. Hypoxic tumor stem cells of solid tumors exist in an environment conducive to reductive reactions and are more sensitive to the cytotoxic effects of mitomycin than normal cells and oxygenated tumor cells. It is active in all phases of the cell cycle, and is the best available drug for use in combination with radiation therapy to attack hypoxic tumor cells. Its main clinical use is in the treatment of squamous cell cancer of the anus in combination with 5-FU and radiation therapy. In addition, it is used in combination chemotherapy for squamous cell carcinoma of the cervix and for breast, gastric, and pancreatic cancer. One special application of mitomycin has been in the intravesical treatment of superficial bladder cancer. Because virtually none of the agent is absorbed systemically, there is little to no systemic toxicity when used in this setting.

The common toxicities of mitomycin are outlined in Table 54–4. Hemolytic-uremic syndrome, manifested as microangiopathic hemolytic anemia, thrombocytopenia, and renal failure, as well as occasional instances of interstitial pneumonitis have been reported.

BLEOMYCIN

Bleomycin is a small peptide that contains a DNA-binding region and an iron-binding domain at opposite ends of the molecule. It acts by binding to DNA, which results in single- and double-strand breaks following free radical formation, and inhibition of DNA biosynthesis. The fragmentation of DNA is due to oxidation of a DNA-bleomycin-Fe(II) complex and leads to chromosomal aberrations. Bleomycin is a cell cycle-specific drug that causes accumulation of cells in the G_2 phase of the cell cycle.

Bleomycin is indicated for the treatment of Hodgkin's and non-Hodgkin's lymphomas, germ cell tumor, head and neck cancer, and squamous cell cancer of the skin, cervix, and vulva. One advantage of this agent is that it can be given subcutaneously, intramuscularly, or intravenously. Elimination of bleomycin is mainly via renal excretion, and dose modification is recommended in patients with renal dysfunction.

Pulmonary toxicity is dose-limiting for bleomycin and usually presents as pneumonitis with cough, dyspnea, dry inspiratory crackles on physical examination, and infiltrates on chest X-ray. The incidence of pulmonary toxicity is increased in patients older than 70 years of age, in those who receive cumulative doses greater than 400 units, in those with underlying pulmonary disease, and in those who have received prior mediastinal or chest irradiation. In rare cases, pulmonary toxicity can be fatal. Other toxicities are listed in Table 54–4.

MISCELLANEOUS ANTICANCER DRUGS

A large number of anticancer drugs that do not fit traditional categories have been approved for clinical use by the Food and Drug Administration (FDA); they are listed in Table 54–5.

IMATINIB, DASATINIB, & NILOTINIB

Imatinib is an inhibitor of the tyrosine kinase domain of the Bcr-Abl oncoprotein and prevents phosphorylation of the kinase substrate by ATP. It is indicated for the treatment of chronic myelogenous leukemia (CML), a pluripotent hematopoietic stem cell disorder characterized by the t(9:22) Philadelphia chromosomal translocation. This translocation results in the Bcr-Abl fusion protein, the causative agent in CML, and is present in up to 95% of patients with this disease. This agent also inhibits other receptor tyrosine kinases for platelet-derived growth factor receptor (PDGFR), stem cell factor, and c-kit.

Imatinib is well absorbed orally, and it is metabolized in the liver, with elimination of metabolites occurring mainly in feces via biliary excretion. This agent is approved for use as first-line therapy in chronic phase CML, in blast crisis, and as second-line therapy for chronic phase CML that has progressed on prior interferon-alfa therapy. Imatinib is also effective in the treatment of gastrointestinal stromal tumors expressing the c-kit tyrosine kinase. The main adverse effects are listed in Table 54–5.

Dasatinib is an oral inhibitor of several tyrosine kinases, including Bcr-Abl, Src, c-kit, and PDGFR-α. It differs from imatinib in that it binds to the active and inactive conformations of the Abl kinase domain and overcomes imatinib resistance resulting from mutations in the Bcr-Abl kinase. It is approved for use in CML and Philadelphia chromosome-positive acute lymphoblastic leukemia (ALL) with resistance or intolerance to imatinib therapy.

Nilotinib is a second-generation phenylamino-pyrimidine molecule that inhibits Bcr-Abl, c-kit, and PDGFR-β tyrosine kinases. It has a higher binding affinity (up to 20- to 50-fold) for the Abl kinase when compared with imatinib, and it overcomes imatinib resistance resulting from Bcr-Abl mutations. It was originally approved for chronic phase and accelerated phase CML with resistance or intolerance to prior therapy that included imatinib and was recently approved as first-line therapy of chronic phase CML.

TABLE 54–5 Miscellaneous anticancer drugs: Clinical activity and toxicities.

Drug	Mechanism of Action[1]	Clinical Applications[1]	Acute Toxicity	Delayed Toxicity
Asparaginase	Hydrolyzes circulating L-asparagine, resulting in rapid inhibition of protein synthesis	ALL	Nausea, fever, allergic reactions	Hepatotoxicity, increased risk of bleeding and clotting, mental depression, pancreatitis, renal toxicity
Erlotinib	Inhibits EGFR tyrosine kinase leading to inhibition of EGFR signaling	Non-small cell lung cancer, pancreatic cancer	Diarrhea	Skin rash, diarrhea, anorexia, interstitial lung disease
Gefitinib	Same as erlotinib	Non-small cell lung cancer	Hypertension, diarrhea	Same as above
Imatinib	Inhibits Bcr-Abl tyrosine kinase and other receptor tyrosine kinases, including PDGFR, stem cell factor, and c-kit	CML, gastrointestinal stromal tumor (GIST), Philadelphia chromosome-positive ALL	Nausea and vomiting	Fluid retention with ankle and periorbital edema, diarrhea, myalgias, congestive heart failure
Cetuximab	Binds to EGFR and inhibits downstream EGFR signaling; enhances response to chemotherapy and radiotherapy	Colorectal cancer, head and neck cancer (used in combination with radiotherapy), non-small cell lung cancer	Infusion reaction	Skin rash, hypomagnesemia, fatigue, interstitial lung disease
Panitumumab	Binds to EGFR and inhibits downstream EGFR signaling; enhances response to chemotherapy and radiotherapy	Colorectal cancer	Infusion reaction (rarely)	Skin rash, hypomagnesemia, fatigue, interstitial lung disease
Bevacizumab	Inhibits binding of VEGF to VEGFR leading to inhibition of VEGF signaling; inhibits tumor vascular permeability; enhances tumor blood flow and drug delivery	Colorectal cancer, breast cancer, non-small cell lung cancer, renal cell cancer	Hypertension, infusion reaction	Arterial thromboembolic events, gastrointestinal perforations, wound healing complications, proteinuria
Sorafenib	Inhibits multiple RTKs, including raf kinase, VEGF-R2, VEGF-R3, and PDGFR-β leading to inhibition of angiogenesis, invasion, and metastasis	Renal cell cancer, hepatocellular cancer	Nausea, hypertension	Skin rash, fatigue and asthenia, bleeding complications, hypophosphatemia
Sunitinib	Inhibits multiple RTKs, including VEGF-R1, VEGF-R2, VEGF-R3, PDGFR-α and PDGFR-β leading to inhibition of angiogenesis, invasion, and metastasis	Renal cell cancer, GIST	Hypertension	Skin rash, fatigue and asthenia, bleeding complications, cardiac toxicity leading to congestive heart failure in rare cases

[1]See text for acronyms.

Imatinib, dasatinib, and nilotinib are all metabolized in the liver, mainly by the CYP3A4 liver microsomal enzyme. A large fraction of each drug is eliminated in feces via the hepatobiliary route. It is important to review the patient's current list of prescription and nonprescription drugs because these agents have potential drug-drug interactions, especially with those that are also metabolized by the CYP3A4 system. In addition, patients should avoid grapefruit products and the use of St. John's wort, as they may alter the metabolism of these small molecule inhibitors (see Chapter 4).

GROWTH FACTOR RECEPTOR INHIBITORS

Cetuximab & Panitumumab

The epidermal growth factor receptor (EGFR) is a member of the erb-B family of growth factor receptors, and it is overexpressed in a number of solid tumors, including colorectal cancer, head and neck cancer, non-small cell lung cancer, and pancreatic cancer. Activation of the EGFR signaling pathway results in downstream activation of several key cellular events involved in cellular growth and proliferation, invasion and metastasis, and angiogenesis. In addition, this pathway inhibits the cytotoxic activity of various anticancer agents and radiation therapy, presumably through suppression of key apoptotic mechanisms, thereby leading to the development of cellular drug resistance.

Cetuximab is a chimeric monoclonal antibody directed against the extracellular domain of the EGFR, and it is presently approved for use in combination with irinotecan for metastatic colon cancer in the refractory setting or as monotherapy in patients who are deemed to be irinotecan-refractory. Because cetuximab is of the G_1 isotype, its antitumor activity may also be mediated, in part, by immunologic-mediated mechanisms. There is growing evidence that cetuximab can be effectively and safely combined with irinotecan- and oxaliplatin-based chemotherapy in the first-line

treatment of metastatic colorectal cancer as well. Of note, the efficacy of cetuximab is restricted to only those patients whose tumors express wild-type *KRAS*. Regimens combining cetuximab with cytotoxic chemotherapy may be of particular benefit in the neoadjuvant therapy of patients with liver-limited disease. Although this antibody was initially approved to be administered on a weekly schedule, pharmacokinetic studies have shown that an every-2-week schedule provides the same level of clinical activity as the weekly schedule. This agent is also approved for use in combination with radiation therapy in patients with locally advanced head and neck cancer. Cetuximab is well tolerated, with the main adverse effects being an acneiform skin rash, hypersensitivity infusion reaction, and hypomagnesemia.

Panitumumab is a fully human monoclonal antibody directed against the EGFR and works through inhibition of the EGFR signaling pathway. In contrast to cetuximab, this antibody is of the G_2 isotype, and as such, it would not be expected to exert any immunologic-mediated effects. Presently, panitumumab is approved for patients with refractory metastatic colorectal cancer who have been treated with all other active agents, and as with cetuximab, this antibody is only effective in patients whose tumors express wild-type *KRAS*. Recent clinical studies have shown that this antibody is effectively and safely combined with oxaliplatin- and irinotecan-based chemotherapy in the first- and second-line treatment of metastatic colorectal cancer. Acneiform skin rash and hypomagnesemia are the two main adverse effects associated with its use. Because this is a fully human antibody, infusion-related reactions are rarely observed.

Gefitinib & Erlotinib

Gefitinib and erlotinib are small molecule inhibitors of the tyrosine kinase domain associated with the EGFR, and both are used in the treatment of non-small cell lung cancer that is refractory to at least one prior chemotherapy regimen. Patients who are nonsmokers and who have a bronchoalveolar histologic subtype appear to be more responsive to these agents. In addition, erlotinib has been approved for use in combination with gemcitabine for the treatment of advanced pancreatic cancer. Both agents are metabolized in the liver by the CYP3A4 enzyme system, and elimination is mainly hepatic with excretion in feces. Caution must be taken when using these agents with drugs that are also metabolized by the liver CYP3A4 system, such as phenytoin and warfarin, and the use of grapefruit products should be avoided. An acneiform skin rash, diarrhea, and anorexia and fatigue are the most common adverse effects observed with these small molecules (Table 54-5).

Bevacizumab, Sorafenib, Sunitinib, & Pazopanib

The vascular endothelial growth factor (VEGF) is one of the most important angiogenic growth factors. The growth of both primary and metastatic tumors requires an intact vasculature. As a result, the VEGF-signaling pathway represents an attractive target for chemotherapy. Several approaches have been taken to inhibit VEGF signaling; they include inhibition of VEGF interactions with its receptor by targeting either the VEGF ligand with antibodies or soluble chimeric decoy receptors, or by direct inhibition of the VEGF receptor-associated tyrosine kinase activity by small molecule inhibitors.

Bevacizumab is a recombinant humanized monoclonal antibody that targets all forms of VEGF-A. This antibody binds to and prevents VEGF-A from interacting with the target VEGF receptors. Bevacizumab can be safely and effectively combined with 5-FU-, irinotecan-, and oxaliplatin-based chemotherapy in the treatment of metastatic colorectal cancer. Bevacizumab is FDA approved as a first-line treatment for metastatic colorectal cancer in combination with any intravenous fluoropyrimidine-containing regimen and is now also approved in combination with chemotherapy for metastatic non-small lung cancer and breast cancer. One potential advantage of this antibody is that it does not appear to exacerbate the toxicities typically observed with cytotoxic chemotherapy. The main safety concerns associated with bevacizumab include hypertension, an increased incidence of arterial thromboembolic events (transient ischemic attack, stroke, angina, and myocardial infarction), wound healing complications, gastrointestinal perforations, and proteinuria.

Sorafenib is a small molecule that inhibits multiple receptor tyrosine kinases (RTKs), especially VEGF-R2 and VEGF-R3, platelet-derived growth factor-β (PDGFR-β), and raf kinase. It was initially approved for advanced renal cell cancer and is also approved for advanced hepatocellular cancer.

Sunitinib is similar to sorafenib in that it inhibits multiple RTKs, although the specific types are somewhat different. They include PDGFR-α and PDGFR-β, VEGF-R1, VEGF-R2, VEGF-R3, and c-kit. It is approved for the treatment of advanced renal cell cancer and for the treatment of gastrointestinal stromal tumors (GIST) after disease progression on or with intolerance to imatinib.

Pazopanib is a small molecule that inhibits multiple RTKs, especially VEGF-R2 and VEGF-R3, PDGFR-β, and raf kinase. This oral agent is approved for the treatment of advanced renal cell cancer.

Sorafenib, sunitinib, and pazopanib are metabolized in the liver by the CYP3A4 system, and elimination is primarily hepatic with excretion in feces. Each of these agents has potential interactions with drugs that are also metabolized by the CYP3A4 system, especially warfarin. In addition, patients should avoid grapefruit products and the use of St. John's wort, as they may alter the clinical activity of these agents. Hypertension, bleeding complications, and fatigue are the most common adverse effects seen with both agents. With respect to sorafenib, skin rash and the hand-foot syndrome are observed in up to 30–50% of patients. For sunitinib, there is also an increased risk of cardiac dysfunction, which in some cases can lead to congestive heart failure.

ASPARAGINASE

Asparaginase (L-asparagine amidohydrolase) is an enzyme used to treat childhood ALL. The drug is isolated and purified from *Escherichia coli* or *Erwinia chrysanthemi* for clinical use. It hydrolyzes circulating L-asparagine to aspartic acid and ammonia. Because tumor cells in ALL lack asparagine synthetase, they require an exogenous source of L-asparagine. Thus, depletion of L-asparagine results in effective inhibition of protein synthesis. In

contrast, normal cells can synthesize L-asparagine and thus are less susceptible to the cytotoxic action of asparaginase. The main adverse effect of this agent is a hypersensitivity reaction manifested by fever, chills, nausea and vomiting, skin rash, and urticaria. Severe cases can present with bronchospasm, respiratory failure, and hypotension. Other side effects include an increased risk of both clotting and bleeding as a result of alterations in various clotting factors, pancreatitis, and neurologic toxicity with lethargy, confusion, hallucinations, and in severe cases, coma.

CLINICAL PHARMACOLOGY OF CANCER CHEMOTHERAPEUTIC DRUGS

A thorough knowledge of the kinetics of tumor cell proliferation along with an understanding of the pharmacology and mechanism of action of cancer chemotherapeutic agents is important in designing optimal regimens for patients with cancer. The strategy for developing drug regimens also requires knowledge of the specific characteristics of individual tumors. For example, is there a high growth fraction? Is there a high spontaneous cell death rate? Are most of the cells in G_0? Is a significant fraction of the tumor composed of hypoxic stem cells? Are their normal counterparts under hormonal control? Similarly, an understanding of the pharmacology of specific drugs is important. Are the tumor cells sensitive to the drug? Is the drug cell cycle specific? Does the drug require activation in certain normal tissue such as the liver (cyclophosphamide), or is it activated in the tumor tissue itself (capecitabine)? Knowledge of specific pathway abnormalities (eg, EGFR mutations, *KRAS* mutations) for intracellular signaling may prove important for the next generation of anticancer drugs.

For some tumor types, knowledge of receptor expression is important. In patients with breast cancer, analysis of the tumor for expression of estrogen or progesterone receptors is important in guiding therapy with selective estrogen receptor modulators. In addition, analysis of breast cancer for expression of the HER-2/*neu* growth factor receptor can determine whether the humanized monoclonal anti-HER-2/*neu* antibody, trastuzumab, would be appropriate therapy. In the case of prostate cancer, chemical suppression of androgen secretion with gonadotropin-releasing hormone agonists or antagonists is important. The basic pharmacology of hormonal therapy is discussed in Chapter 40. The use of specific cytotoxic and biologic agents for each of the main cancers is discussed in this section.

THE LEUKEMIAS

ACUTE LEUKEMIA

Childhood Leukemia

Acute lymphoblastic leukemia (ALL) is the main form of leukemia in childhood, and it is the most common form of cancer in children. Children with this disease have a relatively good prognosis. A subset of patients with neoplastic lymphocytes expressing surface antigenic features of T lymphocytes has a poor prognosis (see Chapter 55). A cytoplasmic enzyme expressed by normal thymocytes, terminal deoxycytidyl transferase (terminal transferase), is also expressed in many cases of ALL. T-cell ALL also expresses high levels of the enzyme adenosine deaminase (ADA). This led to interest in the use of the ADA inhibitor pentostatin (deoxycoformycin) for treatment of such T-cell cases. Until 1948, the median length of survival in ALL was 3 months. With the advent of methotrexate, the length of survival was greatly increased. Subsequently, corticosteroids, 6-mercaptopurine, cyclophosphamide, vincristine, daunorubicin, and asparaginase have all been found to be active against this disease. A combination of vincristine and prednisone plus other agents is currently used to induce remission. Over 90% of children enter complete remission with this therapy with only minimal toxicity. However, circulating leukemic cells often migrate to sanctuary sites located in the brain and testes. The value of prophylactic intrathecal methotrexate therapy for prevention of central nervous system leukemia (a major mechanism of relapse) has been clearly demonstrated. Intrathecal therapy with methotrexate should therefore be considered as a standard component of the induction regimen for children with ALL.

Adult Leukemia

Acute myelogenous leukemia (AML) is the most common leukemia in adults. The single most active agent for AML is cytarabine; however, it is best used in combination with an anthracycline, which leads to complete remissions in about 70% of patients. While there are several anthracyclines that can be effectively combined with cytarabine, idarubicin is preferred.

Patients often require intensive supportive care during the period of induction chemotherapy. Such care includes platelet transfusions to prevent bleeding, the granulocyte colony-stimulating factor filgrastim to shorten periods of neutropenia, and antibiotics to combat infections. Younger patients (eg, age < 55) who are in complete remission and have an HLA-matched donor are candidates for allogeneic bone marrow transplantation. The transplant procedure is preceded by high-dose chemotherapy and total body irradiation followed by immunosuppression. This approach may cure up to 35–40% of eligible patients. Patients over age 60 respond less well to chemotherapy, primarily because their tolerance for aggressive therapy and resistance to infection are lower.

Once remission of AML is achieved, consolidation chemotherapy is required to maintain a durable remission and to induce cure.

CHRONIC MYELOGENOUS LEUKEMIA

Chronic myelogenous leukemia (CML) arises from a chromosomally abnormal hematopoietic stem cell in which a balanced translocation between the long arms of chromosomes 9 and 22, t(9:22), is observed in 90–95% of cases. This translocation results in constitutive expression of the Bcr-Abl fusion oncoprotein with a molecular weight of 210 kDa. The clinical symptoms and course are related to the white blood cell count and its rate of increase. Most patients with

white cell counts over 50,000/μL should be treated. The goals of treatment are to reduce the granulocytes to normal levels, to raise the hemoglobin concentration to normal, and to relieve disease-related symptoms. The tyrosine kinase inhibitor imatinib is considered as standard first-line therapy in previously untreated patients with chronic phase CML. Nearly all patients treated with imatinib exhibit a complete hematologic response, and up to 40–50% of patients show a complete cytogenetic response. As described previously, this drug is generally well tolerated and is associated with relatively minor adverse effects. Initially, dasatinib and nilotinib were approved for patients who were intolerant or resistant to imatinib; each shows clinical activity, but both are now also indicated as first-line treatment of chronic phase CML. In addition to these tyrosine kinase inhibitors, other treatment options include interferon-α, busulfan, other oral alkylating agents, and hydroxyurea.

CHRONIC LYMPHOCYTIC LEUKEMIA

Patients with early-stage chronic lymphocytic leukemia (CLL) have a relatively good prognosis, and therapy has not changed the course of the disease. However, in the setting of high-risk disease or in the presence of disease-related symptoms, treatment is indicated.

Chlorambucil and cyclophosphamide are the two most widely used alkylating agents for this disease. Chlorambucil is frequently combined with prednisone, although there is no clear evidence that the combination yields better response rates or survival compared with chlorambucil alone. In most cases, cyclophosphamide is combined with vincristine and prednisone (COP), or it can also be given with these same drugs along with doxorubicin (CHOP). Bendamustine is the newest alkylating agent to be approved for use in this disease, either as monotherapy or in combination with prednisone. The purine nucleoside analog fludarabine is also effective in treating CLL. This agent can be given alone, in combination with cyclophosphamide and with mitoxantrone and dexamethasone, or combined with the anti-CD20 antibody rituximab.

Monoclonal antibody-targeted therapies are being widely used in CLL, especially in relapsed or refractory disease. Rituximab is an anti-CD20 antibody that has documented clinical activity in this setting. This chimeric antibody appears to enhance the antitumor effects of cytotoxic chemotherapy and is also effective in settings in which resistance to chemotherapy has developed. Alemtuzumab is a humanized monoclonal antibody directed against the CD52 antigen and is approved for use in CLL that is refractory to alkylating agent or fludarabine therapy. Response rates up to 30–35% are observed, with disease stabilization in another 30% of patients.

HODGKIN'S & NON-HODGKIN'S LYMPHOMAS

HODGKIN'S LYMPHOMA

The treatment of Hodgkin's lymphoma has undergone dramatic evolution over the last 30 years. This lymphoma is now widely recognized as a B-cell neoplasm in which the malignant Reed-Sternberg cells have rearranged *VH* genes. In addition, the Epstein-Barr virus genome has been identified in up to 80% of tumor specimens.

Complete staging evaluation is required before a definitive treatment plan can be made. For patients with stage I and stage IIA disease, there has been a significant change in the treatment approach. Initially, these patients were treated with extended-field radiation therapy. However, given the well-documented late effects of radiation therapy, which include hypothyroidism, an increased risk of secondary cancers, and coronary artery disease, combined-modality therapy with a brief course of combination chemotherapy and involved field radiation therapy is now the recommended approach. The main advance for patients with advanced stage III and IV Hodgkin's lymphoma came with the development of MOPP (mechlorethamine, vincristine, procarbazine, and prednisone) chemotherapy in the 1960s. This regimen resulted initially in high complete response rates, on the order of 80–90%, with cures in up to 60% of patients. More recently, the anthracycline-containing regimen termed ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine) has been shown to be more effective and less toxic than MOPP, especially with regard to the incidence of infertility and secondary malignancies. In general, four cycles of ABVD are given to patients. An alternative regimen, termed Stanford V, utilizes a 12-week course of combination chemotherapy (doxorubicin, vinblastine, mechlorethamine, vincristine, bleomycin, etoposide, and prednisone), followed by involved radiation therapy.

With all of these regimens, over 80% of previously untreated patients with advanced Hodgkin's lymphoma (stages III and IV) are expected to go into complete remission, with disappearance of all disease-related symptoms and objective evidence of disease. In general, approximately 50–60% of all patients with Hodgkin's lymphoma are cured of their disease.

NON-HODGKIN'S LYMPHOMA

Non-Hodgkin's lymphoma is a heterogeneous disease, and the clinical characteristics of non-Hodgkin's lymphoma subsets are related to the underlying histopathologic features and the extent of disease involvement. In general, the nodular (or follicular) lymphomas have a far better prognosis, with a median survival up to 7 years, compared with the diffuse lymphomas, which have a median survival of about 1–2 years.

Combination chemotherapy is the treatment standard for patients with diffuse non-Hodgkin's lymphoma. The anthracycline-containing regimen CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) has been considered the best treatment in terms of initial therapy. Randomized phase III clinical studies have now shown that the combination of CHOP with the anti-CD20 monoclonal antibody rituximab results in improved response rates, disease-free survival, and overall survival compared with CHOP chemotherapy alone.

The nodular follicular lymphomas are low-grade, relatively slow-growing tumors that tend to present in an advanced stage and are usually confined to lymph nodes, bone marrow, and spleen. This form of non-Hodgkin's lymphomas, when presenting

at an advanced stage, is considered incurable, and treatment is generally palliative. To date, there is no evidence that immediate treatment with combination chemotherapy offers clinical benefit over close observation and "watchful waiting" with initiation of chemotherapy at the onset of disease symptoms.

MULTIPLE MYELOMA

This plasma cell malignancy is one of the models of neoplastic disease in humans as it arises from a single tumor stem cell. Moreover, the tumor cells produce a marker protein (myeloma immunoglobulin) that allows the total body burden of tumor cells to be quantified. Multiple myeloma principally involves the bone marrow and bone, causing bone pain, lytic lesions, bone fractures, and anemia as well as an increased susceptibility to infection.

Most patients with multiple myeloma are symptomatic at the time of initial diagnosis and require treatment with cytotoxic chemotherapy. Treatment with the combination of the alkylating agent melphalan and prednisone (MP protocol) has been a standard regimen for nearly 30 years. About 40% of patients respond to the MP combination, and the median remission is on the order of 2–2.5 years. Recently, combination regimens incorporating **lenalidomide** plus dexamethasone or the proteosome inhibitor **bortezomib** plus melphalan and prednisone have been shown to be more effective as first-line therapy.

In patients who are considered candidates for high-dose therapy with stem cell transplantation, melphalan and other alkylating agents are to be avoided, as they can affect the success of stem cell harvesting.

Thalidomide is a well-established agent for treating refractory or relapsed disease, and about 30% of patients will achieve a response to this therapy. More recently, thalidomide has been used in combination with dexamethasone, and response rates on the order of 65% have been observed. Studies are now under way to directly compare the combination of vincristine, doxorubicin, and dexamethasone (VAD protocol) with the combination of thalidomide and dexamethasone. In some patients, especially those with poor performance status, single-agent pulse dexamethasone administered on a weekly basis can be effective in palliating symptoms. Bortezomib was first approved for use in relapsing or refractory multiple myeloma and is now widely used in the first-line treatment of multiple myeloma. This agent is thought to exert its main cytotoxic effects through inhibition of the 26 S proteosome, which results in down-regulation of the nuclear factor kappa B (NF-κB) signaling pathway. Of note, inhibition of NF-κB has been shown to restore chemosensitivity. Based on this site of action, further efforts are focused on developing bortezomib in various combination regimens.

BREAST CANCER

STAGE I & STAGE II DISEASE

The management of primary breast cancer has undergone a remarkable evolution as a result of major efforts at early diagnosis (through encouragement of self-examination as well as through the use of cancer detection centers) and the implementation of combined modality approaches incorporating systemic chemotherapy as an adjuvant to surgery and radiation therapy. Women with stage I disease (small primary tumors and negative axillary lymph node dissections) are currently treated with surgery alone, and they have an 80% chance of cure.

Women with node-positive disease have a high risk of both local and systemic recurrence. Thus, lymph node status directly indicates the risk of occult distant micrometastasis. In this situation, postoperative use of systemic adjuvant chemotherapy with six cycles of cyclophosphamide, methotrexate, and fluorouracil (CMF protocol) or of fluorouracil, doxorubicin, and cyclophosphamide (FAC) has been shown to significantly reduce the relapse rate and prolong survival. Alternative regimens with equivalent clinical benefit include four cycles of doxorubicin and cyclophosphamide and six cycles of fluorouracil, epirubicin, and cyclophosphamide (FEC). Each of these chemotherapy regimens has benefited women with stage II breast cancer with one to three involved lymph nodes. Women with four or more involved nodes have had limited benefit thus far from adjuvant chemotherapy. Long-term analysis has clearly shown improved survival rates in node-positive premenopausal women who have been treated aggressively with multiagent combination chemotherapy. The results from three randomized clinical trials clearly show that the addition of trastuzumab, a monoclonal antibody directed against the HER-2/*neu* receptor, to anthracycline- and taxane-containing adjuvant chemotherapy benefits women with HER-2-overexpressing breast cancer with respect to disease-free and overall survival.

Breast cancer was the first neoplasm shown to be responsive to hormonal manipulation. Tamoxifen is beneficial in postmenopausal women when used alone or in combination with cytotoxic chemotherapy. The present recommendation is to administer tamoxifen for 5 years of continuous therapy after surgical resection. Longer durations of tamoxifen therapy do not appear to add additional clinical benefit. Postmenopausal women who complete 5 years of tamoxifen therapy should be placed on an aromatase inhibitor such as anastrozole for at least 2.5 years, although the optimal duration is unknown. In women who have completed 2–3 years of tamoxifen therapy, treatment with an aromatase inhibitor for a total of 5 years of hormonal therapy is now recommended (see Chapter 40).

Results from several randomized trials for breast cancer have established that adjuvant chemotherapy for premenopausal women and adjuvant tamoxifen for postmenopausal women are of benefit to women with stage I (node-negative) breast cancer. While this group of patients has the lowest overall risk of recurrence after surgery alone (about 35–50% over 15 years), this risk can be further reduced with adjuvant therapy.

STAGE III & STAGE IV DISEASE

The approach to women with advanced breast cancer remains a major challenge, as current treatment options are only palliative. Combination chemotherapy, endocrine therapy, or a combination of both results in overall response rates of 40–50%, but only a

10–20% complete response rate. Breast cancers expressing estrogen receptors (ER) or progesterone receptors (PR), retain the intrinsic hormonal sensitivities of the normal breast—including the growth-stimulatory response to ovarian, adrenal, and pituitary hormones. Patients who show improvement with hormonal ablative procedures also respond to the addition of tamoxifen. The aromatase inhibitors anastrozole and letrozole are now approved as first-line therapy in women with advanced breast cancer whose tumors are hormone-receptor positive. In addition, these agents and exemestane are approved as second-line therapy following treatment with tamoxifen.

Patients with significant involvement of the lung, liver, or brain and those with rapidly progressive disease rarely benefit from hormonal maneuvers, and initial systemic chemotherapy is indicated in such cases. For the 25–30% of breast cancer patients whose tumors express the HER-2/*neu* cell surface receptor, the humanized monoclonal anti-HER-2/*neu* antibody, trastuzumab, is available for therapeutic use alone or in combination with cytotoxic chemotherapy.

About 50–60% of patients with metastatic disease respond to initial chemotherapy. A broad range of anticancer agents have activity in this disease, including the anthracyclines (doxorubicin, mitoxantrone, and epirubicin), the taxanes (docetaxel, paclitaxel, and albumin-bound paclitaxel) along with the microtubule inhibitor ixabepilone, navelbine, capecitabine, gemcitabine, cyclophosphamide, methotrexate, and cisplatin. The anthracyclines and the taxanes are two of the most active classes of cytotoxic drugs. Combination chemotherapy has been found to induce higher and more durable remissions in up to 50–80% of patients, and anthracycline-containing regimens are now considered the standard of care in first-line therapy. With most combination regimens, partial remissions have a median duration of about 10 months and complete remissions have a duration of about 15 months. Unfortunately, only 10–20% of patients achieve complete remissions with any of these regimens, and as noted, complete remissions are usually not long-lasting.

PROSTATE CANCER

Prostate cancer was the second cancer shown to be responsive to hormonal manipulation. The treatment of choice for patients with advanced prostate cancer is elimination of testosterone production by the testes through either surgical or chemical castration. Bilateral orchiectomy or estrogen therapy in the form of diethylstilbestrol was previously used as first-line therapy. Presently, the use of luteinizing hormone-releasing hormone (LHRH) agonists—including leuprolide and goserelin agonists, alone or in combination with an antiandrogen (eg, flutamide, bicalutamide, or nilutamide)—is the preferred approach. There appears to be no survival advantage of total androgen blockade using a combination of LHRH agonist and antiandrogen agent compared with single-agent therapy. Hormonal treatment reduces symptoms—especially bone pain—in 70–80% of patients and may cause a significant reduction in the prostate-specific antigen (PSA) level, which is now widely accepted as a surrogate marker for response to treatment in prostate cancer. Although initial hormonal manipulation is able to control symptoms for up to 2 years, patients usually develop progressive disease. Second-line hormonal therapies include aminoglutethimide plus hydrocortisone, the antifungal agent ketoconazole plus hydrocortisone, or hydrocortisone alone.

Unfortunately, nearly all patients with advanced prostate cancer eventually become refractory to hormone therapy. A regimen of mitoxantrone and prednisone is approved in patients with hormone-refractory prostate cancer because it provides effective palliation in those who experience significant bone pain. Estramustine is an antimicrotubule agent that produces an almost 20% response rate as a single agent. However, when used in combination with either etoposide or a taxane such as docetaxel or paclitaxel, response rates are more than doubled to 40–50%. The combination of docetaxel and prednisone was recently shown to confer survival advantage when compared with the mitoxantrone-prednisone regimen, and this combination has now become the standard of care for hormone-refractory prostate cancer.

GASTROINTESTINAL CANCERS

Colorectal cancer (CRC) is the most common type of gastrointestinal malignancy. Nearly 145,000 new cases are diagnosed each year in the USA; worldwide, nearly one million cases are diagnosed each year. At the time of initial presentation, only about 40–45% of patients are potentially curable with surgery. Patients presenting with high-risk stage II disease and stage III disease are candidates for adjuvant chemotherapy with an oxaliplatin-based regimen in combination with 5-FU plus leucovorin (FOLFOX or FLOX) or with oral capecitabine (XELOX) and are generally treated for 6 months following surgical resection. Treatment with this combination regimen reduces the recurrence rate after surgery by 35% and clearly improves overall patient survival compared with surgery alone.

Significant advances have been made over the past 10 years with respect to treatment of metastatic CRC. There are four active cytotoxic agents—5-FU, the oral fluoropyrimidine capecitabine, oxaliplatin, and irinotecan; and three active biologic agents—the anti-VEGF antibody bevacizumab and the anti-EGFR antibodies cetuximab and panitumumab. In general, a fluoropyrimidine with either intravenous 5-FU or oral capecitabine serves as the main foundation of cytotoxic chemotherapy regimens. Recent clinical studies have shown that FOLFOX/FOLFIRI regimens in combination with the anti-VEGF antibody bevacizumab or with the anti-EGFR antibody cetuximab result in significantly improved clinical efficacy with no worsening of the toxicities normally observed with chemotherapy. In order for patients to derive maximal benefit, they should be treated with each of these active agents in a continuum of care approach. Using this strategy, median survivals now are in the 24–28 month range, and in some cases, approach 3 years. One of the main challenges facing clinicians at present is to begin to identify which patients would benefit from these various cytotoxic and biologic agents as well as identify those who might experience increased toxicity.

The incidence of gastric cancer, esophageal cancer, and pancreatic cancer is much lower than for CRC, but these malignancies tend to be more aggressive and result in greater tumor-related

symptoms. In most cases, they cannot be completely resected surgically, as most patients present with either locally advanced or metastatic disease at the time of their initial diagnosis. 5-FU-based chemotherapy, using either intravenous 5-FU or oral capecitabine, is generally considered the main backbone for regimens targeting gastroesophageal cancers. In addition, cisplatin-based regimens in combination with either irinotecan or one of the taxanes (paclitaxel or docetaxel) also exhibit clinical activity. Response rates in the 40–50% range are now being reported. Recent studies have shown that the addition of the biologic agent trastuzumab to cisplatin-containing chemotherapy regimens provides significant clinical benefit in gastric cancer patients whose tumors overexpress the HER-2/*neu* receptor. In addition, neoadjuvant approaches with combination chemotherapy and radiation therapy prior to surgery appear to have promise in selected patients.

Although gemcitabine is approved for use as a single agent in metastatic pancreatic cancer, the overall response rate is less than 10%, with complete responses being quite rare. Intense efforts continue to be placed on incorporating gemcitabine into various combination regimens and on identifying novel agents that target signal transduction pathways thought to be critical for the growth of pancreatic cancer. One such agent is the small molecule inhibitor erlotinib, which targets the EGFR-associated tyrosine kinase. This agent is now approved for use in combination with gemcitabine in locally advanced or metastatic pancreatic cancer although the improvement in clinical benefit is relatively small. There is also evidence to support the use of adjuvant chemotherapy with either single-agent gemcitabine or 5-FU/leucovorin in patients with early-stage pancreatic cancer who have undergone successful surgical resection.

LUNG CANCER

Lung cancer is divided into two main histopathologic subtypes, non-small cell and small cell. Non-small cell lung cancer (NSCLC) makes up about 75–80% of all cases of lung cancer, and this group includes adenocarcinoma, squamous cell cancer, and large cell cancer, while small cell lung cancer (SCLC) makes up the remaining 20–25%. When NSCLC is diagnosed in an advanced stage with metastatic disease, the prognosis is extremely poor, with a median survival of about 8 months. It is clear that prevention (primarily through avoidance of cigarette smoking) and early detection remain the most important means of control. When diagnosed at an early stage, surgical resection results in patient cure. Moreover, recent studies have shown that adjuvant platinum-based chemotherapy provides a survival benefit in patients with pathologic stage IB, II, and IIIA disease. However, in most cases, distant metastases have occurred at the time of diagnosis. In certain instances, radiation therapy can be offered for palliation of pain, airway obstruction, or bleeding and to treat patients whose performance status would not allow for more aggressive treatments.

In patients with advanced disease, systemic chemotherapy is generally recommended. Combination regimens that include a platinum agent ("platinum doublets") appear superior to non-platinum doublets, and either cisplatin or carboplatin are appropriate platinum agents for such regimens. For the second drug, paclitaxel and vinorelbine appear to have activity independent of histology, while the antifolate pemetrexed should be used for non-squamous cell cancer, and gemcitabine for squamous cell cancer. For patients with good performance status and those with non-squamous histology, the combination of the anti-VEGF antibody bevacizumab with carboplatin and paclitaxel is a standard treatment option. In patients deemed not to be appropriate candidates for bevacizumab therapy and those with squamous cell histology, a platinum-based chemotherapy regimen in combination with the anti-EGFR antibody cetuximab is a reasonable treatment strategy. Maintenance chemotherapy with pemetrexed is now used in patients with non-squamous NSCLC whose disease has not progressed after four cycles of platinum-based first-line chemotherapy. Finally, first-line therapy with an EGFR tyrosine kinase inhibitor, such as erlotinib or gefitinib, significantly improves outcomes in NSCLC patients with sensitizing EGFR mutations.

Small cell lung cancer is the most aggressive form of lung cancer, and it is exquisitely sensitive, at least initially, to platinum-based combination regimens, including cisplatin and etoposide or cisplatin and irinotecan. When diagnosed at an early stage, this disease is potentially curable using a combined modality approach of chemotherapy and radiation therapy. Unfortunately, drug resistance eventually develops in nearly all patients with extensive disease. The topoisomerase I inhibitor topotecan is used as second-line monotherapy in patients who have failed a platinum-based regimen.

OVARIAN CANCER

In the majority of patients, ovarian cancer remains occult and becomes symptomatic only after it has already metastasized to the peritoneal cavity. At this stage, it usually presents with malignant ascites. It is important to accurately stage this cancer with laparoscopy, ultrasound, and CT scanning. Patients with stage I disease appear to benefit from whole-abdomen radiotherapy and may receive additional benefit from combination chemotherapy with cisplatin and cyclophosphamide.

Combination chemotherapy is the standard approach to stage III and stage IV disease. Randomized clinical studies have shown that the combination of paclitaxel and cisplatin provides survival benefit compared with the previous standard combination of cisplatin plus cyclophosphamide. More recently, carboplatin plus paclitaxel has become the treatment of choice. In patients who present with recurrent disease, the topoisomerase I inhibitor topotecan, the alkylating agent altretamine, and liposomal doxorubicin are used as single agent monotherapy.

TESTICULAR CANCER

The introduction of platinum-based combination chemotherapy has made an impressive change in the treatment of patients with advanced testicular cancer. Presently, chemotherapy is recommended for patients with stage IIC or stage III seminomas and nonseminomatous disease. Over 90% of patients respond to chemotherapy and, depending upon the extent and severity of disease, complete remissions are observed in up to 70–80% of patents. Over 50% of patients achieving complete remission are cured with chemotherapy. In patients with good risk features,

three cycles of cisplatin, etoposide, and bleomycin (PEB protocol) or four cycles of cisplatin and etoposide yield virtually identical results. In patients with high-risk disease, the combination of cisplatin, etoposide, and ifosfamide can be used as well as etoposide and bleomycin with high-dose cisplatin.

MALIGNANT MELANOMA

Malignant melanoma is curable when it presents locally, with surgical resection being the main treatment approach. However, once spread to metastatic sites has been diagnosed, it is one of the most difficult cancers to treat because it is a relatively drug-resistant tumor. While dacarbazine, temozolomide, and cisplatin are the most active cytotoxic agents for this disease, the overall response rates to these agents remain low. Biologic agents, including interferon-α and interleukin-2 (IL-2), have greater activity than traditional cytotoxic agents, and treatment with high-dose IL-2 has led to cures, albeit in a relatively small subset of patients. Significant efforts have focused on utilizing biologic therapy with combination chemotherapy in what have been labeled biochemotherapy regimens. Although overall response rates as well as complete response rates appear to be much higher with biochemotherapy regimens compared with chemotherapy alone, treatment toxicity also seems to be increased. As such, this approach remains investigational.

The BRAFV600E mutation has been identified in the large majority of melanomas. This mutation results in constitutive activation of BRAF kinase, which then leads to activation of downstream signaling pathways involved in cell growth and proliferation. In August 2011, the FDA approved a novel, oral, and highly selective small molecule inhibitor of BRAFV600E **(vemurafenib)** with highly promising activity in metastatic melanoma. Further studies are ongoing to confirm its activity as a single agent as well as in combination with other cytotoxic and biologic agents.

BRAIN CANCER

Chemotherapy has only limited efficacy in the treatment of malignant gliomas. In general, the nitrosoureas, because of their ability to cross the blood-brain barrier, are the most active agents in this disease. Carmustine (BCNU) can be used as a single agent, or lomustine (CCNU) can be used in combination with procarbazine and vincristine (PCV regimen). In addition, the newer alkylating agent temozolomide is active when combined with radiotherapy and used in patients with newly diagnosed glioblastoma multiforme (GBM) as well as in those with recurrent disease. The histopathologic subtype oligodendroglioma has been shown to be especially chemosensitive, and the PCV regimen is the treatment of choice for this disease. There is growing evidence that the anti-VEGF antibody bevacizumab alone or in combination with chemotherapy has promising activity in adult GBM, and bevacizumab was recently approved as a single agent for GBM in the setting of progressive disease following first-line chemotherapy. Of note, small molecule inhibitors of VEGFR-TKs are also undergoing active clinical development because they show interesting activity in adult brain tumors.

SECONDARY MALIGNANCIES & CANCER CHEMOTHERAPY

The development of secondary malignancies is a late complication of the alkylating agents and the epipodophyllotoxin etoposide. The most frequent secondary malignancy is acute myelogenous leukemia (AML). In general, AML develops in up to 15% of patients with Hodgkin's lymphoma who have received radiotherapy plus MOPP chemotherapy and in patients with multiple myeloma, ovarian carcinoma, or breast carcinoma treated with melphalan. The increased risk of AML is observed as early as 2–4 years after the initiation of chemotherapy and typically peaks at 5 and 9 years. With improvements in the clinical efficacy of various combination chemotherapy regimens resulting in prolonged survival and in some cases actual cure of cancer, the issue of how second cancers may affect long-term survival assumes greater importance. There is already evidence that certain alkylating agents (eg, cyclophosphamide) may be less carcinogenic than others (eg, melphalan). In addition to AML, other secondary malignancies have been well-described, including non-Hodgkin's lymphoma and bladder cancer, the latter most typically associated with cyclophosphamide therapy.

SUMMARY Anticancer Drugs

See Tables 54-2, -3, -4, -5

PREPARATIONS AVAILABLE

The reader is referred to the manufacturer's literature for the most recent information on preparations available.

REFERENCES

Books & Monographs

Abeloff MD et al: *Clinical Oncology,* 4th ed. Elsevier, 2008.

Chabner BA, Longo DL: *Cancer Chemotherapy and Biotherapy: Principles and Practice*, 4th ed. Lippincott Williams & Wilkins, 2006.

Chu E, DeVita VT Jr: *Cancer Chemotherapy Drug Manual 2011,* 11th ed. Jones & Bartlett, 2010.

DeVita VT Jr, Hellman S, Rosenberg SA: *Cancer: Principles and Practice of Oncology,* 9th ed. Lippincott Williams & Wilkins, 2011.

Harris JR et al: *Diseases of the Breast*, 4th ed. Lippincott Williams & Wilkins, 2009.

Hoppe R et al: *Textbook of Radiation Oncology*, 3rd ed. Elsevier, 2010.

Hoskins WJ, Perez CA, Young RC: *Principles and Practice of Gynecologic Oncology*, 4th ed. Lippincott Williams & Wilkins, 2004.

Kantoff PW et al: *Prostate Cancer: Principles and Practice.* Lippincott Williams & Wilkins, 2001.

Kelsen DP et al: *Gastrointestinal Oncology: Principles and Practices*, 2nd ed. Lippincott Williams & Wilkins, 2007.

Kufe D et al: *Cancer Medicine*, 7th ed. BC Decker, 2006.

Mendelsohn J et al: *The Molecular Basis of Cancer*. WB Saunders, 2008.

Pass HI et al: *Principles and Practice of Lung Cancer: The Official Reference Text of the International Association for the Study of Lung Cancer (IASLC),* 4th ed. Lippincott Williams & Wilkins, 2010.

Pizzo PA, Poplack AG: *Principles and Practice of Pediatric Oncology,* 6th ed. Lippincott Williams & Wilkins, 2010.

Weinberg RA: *Biology of Cancer*. Taylor & Francis, 2006.

Articles & Reviews

DeVita VT, Chu E: The history of cancer chemotherapy. Cancer Res 2008;68:8643.

Redmond KM et al: Resistance mechanisms to cancer chemotherapy. Front Biosci 2008;13:5138.

CASE STUDY ANSWER

The 5-year survival rate for patients with high-risk stage III CRC is on the order of 25–30%. Because the patient has no symptoms after surgery and has no comorbid illnesses, he would be an appropriate candidate to receive aggressive adjuvant chemotherapy. The usual recommendation would be to administer 6 months of oxaliplatin-based chemotherapy using either infusional 5-FU or oral capecitabine as the fluoropyrimidine base in combination with oxaliplatin. Adjuvant chemotherapy is usually begun 4–6 weeks after surgery to allow sufficient time for surgical wound to heal.

Patients with partial or complete deficiency in the enzyme dihydropyrimidine dehydrogenase (DPD) experience an increased incidence of severe toxicity to fluoropyrimidines in the form of myelosuppression, gastrointestinal toxicity, and neurotoxicity. Although mutations in DPD can be identified in peripheral blood mononuclear cells, nearly 50% of patients who exhibit severe 5-FU toxicity do not have a defined mutation in the *DPD* gene. In addition, such mutations may not result in reduced expression of the DPD protein or in altered enzymatic activity. For this reason, genetic testing is not recommended at this time as part of routine clinical practice.

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CHAPTER 55

Immunopharmacology

Douglas F. Lake, PhD, Adrienne D. Briggs, MD, & Emmanuel T. Akporiaye, PhD

CASE STUDY

A 30-year-old woman has one living child, age 6. Her child and her husband are Rh positive and she is $Rh_o(D)$ and D^u negative. She is now in her ninth month of pregnancy and is in the labor room having frequent contractions. Her Rh antibody test taken earlier in the pregnancy was negative. What immunotherapy is appropriate for this patient? When and how should it be administered?

Agents that suppress the immune system play an important role in preventing the rejection of organ or tissue grafts and in the treatment of certain diseases that arise from dysregulation of the immune response. While precise details of the mechanisms of action of a number of these agents are still obscure, knowledge of the elements of the immune system is useful in understanding their effects. Agents that augment the immune response or selectively alter the balance of various components of the immune system are also becoming important in the management of certain diseases such as cancer, AIDS, and autoimmune or inflammatory diseases. A growing number of other conditions (infections, cardiovascular diseases, organ transplantation) may also be candidates for immune manipulation.

ELEMENTS OF THE IMMUNE SYSTEM

NORMAL IMMUNE RESPONSES

The immune system has evolved to protect the host from invading pathogens and to eliminate disease. At its functioning best, the immune system is exquisitely responsive to invading pathogens while retaining the capacity to recognize self tissues and antigens to which it is tolerant. Protection from infection and disease is provided by the collaborative efforts of the innate and adaptive immune systems.

The Innate Immune System

The innate immune system is the first line of defense against invading pathogens (eg, bacteria, viruses, fungi, parasites) and consists of mechanical, biochemical, and cellular components. Mechanical components include skin/epidermis and mucus; biochemical components include antimicrobial peptides and proteins (eg, defensins), complement, enzymes (eg, lysozyme, acid hydrolases), interferons, acidic pH, and free radicals (eg, hydrogen peroxide, superoxide anions); cellular components include neutrophils, monocytes, macrophages, natural killer (NK), and natural killer-T (NKT) cells. Unlike adaptive immunity, the innate immune response exists prior to infection, is not enhanced by repeated infection, and is generally not antigen-specific. An intact skin or mucosa is the first barrier to infection. When this barrier is breached, an immediate innate immune response, referred to as "inflammation" is provoked that ultimately leads to destruction of the pathogen. The process of pathogen destruction can be accomplished, for example, by biochemical components such as lysozyme (which breaks down the protective peptidoglycan cell wall) and the split products arising from complement activation. Complement components (Figure 55–1) enhance macrophage and neutrophil phagocytosis by acting as opsonins (C3b) and chemoattractants (C3a, C5a), which recruit immune cells from the bloodstream to the site of infection. The activation of complement eventually leads to pathogen lysis via the generation of a membrane attack complex that creates holes in the membrane and results in leakage of cellular components.

During the inflammatory response triggered by infection, neutrophils and monocytes enter the tissue sites from peripheral circulation. This cellular influx is mediated by the action of **chemoattractant cytokines (chemokines)** (eg, interleukin-8 [IL-8; CXCL8], macrophage chemotactic protein-1 [MCP-1; CCL2],

ACRONYMS

ADA	Adenosine deaminase
ALG	Antilymphocyte globulin
APC	Antigen-presenting cell
ATG	Antithymocyte globulin
CD	Cluster of differentiation
CSF	Colony-stimulating factor
CTL	Cytotoxic T lymphocyte
DC	Dendritic cell
DTH	Delayed-type hypersensitivity
FKBP	FK-binding protein
HAMA	Human antimouse antibody
HLA	Human leukocyte antigen
IFN	Interferon
IGIV	Immune globulin intravenous
IL	Interleukin
LFA	Leukocyte function-associated antigen
MAB	Monoclonal antibody
MHC	Major histocompatibility complex
NK cell	Natural killer cell
SCID	Severe combined immunodeficiency disease
TCR	T-cell receptor
TGF-β	Transforming growth factor-β
TH1, TH2	T helper cell types 1 and 2
TNF	Tumor necrosis factor

and macrophage inflammatory protein-1α [MIP-1α; CCL3]) released from activated endothelial cells and immune cells (mostly tissue macrophages) at the inflammatory site. Egress of the immune cells from blood vessels into the inflammatory site is mediated by adhesive interactions between cell surface receptors (eg, L-selectin, integrins) on the immune cells and ligands (eg, sialyl-Lewis x, intercellular adhesion molecule-1 [ICAM-1]) on the activated endothelial cell surface. The tissue macrophages as well as dendritic cells express pattern recognition receptors (PRRs) that include Toll-like receptors (TLRs), nucleotide-binding oligomerization domain (NOD)-like receptors (NLRs), scavenger receptors, mannose receptors, and lipopolysaccharide (LPS)-binding protein, which recognize key evolutionarily conserved pathogen components referred to as pathogen-associated molecular patterns (PAMPs). Examples of PAMPs include microbe-derived unmethylated CpG DNA, flagellin, double-stranded RNA, peptidoglycan, and LPS. The PRRs recognize PAMPs in various components of pathogens and stimulate the release of proinflammatory cytokines, chemokines, and interferons. If the innate immune response is successfully executed, the invading pathogen is ingested, degraded, and eliminated, and disease is either prevented or is of short duration.

In addition to monocytes and neutrophils, **natural killer (NK), natural killer-T (NKT),** and **gamma-delta T (γδ T)** cells recruited to the inflammatory site contribute to the innate response by secreting interferon-gamma (IFN-γ) and IL-17, which activate resident tissue macrophages and dendritic cells and recruit neutrophils respectively to successfully eliminate invading pathogens. NK cells are so called because they are able to recognize and destroy virus-infected normal cells as well as tumor cells without prior stimulation. This activity is regulated by "killer cell immunoglobulin-like receptors" (KIRs) on the NK cell surface that are specific for major histocompatibility complex (MHC) class I molecules. When NK cells bind self MHC class I proteins (expressed on all nucleated cells), these receptors deliver inhibitory signals, preventing them from killing normal host cells. Tumor cells or virus-infected cells that have down-regulated MHC class I expression do not engage these KIRs, resulting in activation of NK cells and subsequent destruction of the target cell. NK cells kill target cells by releasing cytotoxic granules such as perforins and granzymes that induce programmed cell death.

NKT cells express T-cell receptors as well as receptors commonly found on NK cells. NKT cells recognize microbial lipid antigens presented by a unique class of MHC-like molecules known as CD1 and have been implicated in host defense against microbial agents, autoimmune diseases, and tumors.

The Adaptive Immune System

The adaptive immune system is mobilized by cues from the innate response when the innate processes are incapable of coping with an infection. The adaptive immune system has a number of characteristics that contribute to its success in eliminating pathogens. These include the ability to (1) respond to a variety of antigens, each in a specific manner; (2) discriminate between foreign ("non-self") antigens (pathogens) and self antigens of the host; and (3) respond to a previously encountered antigen in a learned way by initiating a vigorous memory response. This adaptive response culminates in the production of **antibodies,** which are the effectors of **humoral immunity;** and the activation of **T lymphocytes,** which are the effectors of **cell-mediated immunity.**

The induction of specific adaptive immunity requires the participation of professional **antigen-presenting cells (APCs),** which include dendritic cells (DCs), macrophages, and B lymphocytes. These cells play pivotal roles in the induction of an adaptive immune response because of their capacity to phagocytize particulate antigens (eg, pathogens) or endocytose protein antigens, and enzymatically digest them to generate peptides, which are then loaded onto class I or class II MHC proteins and "presented" to the cell surface T-cell receptor (TCR) (Figure 55–2). CD8 T cells recognize class I-MHC peptide complexes while CD4 T cells recognize class II-MHC peptide complexes. At least two signals are necessary for the activation of T cells. The first signal is delivered following engagement of the TCR with peptide-bound MHC molecules. In the absence of a second signal, the T cells become unresponsive (anergic) or undergo apoptosis. The second signal involves ligation of costimulatory molecules (CD40, CD80 [also known as B7-1], and CD86 [also known as B7-2]) on the APC to

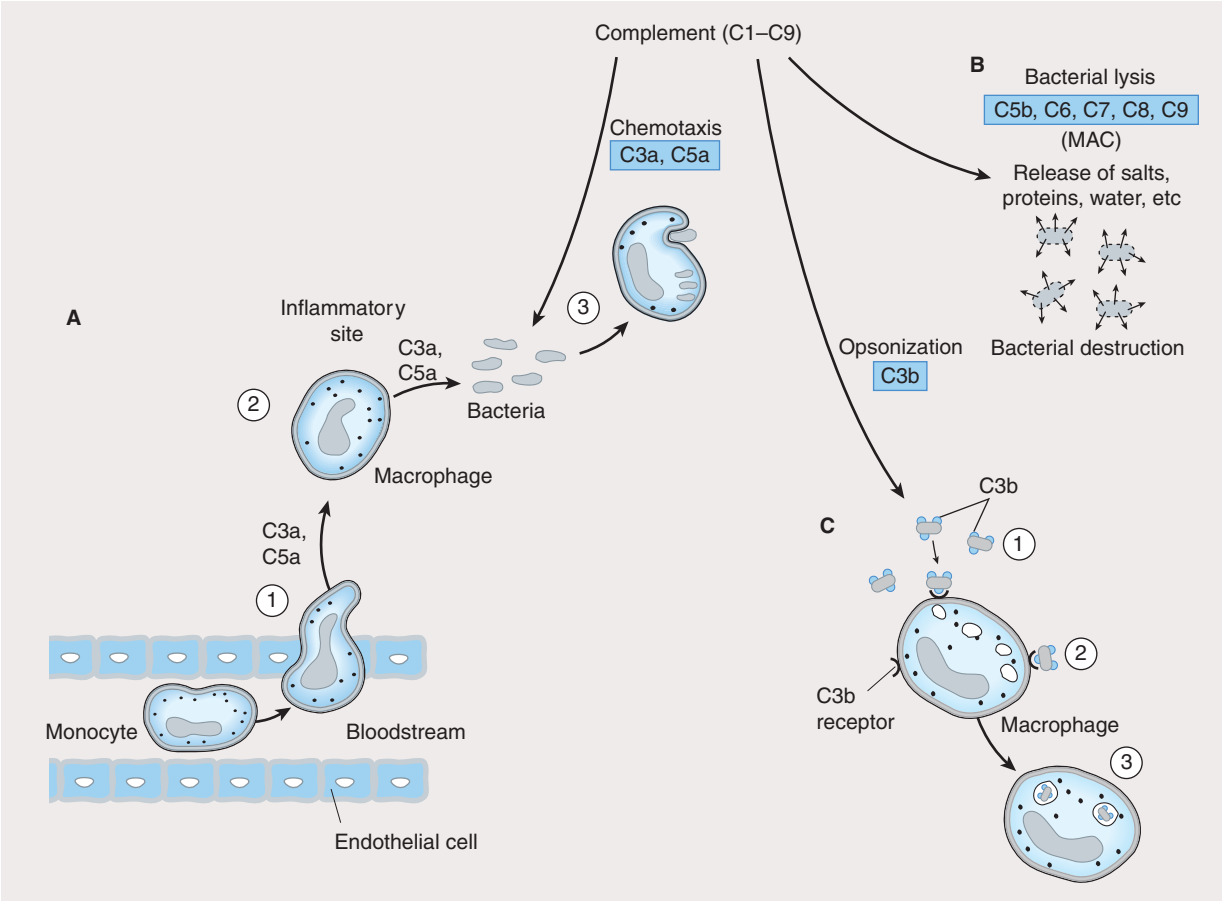

FIGURE 55–1 Role of complement in innate immunity. Complement is made up of nine proteins (C1–C9), which are split into fragments during activation. **A:** Complement components (C3a, C5a) attract phagocytes (1) to inflammatory sites (2), where they ingest and degrade pathogens (3). **B:** Complement components C5b, C6, C7, C8, and C9 associate to form a membrane attack complex (MAC) that lyses bacteria, causing their destruction. **C:** Complement component C3b is an opsonin that coats bacteria (1) and facilitates their ingestion (2) and digestion (3) by phagocytes.

their respective ligands (CD40L for CD40, CD28 for CD80 or CD86). Activation of T cells is regulated via a negative feedback loop involving another molecule known as T-lymphocyte-associated antigen 4 (CTLA-4). Following engagement of CD28 with CD80 or CD86, CTLA-4 in the cytoplasm is mobilized to the cell surface where, because of its higher affinity of binding to CD80 and CD86, it outcompetes or displaces CD28 resulting in suppression of T-cell activation and proliferation. This property of CTLA-4 has been exploited as a strategy for sustaining a desirable immune response such as that directed against cancer. A recombinant humanized antibody that binds CTLA-4 (ipilimumab) prevents its association with CD80/CD86. In so doing, the activated state of T cells is sustained. Recently completed vaccine trials in metastatic melanoma patients receiving anti-CTLA-4 antibody reported objective and durable clinical responses in a few patients. Unfortunately, these beneficial responses were associated with the development of autoimmune toxicity in some patients, raising concern about this approach.

T lymphocytes develop and learn to recognize self and non-self antigens in the thymus; those T cells that bind with high affinity to self antigens in the thymus undergo apoptosis (negative selection),

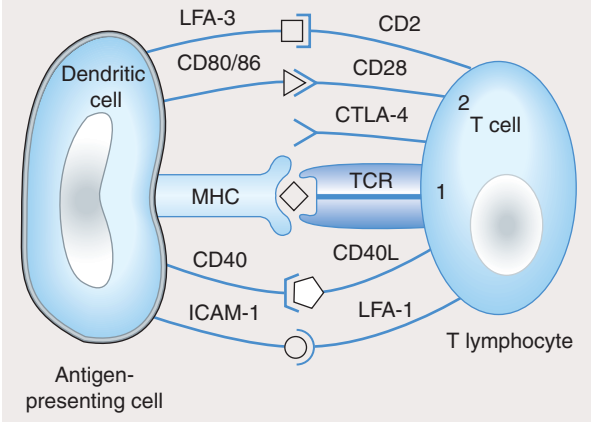

FIGURE 55–2 T-cell activation by an antigen-presenting cell requires engagement of the T-cell receptor by the MHC-peptide complex (signal 1) and binding of the costimulatory molecules (CD80, CD86) on the dendritic cell to CD28 on the T cell (signal 2). The activation signals are strengthened by CD40/CD40L and ICAM-1/LFA-1 interactions. In a normal immune response, T-cell activation is regulated by T-cell-derived CTLA-4, which binds to CD80 or CD86 with higher affinity than CD28 and sends inhibitory signals to the nucleus of the T cell.

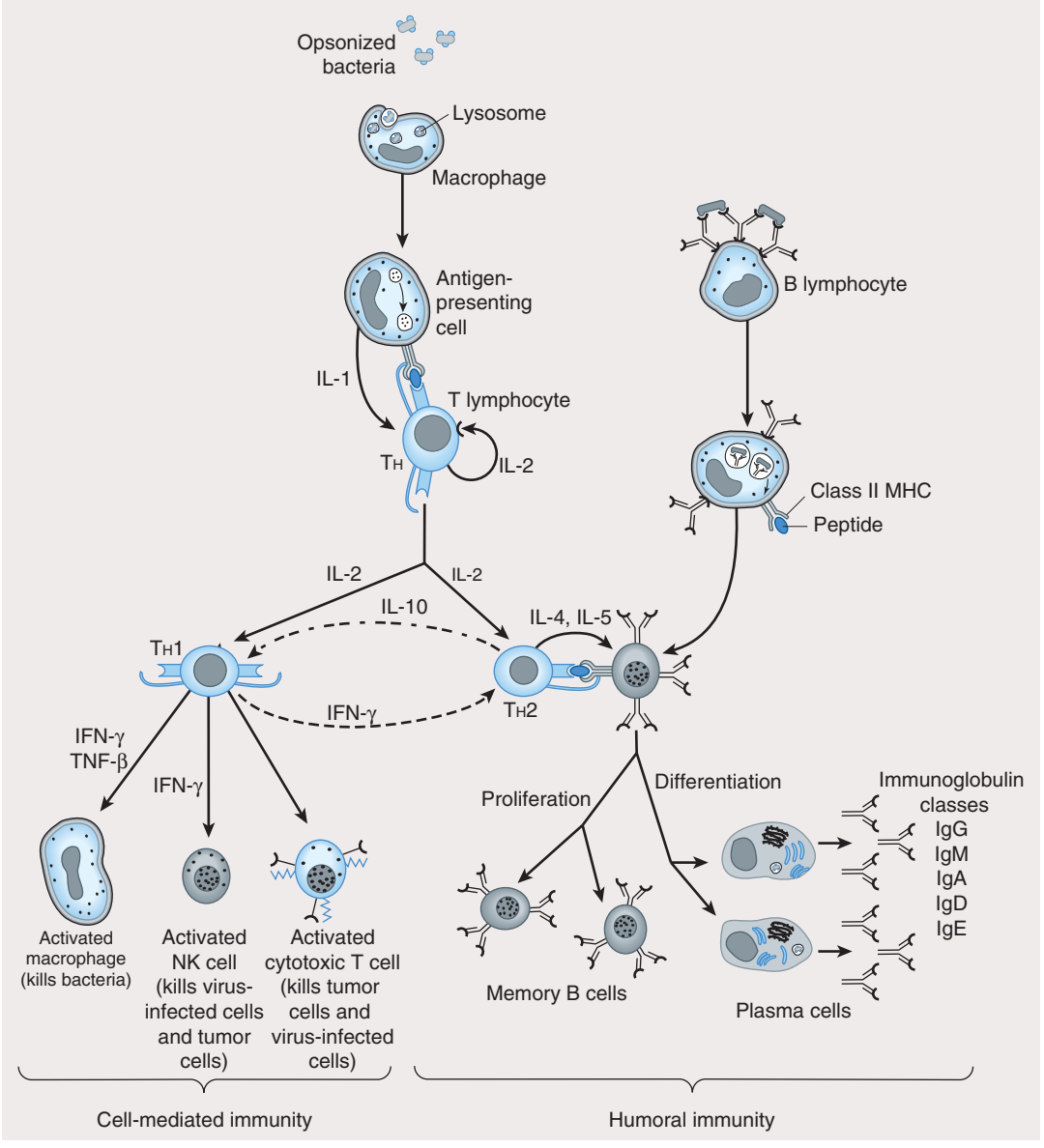

FIGURE 55–3 Scheme of cellular interactions during the generation of cell-mediated and humoral immune responses (see text). The cell-mediated arm of the immune response involves the ingestion and digestion of antigen by antigen-presenting cells such as macrophages. Activated TH cells secrete IL-2, which causes proliferation and activation of cytotoxic T lymphocytes, and TH1 and TH2 cell subsets. TH1 cells also produce IFN-γ and TNF-β, which can directly activate macrophages and NK cells. The humoral response is triggered when B lymphocytes bind antigen via their surface immunoglobulin. They are then induced by TH2-derived IL-4 and IL-5 to proliferate and differentiate into memory cells and antibody-secreting plasma cells. Regulatory cytokines such as IFN-γ and IL-10 down-regulate TH2 and TH1 responses, respectively.

while those that are capable of recognizing foreign antigens in the presence of self MHC molecules are retained and expanded (positive selection) for export to the periphery (lymph nodes, spleen, mucosa-associated lymphoid tissue, peripheral blood), where they become activated after encountering MHC-presented peptides (Figures 55–2 and 55–3).

Studies using murine T-cell clones have demonstrated the presence of two subsets of T helper lymphocytes **(TH1** and **TH2)** based on the cytokines they secrete after activation. This demarcation is not so clear-cut in humans. The TH1 subset characteristically produces IFN-γ, IL-2, and IL-12 and induces cell-mediated immunity by activation of macrophages, cytotoxic T cells (CTLs), and NK cells. The TH2 subset produces IL-4, IL-5, IL-6, and IL-10 (and sometimes IL-13), which induce B-cell proliferation and differentiation into antibody-secreting plasma cells. IL-10 produced by TH2 cells inhibits cytokine production by TH1 cells via the down-regulation of MHC expression by APCs. Conversely, IFN-γ produced by TH1 cells inhibits the proliferation of TH2 cells (Figure 55–3). Although these subsets have been well described in vitro, the nature of the antigenic challenge that elicits

a TH1 or TH2 phenotype is less clear. Extracellular bacteria typically cause the elaboration of TH2 cytokines, culminating in the production of neutralizing or opsonic antibodies. In contrast, intracellular organisms (eg, mycobacteria) elicit the production of TH1 cytokines, which lead to the activation of effector cells such as macrophages. A less well-defined T-cell subset (TH3) has been described that produces transforming growth factor-β (TGF-β), whose numerous functions include down-regulation of proliferation and differentiation of T lymphocytes.

Recently, a subset of CD4 T cells that secrete IL-17 (TH17) has been implicated in neutrophil recruitment to sites of inflammation. A population of CD4 T cells that is essential for preventing autoimmunity and allergy as well as maintaining homeostasis and tolerance to self antigens is the regulatory (Treg) T cell. In the mouse, this cell population exists as natural Treg (nTreg), derived directly from the thymus, and induced (adaptive) Treg (iTreg), generated from naïve CD4 T cells in the periphery. Both populations have also been shown to inhibit antitumor immune responses and are implicated in fostering tumor growth and progression. Recent attempts to distinguish both populations have resulted in the discovery of a transcription factor, Helios, in nTreg but not in iTreg cells.

CD8 T lymphocytes recognize endogenously processed peptides presented by virus-infected cells or tumor cells. These peptides are usually nine-amino-acid fragments derived from virus or protein tumor antigens in the cytoplasm and are loaded onto MHC class I molecules (Figure 55–2) in the endoplasmic reticulum. In contrast, class II MHC molecules present peptides (usually 11–22 amino acids) derived from extracellular (exogenous) pathogens to CD4 T helper cells. In some instances, exogenous antigens, upon ingestion by APCs, can be presented on class I MHC molecules to CD8 T cells. This phenomenon, referred to as "cross-presentation," involves retro-translocation of antigens from the endosome to the cytosol for peptide generation in the proteosome and is thought to be useful in generating effective immune responses against infected host cells that are incapable of priming T lymphocytes. Upon activation, CD8 T cells induce target cell death via lytic granule enzymes ("granzymes"), perforin, and the Fas-Fas ligand (Fas-FasL) apoptosis pathways.

B lymphocytes undergo selection in the bone marrow, during which self-reactive B lymphocytes are clonally deleted while B-cell clones specific for foreign antigens are retained and expanded. The repertoire of antigen specificities by T cells is genetically determined and arises from T-cell *receptor* gene rearrangement while the specificities of B cells arise from *immunoglobulin* gene rearrangement; for both types of cells, these determinations occur prior to encounters with antigen. Upon an encounter with antigen, a mature B cell binds the antigen, internalizes and processes it, and presents its peptide—bound to class II MHC—to CD4 helper cells, which in turn secrete IL-4 and IL-5. These interleukins stimulate B-cell proliferation and differentiation into memory B cells and antibody-secreting plasma cells. The primary antibody response consists mostly of IgM-class immunoglobulins. Subsequent antigenic stimulation results in a vigorous "booster" response accompanied by class (isotype) switching to produce IgG, IgA, and IgE antibodies with diverse effector functions (Figure 55–3). These antibodies also undergo affinity maturation, which allows them to bind more efficiently to the antigen. With the passage of time, this results in accelerated elimination of microorganisms in subsequent infections. Antibodies mediate their functions by acting as opsonins to enhance phagocytosis and cellular cytotoxicity and by activating complement to elicit an inflammatory response and induce bacterial lysis (Figure 55–4).

ABNORMAL IMMUNE RESPONSES

Whereas the normally functioning immune response can successfully neutralize toxins, inactivate viruses, destroy transformed cells, and eliminate pathogens, inappropriate responses can lead to extensive tissue damage (hypersensitivity) or reactivity against self antigens (autoimmunity); conversely, impaired reactivity to appropriate targets (immunodeficiency) may occur and abrogate essential defense mechanisms.

Hypersensitivity

Hypersensitivity can be classified as antibody-mediated or cell-mediated. Three types of hypersensitivity are antibody-mediated (types I–III), while the fourth is cell-mediated (type IV). Hypersensitivity occurs in two phases: the sensitization phase and the effector phase. Sensitization occurs upon initial encounter with an antigen; the effector phase involves immunologic memory and results in tissue pathology upon a subsequent encounter with that antigen.

1. Type I—Immediate, or type I, hypersensitivity is IgE-mediated, with symptoms usually occurring within minutes following the patient's reencounter with antigen. Type I hypersensitivity results from cross-linking of membrane-bound IgE on blood basophils or tissue mast cells by antigen. This cross-linking causes cells to degranulate, releasing substances such as histamine, leukotrienes, and eosinophil chemotactic factor, which induce anaphylaxis, asthma, hay fever, or urticaria (hives) in affected individuals (Figure 55–5). A severe type I hypersensitivity reaction such as systemic anaphylaxis (eg, from insect envenomation, ingestion of certain foods, or drug hypersensitivity) requires immediate medical intervention.

2. Type II—Type II hypersensitivity results from the formation of antigen-antibody complexes between foreign antigen and IgM or IgG immunoglobulins. One example of this type of hypersensitivity is a blood transfusion reaction that can occur if blood is not cross-matched properly. Preformed antibodies bind to red blood cell membrane antigens that activate the complement cascade, generating a membrane attack complex that lyses the transfused red blood cells. In hemolytic disease of the newborn, anti-Rh IgG antibodies produced by an Rh-negative mother cross the placenta, bind to red blood cells of an Rh-positive fetus, and damage them. The disease is prevented in subsequent pregnancies by the administration of anti-Rh antibodies to the mother 24–48 hours after delivery (see Immunosuppressive Antibodies, below).

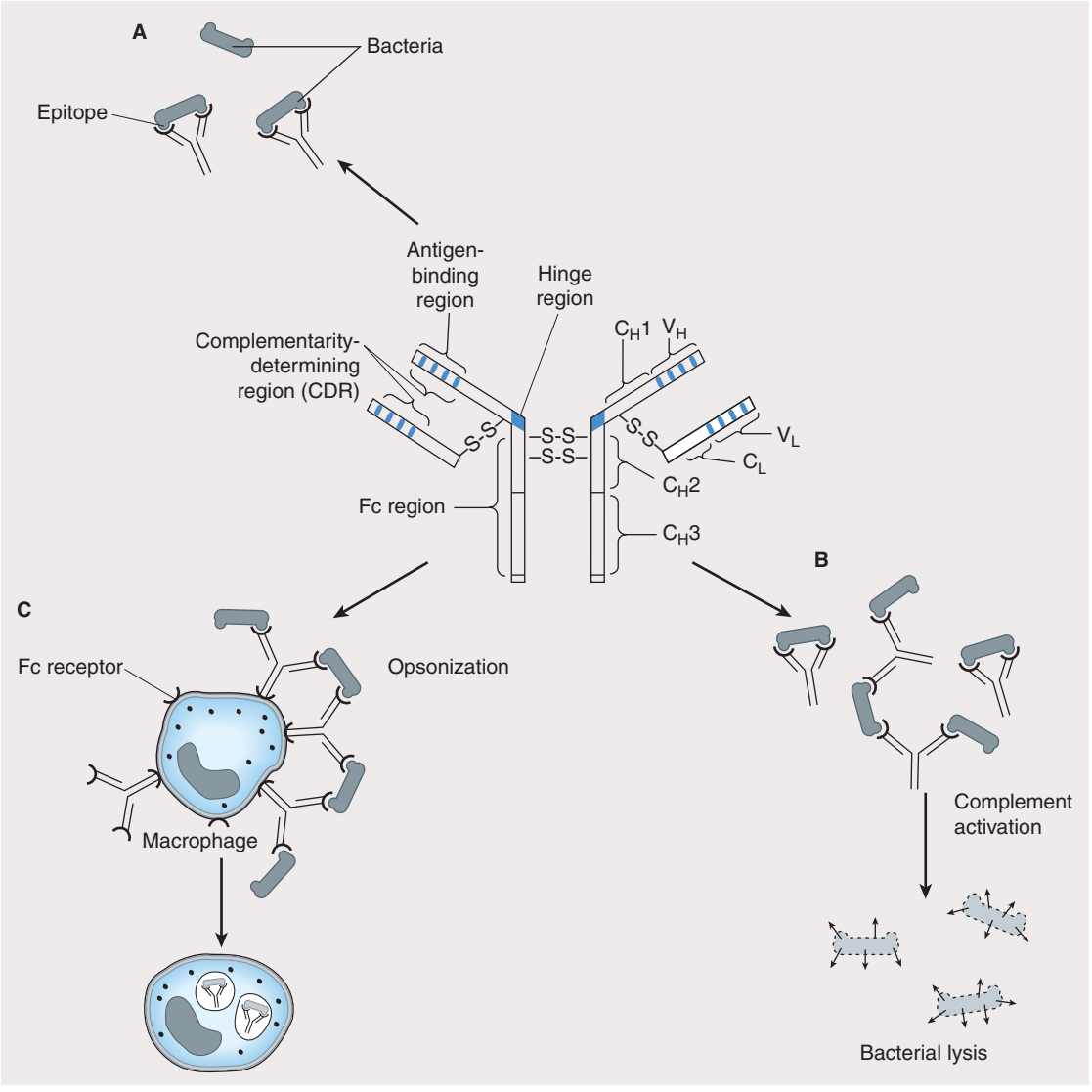

FIGURE 55–4 Antibody has multiple functions. The prototypical antibody consists of two heavy (H) and two light (L) chains, each subdivided into constant (C_L, C_H) and variable (V_L, V_H) domains. The structure is held together by intra- and interchain disulfide bridges. **A:** The complementarity-determining region (CDR) of the antigen-binding portion of the antibody engages the antigenic determinant (epitope) in a lock and key fashion. **B:** Antigen-antibody complexes activate complement to produce split complement components that cause bacterial lysis. **C:** The Fc portion of antibodies binds to Fc receptors on phagocytes (eg, macrophages, neutrophils) and facilitates uptake of bacteria (opsonization).

Type II hypersensitivity can also be drug-induced and may occur during the administration of penicillin (for example) to allergic patients. In these patients, penicillin binds to red blood cells or other host tissue to form a neoantigen that evokes production of antibodies capable of inducing complement-mediated red cell lysis. In some circumstances, subsequent administration of the drug can lead to systemic anaphylaxis (type I hypersensitivity).

3. Type III—Type III hypersensitivity is due to the presence of elevated levels of antigen-antibody complexes in the circulation that ultimately deposit on basement membranes in tissues and vessels. Immune complex deposition activates complement to produce components with anaphylatoxic and chemotactic activities (C5a, C3a, C4a) that increase vascular permeability and recruit neutrophils to the site of complex deposition. Complex deposition and the action of lytic enzymes released by neutrophils can cause skin rashes, glomerulonephritis, and arthritis in these individuals. If patients have type III hypersensitivity against a particular antigen, clinical symptoms usually occur 3–4 days after exposure to the antigen.

4. Type IV: Delayed-type hypersensitivity—Unlike type I, II, and III hypersensitivities, delayed-type hypersensitivity (DTH) is cell-mediated, and responses occur 2–3 days after exposure to the sensitizing antigen. DTH is caused by antigen-specific DTH TH1 cells and induces a local inflammatory response that causes tissue damage characterized by the influx of antigen-*non*specific inflammatory cells, especially macrophages. These cells are

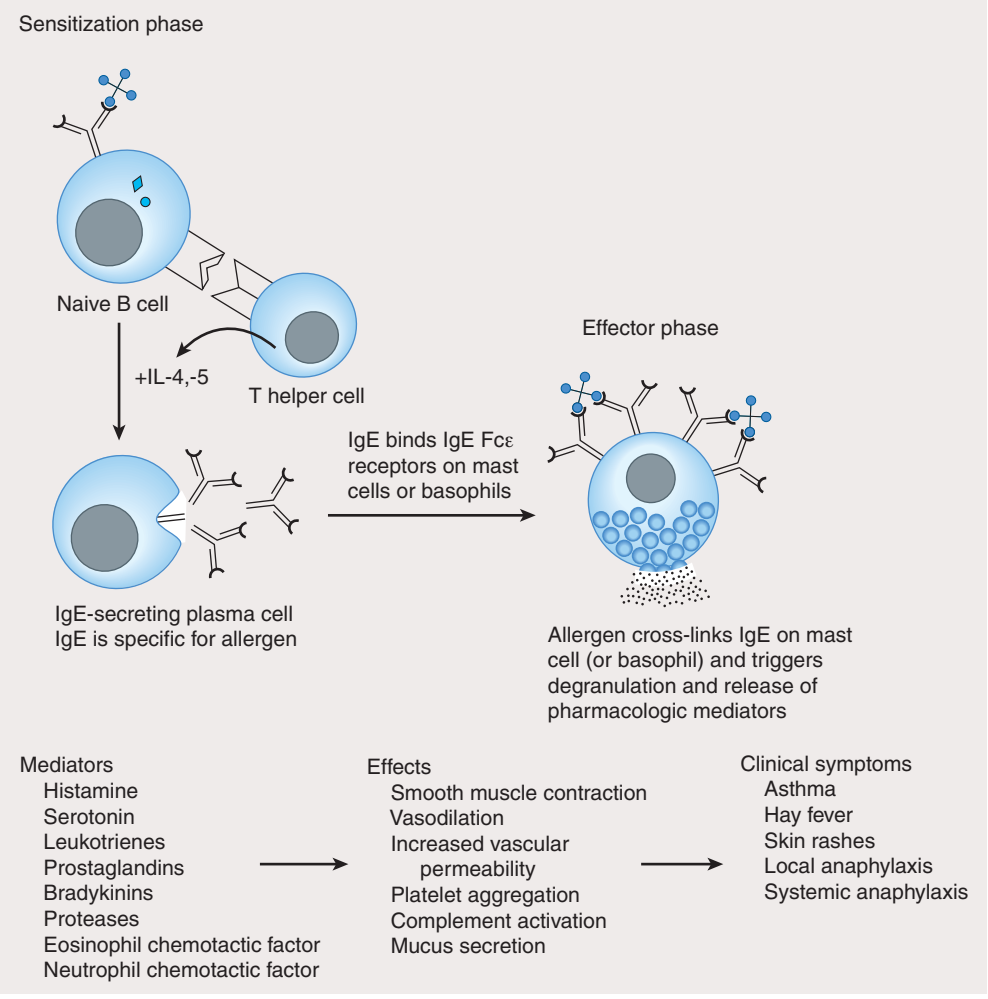

FIGURE 55–5 Mechanism of type I hypersensitivity. Initial exposure to allergen **(sensitization phase)** leads to production of IgE by plasma cells differentiated from allergen-specific B cells (not shown). The secreted IgE binds IgE-specific receptors (FcεR) on blood basophils and tissue mast cells. Reexposure to allergen leads to cross-linking of membrane-bound IgE **(effector phase).** This cross-linking causes degranulation of cytoplasmic granules and release of mediators that induce vasodilation, smooth muscle contraction, and increased vascular permeability. These effects lead to the clinical symptoms characteristic of type I hypersensitivity.

recruited under the influence of TH1-produced cytokines (Figure 55–6), which chemoattract circulating monocytes and neutrophils, induce myelopoiesis, and activate macrophages. The activated macrophages are primarily responsible for the tissue damage associated with DTH. Although widely considered to be deleterious, DTH responses are very effective in eliminating infections caused by intracellular pathogens such as *Mycobacterium tuberculosis* and *Leishmania* species. Clinical manifestations of DTH include **tuberculin** and **contact hypersensitivities.** Tuberculosis exposure is determined using a DTH skin test. Positive responses show erythema and induration caused by accumulation of macrophages and DTH T (T_{DTH}) cells at the site of the tuberculin injection. **Poison ivy** is the most common cause of contact hypersensitivity, in which pentadecacatechol, the lipophilic chemical in poison ivy, modifies cellular tissue and results in a DTH T-cell response.

Autoimmunity

Autoimmune disease arises when the body mounts an immune response against itself due to failure to distinguish self tissues and cells from foreign (nonself) antigens or loss of tolerance to self. This phenomenon derives from the activation of self-reactive T and B lymphocytes that generate cell-mediated or humoral immune responses directed against self antigens. The pathologic consequences of this reactivity constitute several types of autoimmune diseases. Autoimmune diseases are highly complex due to MHC genetics, environmental conditions, infectious entities, and dysfunctional immune regulation. Examples of such diseases include rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis, and insulin-dependent diabetes mellitus (type 1 diabetes). In rheumatoid arthritis, IgM antibodies (rheumatoid factors) are produced that react with the Fc portion of IgG and may form immune complexes that activate the complement cascade, causing chronic

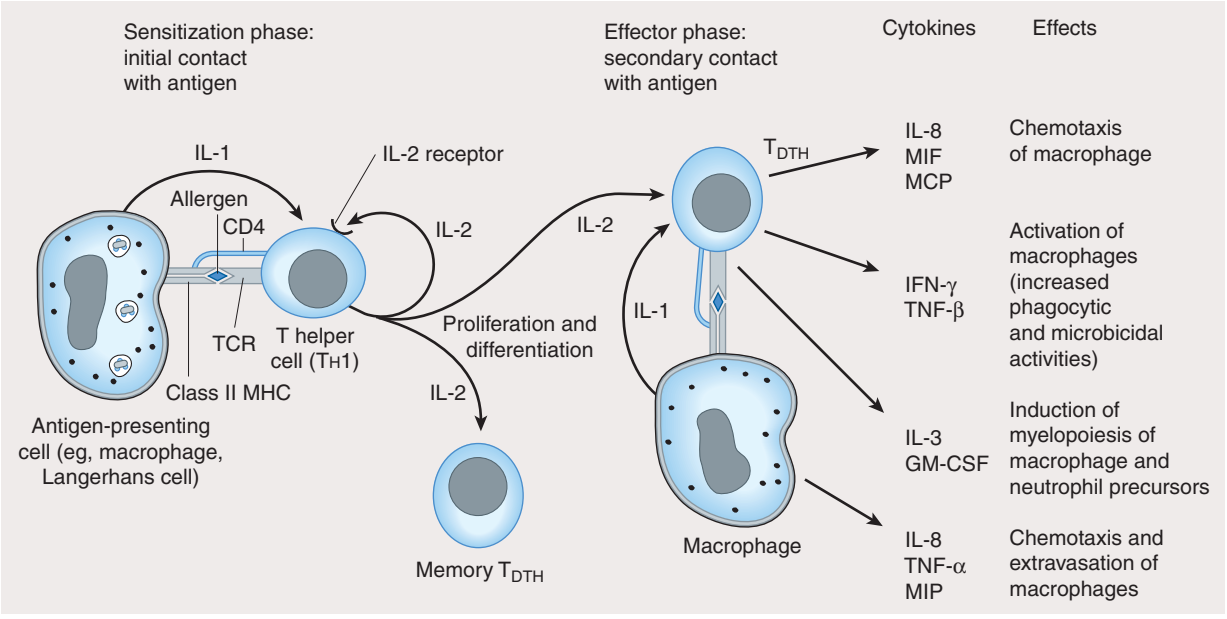

FIGURE 55–6 Mechanism of type IV hypersensitivity (DTH). In the **sensitization phase,** the processed allergen (eg, from poison oak) is presented to CD4 TH1 cells by antigen-presenting cells in association with class II MHC. T cells are induced to express IL-2 receptors and are stimulated to proliferate and differentiate into memory T_{DTH} cells. Secondary contact with antigen triggers the **effector phase,** in which memory T_{DTH} cells release cytokines that attract and activate nonspecific inflammatory macrophages and neutrophils. These cells display increased phagocytic and microbicidal activities and release large quantities of lytic enzymes that cause extensive tissue damage.

inflammation of the joints and kidneys. In systemic lupus erythematosus, antibodies are made against DNA, histones, red blood cells, platelets, and other cellular components. In multiple sclerosis and type 1 diabetes, cell-mediated autoimmune attack destroys myelin surrounding nerve cells and insulin-producing islet beta cells of the pancreas, respectively. In type 1 diabetes, activated CD4 T_{DTH} cells that infiltrate the islets of Langerhans and recognize self islet beta cell peptides are thought to produce cytokines that stimulate macrophages to produce lytic enzymes, which destroy islet beta cells. Autoantibodies directed against the islet beta cell antigens are produced, but do not contribute significantly to disease.

A number of mechanisms have been proposed to explain autoimmunity:

1. Exposure of antigens previously sequestered from the immune system (eg, lens protein, myelin basic protein) to self-reactive T lymphocytes.
2. Molecular mimicry by invading pathogens, in which immune responses are directed at antigenic determinants on pathogens that share identical or similar epitopes with normal host tissue. This phenomenon occurs in rheumatic fever following *Streptococcus pyogenes* infection, in which heart damage is thought to arise from an immune response directed against streptococcal antigens shared with heart muscle. The suggested viral etiology of autoimmune diseases has been ascribed to immune responses (both cell-mediated and humoral) directed against virus epitopes that mimic self antigens.
3. Inappropriate expression of class II MHC molecules on the membranes of cells that normally do not express class II MHC (eg, islet beta cells). Increased expression of MHC II may increase presentation of self peptides to T helper cells, which in turn induce CTL, T_{DTH}, and B-lymphocyte cells that react against self antigens.

Immunodeficiency Diseases

Immunodeficiency diseases result from inadequate function in the immune system; the consequences include increased susceptibility to infections and prolonged duration and severity of disease. Immunodeficiency diseases are either congenital or arise from extrinsic factors such as bacterial or viral infections or drug treatment. Affected individuals frequently succumb to infections caused by opportunistic organisms of low pathogenicity for the immunocompetent host. Examples of congenitally acquired immunodeficiency diseases include X-linked agammaglobulinemia, DiGeorge's syndrome, and severe combined immunodeficiency disease (SCID) due to adenosine deaminase (ADA) deficiency.

X-linked agammaglobulinemia is a disease affecting males that is characterized by a failure of immature B lymphocytes to mature into antibody-producing plasma cells. These individuals are susceptible to recurrent bacterial infections, although the cell-mediated responses directed against viruses and fungi are preserved. DiGeorge's syndrome is due to failure of the thymus to develop, resulting in diminished T-cell responses (T_{DTH}, CTL), while the humoral response remains functional, but does not benefit from T-cell help.

The ADA enzyme normally prevents the accumulation of toxic deoxy-ATP in cells. Deoxy-ATP is particularly toxic to lymphocytes, and leads to death of T and B cells. Absence of the enzyme therefore results in SCID. Infusion of the purified enzyme (**pegademase,** from bovine sources) and transfer of ADA

gene-modified lymphocytes have both been used successfully to treat this disease.

AIDS represents the classic example of immunodeficiency disease caused by extrinsic viral infection, in this instance the human immunodeficiency virus (HIV). This virus exhibits a strong tropism for CD4 T helper cells; these become depleted, giving rise to increased frequency of opportunistic infections and malignancies in infected individuals. AIDS is also characterized by an imbalance in TH1 and TH2 cells, and the ratios of cells and their functions are skewed toward TH2. This results in loss of cytotoxic T-lymphocyte activity, loss of delayed hypersensitivity, and hypergammaglobulinemia.

IMMUNOSUPPRESSIVE AGENTS

Immunosuppressive agents have proved very useful in minimizing the occurrence or impact of deleterious effects of exaggerated or inappropriate immune responses. Unfortunately, these agents also have the potential to cause disease and to increase the risk of infection and malignancies.

GLUCOCORTICOIDS

Glucocorticoids (corticosteroids) were the first hormonal agents recognized as having lympholytic properties. Administration of any glucocorticoid reduces the size and lymphoid content of the lymph nodes and spleen, although it has no toxic effect on proliferating myeloid or erythroid stem cells in the bone marrow.

Glucocorticoids are thought to interfere with the cell cycle of activated lymphoid cells. The mechanism of their action is described in Chapter 39. Glucocorticoids are quite cytotoxic to certain subsets of T cells, but their immunologic effects are probably due to their ability to modify cellular functions rather than to direct cytotoxicity. Although cellular immunity is more affected than humoral immunity, the primary antibody response can be diminished, and with continued use, previously established antibody responses are also decreased. Additionally, continuous administration of corticosteroid increases the fractional catabolic rate of IgG, the major class of antibody immunoglobulins, thus lowering the effective concentration of specific antibodies. Contact hypersensitivity mediated by T_{DTH} cells, for example, is usually abrogated by glucocorticoid therapy.

Glucocorticoids are used in a wide variety of conditions (Table 55–1). It is thought that the immunosuppressive and anti-

TABLE 55–1 Clinical uses of immunosuppressive agents.

Source	Immunopharmacologic Agents Used	Response
Autoimmune diseases		
Idiopathic thrombocytopenic purpura (ITP)	Prednisone,[1] vincristine, occasionally cyclophosphamide, mercaptopurine, or azathioprine; commonly high-dose gamma globulin, plasma immunoadsorption or plasma exchange	Usually good
Autoimmune hemolytic anemia	Prednisone,[1] cyclophosphamide, chlorambucil, mercaptopurine, azathioprine, high-dose gamma globulin	Usually good
Acute glomerulonephritis	Prednisone,[1] mercaptopurine, cyclophosphamide	Usually good
Acquired factor XIII antibodies	Cyclophosphamide plus factor XIII	Usually good
Autoreactive tissue disorders (autoimmune diseases)[2]	Prednisone, cyclophosphamide, methotrexate, interferon-α and -β, azathioprine, cyclosporine, infliximab, etanercept, adalimumab	Often good, variable
Isoimmune disease		
Hemolytic disease of the newborn	Rh_o(D) immune globulin	Excellent
Organ transplantation		
Renal	Cyclosporine, azathioprine, prednisone, ALG, OKT3, tacrolimus, basiliximab,[3] daclizumab,[3] sirolimus	Very good
Heart	Cyclosporine, azathioprine, prednisone, ALG, OKT3, tacrolimus, basiliximab,[3] daclizumab,[3] sirolimus	Good
Liver	Cyclosporine, prednisone, azathioprine, tacrolimus, sirolimus	Fair
Bone marrow	Cyclosporine, cyclophosphamide, prednisone, methotrexate, ALG	Good
Prevention of cell proliferation		
Coronary stents	Sirolimus (impregnated stent)	Good
Neovascular macular degeneration	Ranibizumab (labeled), bevacizumab (off-label)	Fair

[1]Drug of choice.

[2]Including systemic lupus erythematosus, rheumatoid arthritis, scleroderma, dermatomyositis, mixed tissue disorder, multiple sclerosis, Wegener's granulomatosis, chronic active hepatitis, lipoid nephrosis, and inflammatory bowel disease.

[3]Basiliximab and daclizumab are approved for renal transplant only.

inflammatory properties of corticosteroids account for their beneficial effects in diseases like idiopathic thrombocytopenic purpura and rheumatoid arthritis. Glucocorticoids modulate allergic reactions and are useful in the treatment of diseases like asthma or as premedication for other agents (eg, blood products, chemotherapy) that might cause undesirable immune responses. Glucocorticoids are first-line immunosuppressive therapy for both solid organ and hematopoietic stem cell transplant recipients, with variable results. The toxicities of long-term glucocorticoid therapy can be severe and are discussed in Chapter 39.

CALCINEURIN INHIBITORS

Cyclosporine

Cyclosporine (cyclosporin A, CSA) is an immunosuppressive agent with efficacy in human organ transplantation, in the treatment of graft-versus-host disease after hematopoietic stem cell transplantation, and in the treatment of selected autoimmune disorders. Cyclosporine is a peptide antibiotic that appears to act at an early stage in the antigen receptor-induced differentiation of T cells and blocks their activation. Cyclosporine binds to **cyclophilin,** a member of a class of intracellular proteins called immunophilins. Cyclosporine and cyclophilin form a complex that inhibits the cytoplasmic phosphatase, calcineurin, which is necessary for the activation of a T-cell-specific transcription factor. This transcription factor, NF-AT, is involved in the synthesis of interleukins (eg, IL-2) by activated T cells. In vitro studies have indicated that cyclosporine inhibits the gene transcription of IL-2, IL-3, IFN-γ, and other factors produced by antigen-stimulated T cells, but it does not block the effect of such factors on primed T cells nor does it block interaction with antigen.

Cyclosporine may be given intravenously or orally, though it is slowly and incompletely absorbed (20–50%). The absorbed drug is primarily metabolized by the P450 3A enzyme system in the liver with resultant multiple drug interactions. This propensity for drug interaction contributes to significant interpatient variability in bioavailability, such that cyclosporine requires individual patient dosage adjustments based on steady-state blood levels and the desired therapeutic ranges for the drug. Cyclosporine ophthalmic solution is now available for severe dry eye syndrome, as well as ocular graft-versus-host disease. Inhaled cyclosporine is being investigated for use in lung transplantation.

Toxicities are numerous and include nephrotoxicity, hypertension, hyperglycemia, liver dysfunction, hyperkalemia, altered mental status, seizures, and hirsutism. However, cyclosporine causes very little bone marrow toxicity. While an increased incidence of lymphoma and other cancers (Kaposi's sarcoma, skin cancer) have been observed in transplant recipients receiving cyclosporine, other immunosuppressive agents may also predispose recipients to cancer. Some evidence suggests that tumors may arise after cyclosporine treatment because the drug induces TGF-β, which promotes tumor invasion and metastasis.

Cyclosporine may be used alone or in combination with other immunosuppressants, particularly glucocorticoids. It has been used successfully as the sole immunosuppressant for cadaveric transplantation of the kidney, pancreas, and liver, and it has proved extremely useful in cardiac transplantation as well. In combination with methotrexate, cyclosporine is a standard prophylactic regimen to prevent graft-versus-host disease after allogeneic stem cell transplantation. Cyclosporine has also proved useful in a variety of autoimmune disorders, including uveitis, rheumatoid arthritis, psoriasis, and asthma. Its combination with newer agents is showing considerable efficacy in clinical and experimental settings where effective and less toxic immunosuppression is needed. Newer formulations of cyclosporine have been developed that are improving patient compliance (smaller, better tasting pills) and increasing bioavailability.

Tacrolimus

Tacrolimus (FK 506) is an immunosuppressant macrolide antibiotic produced by *Streptomyces tsukubaensis.* It is not chemically related to cyclosporine, but their mechanisms of action are similar. Both drugs bind to cytoplasmic peptidylprolyl isomerases that are abundant in all tissues. While cyclosporine binds to cyclophilin, tacrolimus binds to the immunophilin **FK-binding protein (FKBP).** Both complexes inhibit calcineurin, which is necessary for the activation of the T-cell-specific transcription factor NF-AT.

On a weight basis, tacrolimus is 10–100 times more potent than cyclosporine in inhibiting immune responses. Tacrolimus is utilized for the same indications as cyclosporine, particularly in organ and stem cell transplantation. Multicenter studies in the USA and in Europe indicate that both graft and patient survival are similar for the two drugs. Tacrolimus has proved to be effective therapy for preventing rejection in solid-organ transplant patients even after failure of standard rejection therapy, including anti-T-cell antibodies. It is now considered a standard prophylactic agent (usually in combination with methotrexate or mycophenolate mofetil) for graft-versus-host disease.

Tacrolimus can be administered orally or intravenously. The half-life of the intravenous form is approximately 9–12 hours. Like cyclosporine, tacrolimus is metabolized primarily by P450 enzymes in the liver, and there is potential for drug interactions. The dosage is determined by trough blood level at steady state. Its toxic effects are similar to those of cyclosporine and include nephrotoxicity, neurotoxicity, hyperglycemia, hypertension, hyperkalemia, and gastrointestinal complaints.

Because of the effectiveness of systemic tacrolimus in some dermatologic diseases, a topical preparation is now available. Tacrolimus ointment is currently used in the therapy of atopic dermatitis and psoriasis.

MAMMALIAN TARGET OF RAPAMYCIN (mTOR) INHIBITORS

The mTOR inhibitors include **sirolimus** (rapamycin) as well as its analogs (called "rapalogs") such as **everolimus** and **temsirolimus.**

Sirolimus is an immunosuppressant macrolide antibiotic produced by *Streptomyces hygroscopicus* and is structurally similar to tacrolimus. Sirolimus binds the circulating immunophilin FK506-binding protein 12, resulting in an active complex that inhibits the kinase activity of mammalian target of rapamycin (mTOR). The mTOR is a key component of a complex intracellular signaling pathway involved in cellular processes such as cell growth and proliferation, angiogenesis, and metabolism. Thus, blockade of mTOR ultimately can, for example, lead to inhibition of interleukin-driven T-cell proliferation. The signaling pathways involved in mTor are an active area of investigation in immunotherapy and targeted cancer therapy. Sirolimus is available only as an oral drug. Its half-life is about 60 hours, while that of everolimus is about 43 hours. Both drugs are rapidly absorbed and elimination is similar to that of cyclosporine and tacrolimus, being substrates for both cytochrome P450 3A and P-glycoprotein. Hence, significant drug interactions can occur. For example, use with cyclosporine can increase the plasma levels of both sirolimus and everolimus such that drug levels need to be monitored. The target dose-range of these drugs will vary depending on clinical use.

Sirolimus has been used effectively alone and in combination with other immunosuppressants (corticosteroids, cyclosporine, tacrolimus, and mycophenolate mofetil) to prevent rejection of solid organ allografts. It is used as prophylaxis and as therapy for steroid-refractory acute and chronic graft-versus-host disease in hematopoietic stem cell transplant recipients. Topical sirolimus is also used in some dermatologic disorders and, in combination with cyclosporine, in the management of uveoretinitis. Recently, sirolimus-eluting coronary stents have been shown to reduce restenosis and other adverse cardiac events in patients with severe coronary artery disease. These benefits appear to be due to its antiproliferative effects. Everolimus is a rapalog with better bioavailability than sirolimus, but it appears that its clinical efficacy is similar to sirolimus in solid organ transplant recipients. Temsirolimus is not currently used as an immunosuppressant. Both temsirolimus and everolimus are used and being investigated as targeted therapy for various cancers.

Toxicities of the mTOR inhibitors can include profound myelosuppression (especially thrombocytopenia), hepatotoxicity, diarrhea, hypertriglyceridemia, pneumonitis, and headache. Because nephrotoxicity is of major concern when administering calcineurin inhibitors, sirolimus is frequently employed as first-line immunosuppressant therapy in both solid organ and stem cell transplantation because renal toxicity is usually not seen. However, increased use in stem cell transplantation regimens as graft-versus-host disease prophylaxis, particularly when combined with tacrolimus, has revealed an increased incidence of hemolytic-uremic syndrome.

MYCOPHENOLATE MOFETIL

Mycophenolate mofetil (MMF) is a semisynthetic derivative of mycophenolic acid, isolated from the mold *Penicillium glaucus*. In vitro, it inhibits T- and B-lymphocyte responses, including mitogen and mixed lymphocyte responses, probably by inhibition of de novo synthesis of purines. Mycophenolate mofetil is hydrolyzed to mycophenolic acid, the active immunosuppressive moiety; it is synthesized and administered as MMF to enhance bioavailability.

Mycophenolate mofetil is available in both oral and intravenous forms. The oral form is rapidly metabolized to mycophenolic acid. Although the cytochrome P450 3A system is not involved, some drug interactions still occur. Plasma drug levels are frequently monitored, similar to the calcineurin inhibitors and PSIs.

Mycophenolate mofetil is used in solid organ transplant patients for refractory rejection and, in combination with prednisone, as an alternative to cyclosporine or tacrolimus in patients who do not tolerate those drugs. Its antiproliferative properties make it the first-line drug for preventing or reducing chronic allograft vasculopathy in cardiac transplant recipients. Mycophenolate mofetil is used as prophylaxis for and treatment of both acute and chronic graft-versus-host disease in hematopoietic stem cell transplant patients. Newer immunosuppressant applications for MMF include lupus nephritis, rheumatoid arthritis, inflammatory bowel disease, and some dermatologic disorders.

Toxicities include gastrointestinal disturbances (nausea and vomiting, diarrhea, abdominal pain) headache, hypertension, and reversible myelosuppression (primarily neutropenia).

IMMUNOMODULATORY DERIVATIVES OF THALIDOMIDE (IMiDs)

Thalidomide is a sedative drug that was withdrawn from the market in the 1960s because of its disastrous teratogenic effects when used during pregnancy. Nevertheless, it has significant immunomodulatory actions and is currently in active use or in clinical trials for over 40 different illnesses. Thalidomide inhibits angiogenesis and has anti-inflammatory and immunomodulatory effects. It inhibits tumor necrosis factor-alpha (TNF-α), reduces phagocytosis by neutrophils, increases production of IL-10, alters adhesion molecule expression, and enhances cell-mediated immunity via interactions with T cells. The complex actions of thalidomide continue to be studied as its clinical use evolves. Owing to thalidomide's serious toxicity profile, considerable effort has been expended in the development of analogs. Immunomodulatory derivatives of thalidomide are termed **IMiDs.** Some IMiDs are much more potent than thalidomide in regulating cytokines and affecting T-cell proliferation.

Thalidomide is currently used in the treatment of multiple myeloma at initial diagnosis and for relapsed-refractory disease. Patients generally show signs of response within 2–3 months of starting the drug, with response rates from 20% to 70%. When combined with dexamethasone, the response rates in myeloma are 90% or more in some studies. Many patients have durable responses—up to 12–18 months in refractory disease and even longer in some patients treated at diagnosis. The success of thalidomide in myeloma has led to numerous clinical trials in other diseases such as myelodysplastic syndrome, acute myelogenous leukemia, and graft-versus-host disease, as well as in solid tumors like colon cancer, renal cell carcinoma, melanoma, and prostate

cancer, with variable results to date. Thalidomide has been used for many years in the treatment of some manifestations of leprosy and has been reintroduced in the USA for erythema nodosum leprosum; it is also useful in management of the skin manifestations of lupus erythematosus.

The adverse effect profile of thalidomide is extensive. The most important toxicity is teratogenesis. Because of this effect, thalidomide prescription and use are closely regulated by the manufacturer. Other adverse effects of thalidomide include peripheral neuropathy, constipation, rash, fatigue, hypothyroidism, and increased risk of deep vein thrombosis. Thrombosis is sufficiently frequent, particularly in the hematologic malignancy population, that most patients are placed on some type of anticoagulant when thalidomide treatment is initiated. **Lenalidomide** is an IMiD that in animal and in vitro studies has been shown to be similar to thalidomide in action, but with less toxicity, especially teratogenicity. Lenalidomide was approved by the Food and Drug Administration (FDA) in late 2005 as a consequence of trials that showed its effectiveness in the treatment of the myelodysplastic syndrome with the chromosome 5q31 deletion. Clinical trials using lenalidomide to treat newly diagnosed as well as relapsed or refractory multiple myeloma showed similar efficacy, leading to FDA approval for myeloma as well. Its side effect profile is similar to that of thalidomide, although with less teratogenic effect and fewer thromboembolic events. Pomalidomide (CC4047) is another oral IMiD that is being investigated for the treatment of multiple myeloma and myelodysplasia. The only IMiD currently used as an immunosuppressive medication (ie, in transplant recipients) is thalidomide.

CYTOTOXIC AGENTS

Azathioprine

Azathioprine is a prodrug of mercaptopurine and, like mercaptopurine, functions as an antimetabolite (see Chapter 54). Although its action is presumably mediated by conversion to mercaptopurine and further metabolites, it has been more widely used than mercaptopurine for immunosuppression in humans. These agents represent prototypes of the antimetabolite group of cytotoxic immunosuppressive drugs, and many other agents that kill proliferative cells appear to work at a similar level in the immune response.

Azathioprine is well absorbed from the gastrointestinal tract and is metabolized primarily to mercaptopurine. Xanthine oxidase splits much of the active material to 6-thiouric acid prior to excretion in the urine. After administration of azathioprine, small amounts of unchanged drug and mercaptopurine are also excreted by the kidney, and as much as a twofold increase in toxicity may occur in anephric or anuric patients. Since much of the drug's inactivation depends on xanthine oxidase, patients who are also receiving allopurinol (see Chapters 36 and 54) for control of hyperuricemia should have the dose of azathioprine reduced to one-fourth to one-third the usual amount to prevent excessive toxicity.

Azathioprine and mercaptopurine appear to produce immunosuppression by interfering with purine nucleic acid metabolism at steps that are required for the wave of lymphoid cell proliferation that follows antigenic stimulation. The purine analogs are thus cytotoxic agents that destroy stimulated lymphoid cells. Although continued messenger RNA synthesis is necessary for sustained antibody synthesis by plasma cells, these analogs appear to have less effect on this process than on nucleic acid synthesis in proliferating cells. Cellular immunity as well as primary and secondary serum antibody responses can be blocked by these cytotoxic agents.

Azathioprine and mercaptopurine appear to be of definite benefit in maintaining renal allografts and may be of value in transplantation of other tissues. These antimetabolites have been used with some success in the management of acute glomerulonephritis and in the renal component of systemic lupus erythematosus. They have also proved useful in some cases of rheumatoid arthritis, Crohn's disease, and multiple sclerosis. The drugs have been of occasional use in prednisone-resistant antibody-mediated idiopathic thrombocytopenic purpura and autoimmune hemolytic anemias.

The chief toxic effect of azathioprine and mercaptopurine is bone marrow suppression, usually manifested as leukopenia, although anemia and thrombocytopenia may occur. Skin rashes, fever, nausea and vomiting, and sometimes diarrhea occur, with the gastrointestinal symptoms seen mainly at higher dosages. Hepatic dysfunction, manifested by very high serum alkaline phosphatase levels and mild jaundice, occurs occasionally, particularly in patients with preexisting hepatic dysfunction.

Cyclophosphamide

The alkylating agent cyclophosphamide is one of the most efficacious immunosuppressive drugs available. Cyclophosphamide destroys proliferating lymphoid cells (see Chapter 54) but also appears to alkylate DNA and other molecules in some resting cells. It has been observed that very large doses (eg, > 120 mg/kg intravenously over several days) may induce an apparent specific tolerance to a new antigen if the drug is administered simultaneously with, or shortly after, the antigen. In smaller doses, it has been effective against autoimmune disorders (including systemic lupus erythematosus) and in patients with acquired factor XIII antibodies and bleeding syndromes, autoimmune hemolytic anemia, antibody-induced pure red cell aplasia, and Wegener's granulomatosis.

Treatment with large doses of cyclophosphamide carries considerable risk of pancytopenia and hemorrhagic cystitis and therefore is generally combined with stem cell rescue (transplant) procedures. Although cyclophosphamide appears to induce tolerance for marrow or immune cell grafting, its use does not prevent the subsequent graft-versus-host disease syndrome, which may be serious or lethal if the donor is a poor histocompatibility match (despite the severe immunosuppression induced by high doses of cyclophosphamide). Other adverse effects of cyclophosphamide include nausea, vomiting, cardiac toxicity, and electrolyte disturbances.

Leflunomide

Leflunomide is a prodrug of an inhibitor of pyrimidine synthesis (rather than purine synthesis). It is orally active, and the active metabolite has a long half-life of several weeks. Thus, the drug should be started with a loading dose, but it can be taken once daily after reaching steady state. It is approved only for rheumatoid arthritis at present, although studies are underway combining leflunomide with mycophenolate mofetil for a variety of autoimmune and inflammatory skin disorders, as well as preservation of allografts in solid organ transplantation. Leflunomide also appears (from murine data) to have antiviral activity.

Toxicities include elevation of liver enzymes with some risk of liver damage, renal impairment, and teratogenic effects. A low frequency of cardiovascular effects (angina, tachycardia) was reported in clinical trials of leflunomide.

Hydroxychloroquine

Hydroxychloroquine is an antimalarial agent with immunosuppressant properties. It is thought to suppress intracellular antigen processing and loading of peptides onto MHC class II molecules by increasing the pH of lysosomal and endosomal compartments, thereby decreasing T-cell activation.

Because of these immunosuppressant activities, hydroxychloroquine is used to treat some autoimmune disorders, eg, rheumatoid arthritis and systemic lupus erythematosus. It has also been used to both treat and prevent graft-versus-host disease after allogeneic stem cell transplantation.

Other Cytotoxic Agents

Other cytotoxic agents, including **vincristine, methotrexate,** and **cytarabine** (see Chapter 54), also have immunosuppressive properties. Methotrexate has been used extensively in rheumatoid arthritis (see Chapter 36) and in the treatment of graft-versus-host disease. Although the other agents can be used for immunosuppression, their use has not been as widespread as the purine antagonists, and their indications for immunosuppression are less certain. The use of methotrexate (which can be given orally) appears reasonable in patients with idiosyncratic reactions to purine antagonists. The antibiotic dactinomycin has also been used with some success at the time of impending renal transplant rejection. Vincristine appears to be quite useful in idiopathic thrombocytopenic purpura refractory to prednisone. The related vinca alkaloid **vinblastine** has been shown to prevent mast cell degranulation in vitro by binding to microtubule units within the cell and to prevent release of histamine and other vasoactive compounds.

Pentostatin is an adenosine deaminase inhibitor primarily used as an antineoplastic agent for lymphoid malignancies, and produces a profound lymphopenia. It is now frequently used for steroid-resistant graft-versus-host disease after allogeneic stem cell transplantation, as well as in preparative regimens prior to those transplants to provide severe immunosuppression to prevent allograft rejection.

IMMUNOSUPPRESSIVE ANTIBODIES

The development of hybridoma technology by Milstein and Kohler in 1975 revolutionized the antibody field and radically increased the purity and specificity of antibodies used in the clinic and for diagnostic tests in the laboratory. Hybridomas consist of antibody-forming cells fused to immortal plasmacytoma cells. Hybrid cells that are stable and produce the required antibody can be subcloned for mass culture for antibody production. Large-scale fermentation facilities are now used for this purpose in the pharmaceutical industry.

More recently, molecular biology has been used to develop monoclonal antibodies. Combinatorial libraries of cDNAs encoding immunoglobulin heavy and light chains expressed on bacteriophage surfaces are screened against purified antigens. The result is an antibody fragment with specificity and high affinity for the antigen of interest. This technique has been used to develop antibodies specific for viruses (eg, HIV), bacterial proteins, tumor antigens, and even cytokines. Several antibodies developed in this manner are FDA-approved for use in humans.

Other genetic engineering techniques involve production of chimeric and humanized versions of murine monoclonal antibodies in order to reduce their antigenicity and increase the half-life of the antibody in the patient. Murine antibodies administered as such to human patients elicit production of human antimouse antibodies (HAMAs), which clear the original murine proteins very rapidly. Humanization involves replacing most of the murine antibody with equivalent human regions while keeping only the variable, antigen-specific regions intact. Chimeric mouse-human antibodies have similar properties with less complete replacement of the murine components. The current naming convention for these engineered substances uses the suffix "-umab" or "-zumab" for humanized antibodies, and "-imab" or "-ximab" for chimeric products. These procedures have been successful in reducing or preventing HAMA production for many of the antibodies discussed below.

Antilymphocyte & Antithymocyte Antibodies

Antisera directed against lymphocytes have been prepared sporadically for over 100 years. With the advent of human organ transplantation as a therapeutic option, heterologous antilymphocyte globulin (ALG) took on new importance. ALG and antithymocyte globulin (ATG) are now in clinical use in many medical centers, especially in transplantation programs. The antiserum is usually obtained by immunization of horses, sheep, or rabbits with human lymphoid cells.

ALG acts primarily on the small, long-lived peripheral lymphocytes that circulate between the blood and lymph. With continued administration, "thymus-dependent" (T) lymphocytes from lymphoid follicles are also depleted, as they normally participate in the recirculating pool. As a result of the destruction or inactivation of T cells, an impairment of delayed hypersensitivity and cellular immunity occurs while humoral antibody formation remains relatively intact. ALG and ATG are useful for suppressing

certain major compartments (ie, T cells) of the immune system and play a definite role in the management of solid organ and bone marrow transplantation.

Monoclonal antibodies directed against specific cell surface and soluble proteins such as CD3, CD4, CD25, CD40, IL-2 receptor, and TNF-α (discussed below) much more selectively influence T-cell subset function. The high specificity of these antibodies improves selectivity and reduces toxicity of the therapy and alters the disease course in several different autoimmune disorders.

In the management of transplants, ALG and monoclonal antibodies can be used in the induction of immunosuppression, in the treatment of initial rejection, and in the treatment of steroid-resistant rejection. There has been some success in the use of ALG and ATG plus cyclosporine to prepare recipients for bone marrow transplantation. In this procedure, the recipient is treated with ALG or ATG in large doses for 7–10 days prior to transplantation of bone marrow cells from the donor. ALG appears to destroy the T cells in the donor marrow graft, and the probability of severe graft-versus-host syndrome is reduced.

The adverse effects of ALG are mostly those associated with injection of a foreign protein. Local pain and erythema often occur at the injection site (type III hypersensitivity). Since the humoral antibody mechanism remains active, skin-reactive and precipitating antibodies may be formed against the foreign IgG. Similar reactions occur with monoclonal antibodies of murine origin, and reactions thought to be caused by the release of cytokines by T cells and monocytes have also been described.

Anaphylactic and serum sickness reactions to ALG and murine monoclonal antibodies have been observed and usually require cessation of therapy. Complexes of host antibodies with horse ALG may precipitate and localize in the glomeruli of the kidneys. The incidence of lymphoma as well as other forms of cancer is increased in kidney transplant patients. It appears likely that part of the increased risk of cancer is related to the suppression of a normally potent defense system against oncogenic viruses or transformed cells. The preponderance of lymphoma in these cancer cases is thought to be related to the concurrence of chronic immune suppression with chronic low-level lymphocyte proliferation.

Muromonab-CD3

Monoclonal antibodies against T-cell surface proteins are increasingly being used in the clinic for autoimmune disorders and in transplantation settings. Clinical studies have shown that the murine monoclonal antibody muromonab-CD3 (OKT3) directed against the CD3 molecule on the surface of human T cells can be useful in the treatment of renal transplant rejection. In vitro, muromonab CD3 blocks killing by cytotoxic human T cells and several other T-cell functions. In a prospective randomized multicenter trial with cadaveric renal transplants, use of muromonab-CD3 (along with lower doses of steroids or other immunosuppressive drugs) proved more effective at reversing acute rejection than did conventional steroid treatment. Muromonab-CD3 is approved for the treatment of acute renal allograft rejection and steroid-resistant acute cardiac and hepatic transplant rejection. Many other monoclonal antibodies directed against surface markers on lymphocytes are approved for certain indications (see monoclonal antibody section below), while others are in various stages of development.

Immune Globulin Intravenous (IGIV)

A different approach to immunomodulation is the intravenous use of polyclonal human immunoglobulin. This immunoglobulin preparation (usually IgG) is prepared from pools of thousands of healthy donors, and no single, specific antigen is the target of the "therapeutic antibody." Rather, one expects that the pool of different antibodies will have a normalizing effect upon the patient's immune networks.

IGIV in high doses (2 g/kg) has proved effective in a variety of different applications ranging from immunoglobulin deficiencies to autoimmune disorders to HIV disease to bone marrow transplantation. In patients with Kawasaki's disease, it has been shown to be safe and effective, reducing systemic inflammation and preventing coronary artery aneurysms. It has also brought about good clinical responses in systemic lupus erythematosus and refractory idiopathic thrombocytopenic purpura. Possible mechanisms of action of IGIV include a reduction of T helper cells, increase of regulatory T cells, decreased spontaneous immunoglobulin production, Fc receptor blockade, increased antibody catabolism, and idiotypic-anti-idiotypic interactions with "pathologic antibodies." Although its precise mechanism of action is still unknown, IGIV brings undeniable clinical benefit to many patients with a variety of immune syndromes.

Rh_o(D) Immune Globulin Micro-Dose

One of the earliest major advances in immunopharmacology was the development of a technique for preventing Rh hemolytic disease of the newborn. The technique is based on the observation that a *primary* antibody response to a foreign antigen can be blocked if specific antibody to that antigen is administered passively at the time of exposure to antigen. Rh_o(D) immune globulin is a concentrated (15%) solution of human IgG containing a higher titer of antibodies against the Rh_o(D) antigen of the red cell.

Sensitization of Rh-negative mothers to the D antigen occurs usually at the time of birth of an Rh_o(D)-positive or D^u-positive infant, when fetal red cells leak into the mother's bloodstream. Sensitization might also occur occasionally with miscarriages or ectopic pregnancies. In subsequent pregnancies, maternal antibody against Rh-positive cells is transferred to the fetus during the third trimester, leading to the development of erythroblastosis fetalis (hemolytic disease of the newborn).

If an injection of Rh_o(D) antibody is administered to the mother within 24–72 hours after the birth of an Rh-positive infant, the mother's own antibody response to the foreign Rh_o(D)-positive cells is suppressed because the infant's red cells are cleared from circulation before the mother can generate a B-cell response against Rh_o(D). Therefore she has no memory B cells that can activate upon subsequent pregnancies with an Rh_o(D)-positive fetus.

When the mother has been treated in this fashion, Rh hemolytic disease of the newborn has not been observed in subsequent pregnancies. For this prophylactic treatment to be successful, the

mother must be $Rh_o(D)$-negative and D^u-negative and must not already be immunized to the $Rh_o(D)$ factor. Treatment is also often advised for Rh-negative mothers antepartum at 26–28 weeks' gestation who have had miscarriages, ectopic pregnancies, or abortions, when the blood type of the fetus is unknown. ***Note:*** *$Rh_o(D)$ immune globulin is administered to the mother and must not be given to the infant.*

The usual dose of $Rh_o(D)$ immune globulin is 2 mL intramuscularly, containing approximately 300 mcg anti-$Rh_o(D)$ IgG. Adverse reactions are infrequent and consist of local discomfort at the injection site or, rarely, a slight temperature elevation.

Hyperimmune Immunoglobulins

Hyperimmune immunoglobulins are IGIV preparations made from pools of selected human or animal donors with high titers of antibodies against particular agents of interest such as viruses or toxins (see also Appendix I). Various hyperimmune IGIVs are available for treatment of respiratory syncytial virus, cytomegalovirus, varicella zoster, human herpesvirus 3, hepatitis B virus, rabies, tetanus, and digoxin overdose. Intravenous administration of the hyperimmune globulins is a passive transfer of high titer antibodies that either reduces risk or reduces the severity of infection. Rabies hyperimmune globulin is injected around the wound and given intravenously. Tetanus hyperimmune globulin is administered intravenously when indicated for prophylaxis. Rattlesnake and coral snake hyperimmune globulins (antivenoms) are of equine or ovine origin and are effective for North and South American rattlesnakes and some coral snakes (but not Arizona coral snake). Equine and ovine antivenoms are available for rattlesnake envenomations, but only equine antivenom is available for coral snake bite. The ovine antivenom is a Fab preparation and is less immunogenic than whole equine IgG antivenoms, but retains the ability to neutralize the rattlesnake venom.

MONOCLONAL ANTIBODIES (MABs)

Recent advances in the ability to manipulate the genes of immunoglobulins have resulted in development of a wide array of humanized and chimeric monoclonal antibodies directed against therapeutic targets. The only murine elements of humanized monoclonal antibodies are the complementarity-determining regions in the variable domains of immunoglobulin heavy and light chains. Complementarity-determining regions are primarily responsible for the antigen-binding capacity of antibodies. Chimeric antibodies typically contain antigen-binding murine variable regions and human constant regions. The following are brief descriptions of the engineered antibodies that have been approved by the FDA.

Antitumor MABs

Alemtuzumab is a humanized IgG_1 with a kappa chain that binds to CD52 found on normal and malignant B and T lymphocytes, NK cells, monocytes, macrophages, and a small population of granulocytes. Currently, alemtuzumab is approved for the treatment of B-cell chronic lymphocytic leukemia in patients who have been treated with alkylating agents and have failed fludarabine therapy. Alemtuzumab appears to deplete leukemic and normal cells by direct antibody-dependent lysis. Patients receiving this antibody become lymphopenic and may also become neutropenic, anemic, and thrombocytopenic. As a result patients should be closely monitored for opportunistic infections and hematologic toxicity.

Bevacizumab is a humanized IgG_1 monoclonal antibody that binds to vascular endothelial growth factor (VEGF) and inhibits VEGF from binding to its receptor, especially on endothelial cells. It is an antiangiogenic drug that has been shown to inhibit growth of blood vessels (angiogenesis) in tumors. It is approved for first-line treatment of patients with metastatic colorectal cancer alone or in combination with 5-FU-based chemotherapy. It is also approved for treatment of non-small cell lung cancer, glioblastoma multiforme that has progressed after prior treatment, and metastatic kidney cancer when used with interferon-alpha. Since bevacizumab is antiangiogenic, it should not be administered until patients heal from surgery. Patients taking the drug should be watched for hemorrhage, gastrointestinal perforations, and wound healing problems. Bevacizumab has also been used off label by intravitreal injection to slow progression of neovascular macular degeneration (see ranibizumab under Other MABs, below).

Cetuximab is a human-mouse chimeric monoclonal antibody that targets epidermal growth factor receptor (EGFR). Binding of cetuximab to EGFR inhibits tumor cell growth by a variety of mechanisms, including decreases in kinase activity, matrix metalloproteinase activity, and growth factor production, and increased apoptosis. It is indicated for use in patients with EGFR-positive metastatic colorectal cancer and, along with radiation therapy, in patients with head and neck cancer. Cetuximab may be administered in combination with irinotecan or alone in patients who cannot tolerate irinotecan. HAMAs are generated by about 4% of patients being treated with cetuximab.

Ofatumumab is a human IgG_1 monoclonal antibody directed against a different epitope on CD20 than rituximab. It is approved for patients with chronic lymphocytic leukemia (CLL) who are refractory to fludarabine and alemtuzumab. Ofatumumab binds to all B cells including B-CLL. It is thought to lyse B-CLL cells in the presence of complement and to mediate antibody-dependent cellular cytotoxicity. There is a slight risk of hepatitis B virus reactivation in patients taking ofatumumab.

Panitumumab is a fully human IgG_2 kappa light chain monoclonal antibody. It is approved for the treatment of EGFR-expressing metastatic colorectal carcinoma with disease progression on or following fluoropyrimidine-, oxaliplatin-, and irinotecan-containing chemotherapy regimens. Panitumumab binds to EGFR (similar to cetuximab), inhibiting epidermal growth factor from binding to its receptor, and prevents ligand-induced receptor autophosphorylation and activation of receptor-associated kinases. It inhibits cell growth, induces apoptosis, decreases vascular growth factor production, and suppresses internalization of the EGFR. Although some dermatologic and infusion-related toxicities have been observed following infusion of panitumumab, the distinct advantage over cetuximab is that it is fully human, and

therefore does not elicit HAMAs. This is the first FDA-approved monoclonal antibody produced from transgenic mice expressing the human immunoglobulin gene loci.

Rituximab is a chimeric murine-human monoclonal IgG_1 (human Fc) that binds to the CD20 molecule on normal and malignant B lymphocytes and is approved for the therapy of patients with relapsed or refractory low-grade or follicular B-cell non-Hodgkin's lymphoma and chronic lymphocytic leukemia. It is also approved for the treatment of rheumatoid arthritis in combination with methotrexate in patients for whom anti-TNF-α therapy has failed. The mechanism of action includes complement-mediated lysis, antibody-dependent cellular cytotoxicity, and induction of apoptosis in the malignant lymphoma cells. In lymphoma this drug appears to be synergistic with chemotherapy (eg, fludarabine, CHOP, see Chapter 54). Recent reports indicate that rituximab may also be very useful in autoimmune diseases such as multiple sclerosis and systemic lupus erythematosus.

Trastuzumab is a recombinant DNA-derived, humanized monoclonal antibody that binds to the extracellular domain of the human epidermal growth factor receptor HER-2/*neu*. This antibody blocks the natural ligand from binding and down-regulates the receptor. Trastuzumab is approved for the treatment of HER-2/*neu*-positive tumors in patients with breast cancer and patients with metastatic gastric or gastroesophageal junction adenocarcinoma. As a single agent it induces remission in about 15–20% of breast cancer patients; in combination with chemotherapy, it increases response rates and duration as well as 1-year survival. Trastuzumab is under investigation for other tumors that express HER-2/neu (see Chapter 54).

MABs Used to Deliver Isotopes to Tumors

Arcitumomab is a murine Fab fragment from an anti-carcinoembryonic antigen (CEA) antibody labeled with technetium 99m (^{99m}Tc) that is used for imaging patients with metastatic colorectal carcinoma (immunoscintigraphy) to determine extent of disease. CEA is often upregulated on tumor in patients with gastrointestinal carcinomas. The use of the Fab fragment decreases the immunogenicity of the agent so that it can be given more than once; intact murine monoclonal antibodies would elicit stronger HAMA.

Capromab pendetide is a murine monoclonal antibody specific for prostate specific membrane antigen. It is coupled to isotopic indium (^{111}In) and is used in immunoscintigraphy for patients with biopsy-confirmed prostate cancer and post-prostatectomy in patients with rising prostate specific antibody level to determine extent of disease.

Ibritumomab tiuxetan is an anti-CD20 murine monoclonal antibody labeled with isotopic yttrium (^{90}Y) or ^{111}In. The radiation of the isotope coupled to the antibody provides the major antitumor activity. Ibritumomab is approved for use in patients with relapsed or refractory low-grade, follicular, or B-cell non-Hodgkin's lymphoma, including patients with rituximab-refractory follicular disease. It is used in conjunction with rituximab in a two-step therapeutic regimen.

Tositumomab is another anti-CD20 monoclonal antibody and is complexed with iodine 131 (^{131}I). Tositumomab is used in two-step therapy in patients with CD20-positive, follicular non-Hodgkin's lymphoma whose disease is refractory to rituximab and standard chemotherapy. Toxicities are similar to those for ibritumomab and include severe cytopenias such as thrombocytopenia and neutropenia. Tositumomab should not be administered to patients with greater than 25% bone marrow involvement.

MABs Used as Immunosuppressants and Anti-Inflammatory Agents

A. Anti-TNF-Alpha MABs

Adalimumab, certolizumab pegol, etanercept, golimumab, and infliximab are antibodies that bind TNF-α, a proinflammatory cytokine that is important in rheumatoid arthritis and similar inflammatory diseases (see Chapter 36). Blocking TNF-α from binding to TNF receptors on inflammatory cells results in suppression of downstream inflammatory cytokines such as IL-1 and IL-6 and adhesion molecules involved in leukocyte activation and migration. An increased risk of infection or reactivation of *M tuberculosis,* hepatitis B virus, and invasive systemic fungi is common to each of these anti-TNF monoclonal antibodies. Patients may also be at increased risk for malignancies including lymphoma.

Adalimumab is a completely human IgG_1 approved for use in patients with rheumatoid arthritis, juvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitis, Crohn's disease, and plaque psoriasis. Like the other anti-TNF-α biologicals, adalimumab blocks the interaction of TNF-α with TNF receptors on cell surfaces; it does not bind TNF-β. Adalimumab lyses cells expressing TNF-α in the presence of complement. Pharmacodynamic studies showed that administration of adalimumab reduced levels of C-reactive protein, erythrocyte sedimentation rate, serum IL-6, and matrix metalloproteinases MMP-1 and MMP-3.

Certolizumab pegol is a recombinant humanized Fab fragment that binds to TNF-α. It is coupled to a 40-kDa polyethylene glycol. It neutralizes the activity of membrane-associated and soluble TNF-α without lysing cells. Certolizumab is indicated for patients with Crohn's disease and rheumatoid arthritis.

Etanercept is a dimeric fusion protein composed of human IgG_1 constant regions fused to the TNF receptor. Etanercept binds to both TNF-α and TNF-β and appears to have effects similar to those of adalimumab and infliximab, ie, inhibition of TNF-α-mediated inflammation, but its half-life is shorter due to its physical form (fusion protein) and the route of injection (subcutaneously, twice weekly). Etanercept is approved for adult rheumatoid arthritis, polyarticular juvenile idiopathic arthritis, ankylosing spondylitis and psoriatic arthritis. It may be used in combination with methotrexate in some patients with arthritis.

Golimumab is a human IgG monoclonal antibody that also binds to soluble and membrane-associated TNF-α. It is an intact human IgG_1 and, like certolizumab pegol, it does not lyse cells expressing membrane-associated TNF-α. It is indicated for patients with rheumatoid arthritis, ankylosing spondylitis, and psoriatic arthritis. It has the advantage of increased half-life such that subcutaneous injections may be self-administered only once per month.

Infliximab is a human-mouse chimeric IgG_1 monoclonal antibody possessing human constant (Fc) regions and murine variable regions. It is administered intravenously but has the same anti-TNF-α activity as adalimumab and etanercept. Infliximab is currently approved for use in Crohn's disease, ulcerative colitis, rheumatoid arthritis, ankylosing spondylitis, plaque psoriasis, and psoriatic arthritis.

B. Abatacept

Abatacept is a recombinant fusion protein composed of the extracellular domain of cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) fused to hinge, CH_2, and CH_3 domains of human IgG_1. CTLA-4 delivers an inhibitory signal to T cells. It binds more tightly to CD80/86 than CD28 (Figure 55–7). This fusion protein blocks activation of T cells by binding to CD80 or CD86 so that CD28 on T cells cannot bind and stimulate the T cell and lead to cytokine release. Abatacept is approved for patients with rheumatoid arthritis and juvenile idiopathic arthritis. Patients should not take other anti-TNF drugs or anakinra while taking abatacept. As with anti-TNF monoclonal agents, patients should be screened and treated for latent tuberculosis infection before starting abatacept.

C. Alefacept

Alefacept is an engineered protein consisting of the CD2-binding portion of leukocyte-function-associated antigen-3 (LFA-3) fused to a human IgG_1 Fc region (hinge, CH_2, and CH_3). It is approved for the treatment of plaque psoriasis. It inhibits activation of T cells by binding to cell surface CD2, inhibiting the normal CD2/LFA-3 interaction (Figure 55–7). Treatment of patients with alefacept also results in a dose-dependent reduction of the total number of circulating T cells, especially CD4 and CD8 memory effector subsets that predominate in psoriatic plaques. Peripheral T-cell counts of patients receiving alefacept must be monitored and the drug discontinued if CD4 lymphocyte levels fall below 250 cells/μL.

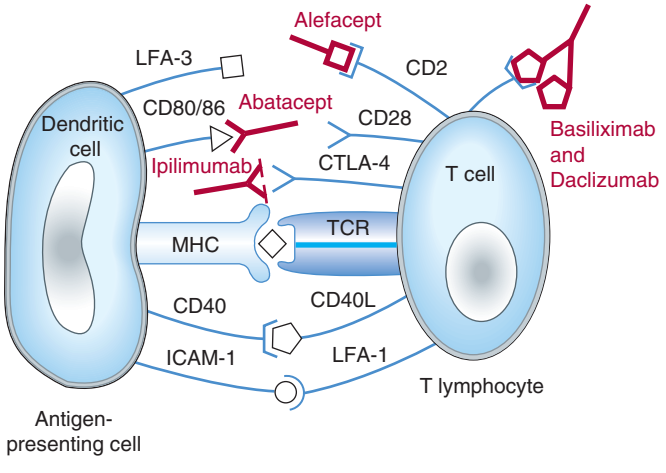

FIGURE 55–7 Actions of some monoclonal antibodies (*shown in red*). CTLA-4-IgFc fusion protein (CTLA-4-Ig, abatacept) binds to CD80/86 on DC and inhibits T-cell costimulation. Alefacept inhibits activation of T cells by blocking the interaction of LFA-3 and CD2. Basiliximab and daclizumab block IL-2 from binding to the IL-2 receptor (CD25) on T cells, preventing activation; CD25 is also important for the survival of T regulatory cells. T-cell activation can be maintained or restored if CTLA-4 interaction with CD80/86 is blocked using an anti-CTLA-4 antibody (ipilimumab, currently in phase 3 clinical trials); ipilimumab inhibits CTLA-4 signaling and prolongs activation.

D. Basiliximab and Daclizumab

Basiliximab is a chimeric mouse-human IgG_1 that binds to CD25, the IL-2 receptor alpha chain on activated lymphocytes. Daclizumab is a humanized IgG_1 that also binds to the alpha subunit of the IL-2 receptor. Both agents function as IL-2 antagonists, blocking IL-2 from binding to activated lymphocytes, and are therefore immunosuppressive. They are indicated for prophylaxis of acute organ rejection in renal transplant patients and either may be used as part of an immunosuppressive regimen that also includes glucocorticoids and cyclosporine A.

E. Natalizumab

Natalizumab is a humanized IgG4 monoclonal antibody that binds to the α4-subunit of α4β1 and α4β7 integrins expressed on the surfaces of all leukocytes except neutrophils, and inhibits the α4-mediated adhesion of leukocytes to their cognate receptor. It is indicated for patients with multiple sclerosis and Crohn's disease who have not tolerated or had inadequate responses to conventional treatments.

F. Omalizumab

Omalizumab is an anti-IgE recombinant humanized monoclonal antibody that is approved for the treatment of allergic asthma in adult and adolescent patients whose symptoms are refractory to inhaled corticosteroids (see Chapter 20). The antibody blocks the binding of IgE to the high-affinity Fcε receptor on basophils and mast cells, which suppresses IgE-mediated release of type I allergy mediators such as histamine and leukotrienes. Total serum IgE levels may remain elevated in patients for up to 1 year after administration of this antibody.

G. Tocilizumab

Tocilizumab is recombinant humanized IgG_1 that binds to soluble and membrane-associated IL-6 receptors. It inhibits IL-6-mediated signaling on lymphocytes, suppressing inflammatory processes. It is indicated for treatment of patients with rheumatoid arthritis who are refractory to other anti-TNF-α biologicals. It may be used alone or in combination with methotrexate or other disease-modifying antirheumatic drugs. Patients taking tocilizumab have the same increased risk of infection as those taking anti-TNF-α monoclonal antibodies.

H. Ustekinumab

Ustekinumab is a human IgG_1 monoclonal antibody that binds to the p40 subunit of IL-12 and IL-23 cytokines. It blocks IL-12 and IL-23 from binding to their receptors, therefore inhibiting receptor-mediated signaling in lymphocytes. Ustekinumab is indicated for patients with moderate to severe plaque psoriasis. The advantage

of ustekinumab over anti-TNF-α drugs for psoriasis is faster and longer term improvement in symptoms along with very infrequent dosing.

Other MABs

Abciximab is a Fab fragment of a murine-human monoclonal antibody that binds to the integrin GPIIb/IIIa receptor on activated platelets and inhibits fibrinogen, von Willebrand factor, and other adhesion molecules from binding to activated platelets, thus preventing their aggregation. It is indicated as an adjunct to percutaneous coronary intervention for the prevention of cardiac ischemic complications. See Chapter 34 for additional details.

Denosumab is a human IgG_2 monoclonal antibody specific for human RANKL (receptor activator of nuclear factor kappa-B ligand). By binding RANKL it inhibits the maturation of osteoclasts, the cells responsible for bone resorption. Denosumab is indicated for treatment of postmenopausal women with osteoporosis at high risk for fracture. Before starting denosumab, patients must be evaluated to be sure they are not hypocalcemic. During treatment, patients should receive supplements of calcium and vitamin D.

Eculizumab is a humanized IgG monoclonal antibody that binds the C5 complement component, inhibiting its cleavage into C5a and C5b thereby inhibiting the terminal pore-forming lytic activity of complement. Eculizumab is approved for patients with paroxysmal nocturnal hemoglobinuria (PNH) and dramatically reduces the need for red blood cell transfusions. It prevents PNH symptoms of anemia, fatigue, thrombosis, and hemoglobinemia by inhibiting intravascular hemolysis due to red cell lysis. Clinicians must be aware of increased risk of meningococcal infection in patients receiving this anti-C5 monoclonal antibody.

Palivizumab is a monoclonal antibody that binds to the fusion protein of respiratory syncytial virus, preventing infection in susceptible cells in the airways. It is used in neonates at risk for this viral infection and reduces the frequency of infection and hospitalization by about 50% (see Chapter 49).

Ranibizumab is a recombinant human IgG_1 Fab that binds to VEGF-A. It also prevents new blood vessel formation by blocking VEGF from binding to its receptor. Ranibizumab is labeled for intravitreal injection in patients with neovascular age-related macular degeneration and sudden blurring or vision loss secondary to macular edema following retinal vein occlusion. **Pegaptanib** is a pegylated oligonucleotide that binds extracellular VEGF and is also given by intravitreous injection to slow macular degeneration.

■ CLINICAL USES OF IMMUNOSUPPRESSIVE DRUGS

Immunosuppressive agents are commonly used in two clinical circumstances: transplantation and autoimmune disorders. The agents used differ somewhat for the specific disorders treated (see specific agents and Table 55–1), as do administration schedules. Because autoimmune disorders are very complex, optimal treatment schedules have yet to be established in many clinical situations.

SOLID ORGAN & BONE MARROW TRANSPLANTATION

In organ transplantation, tissue typing—based on donor and recipient histocompatibility matching with the human leukocyte antigen (HLA) haplotype system—is required. Close histocompatibility matching reduces the likelihood of graft rejection and may also reduce the requirements for intensive immunosuppressive therapy. Prior to transplant, patients may receive an immunosuppressive regimen, including antithymocyte globulin, muromonab-CD3, daclizumab, or basiliximab. Four types of rejection can occur in a solid organ transplant recipient: **hyperacute, accelerated, acute,** and **chronic.** Hyperacute rejection is due to preformed antibodies against the donor organ, such as anti-blood group antibodies. Hyperacute rejection occurs within hours of the transplant and cannot be stopped with immunosuppressive drugs. It results in rapid necrosis and failure of the transplanted organ. Accelerated rejection is mediated by both antibodies and T cells, and it also cannot be stopped by immunosuppressive drugs. Acute rejection of an organ occurs within days to months and involves mainly cellular immunity. Reversal of acute rejection is usually possible with general immunosuppressive drugs such as azathioprine, mycophenolate mofetil, cyclosporine, tacrolimus, glucocorticoids, cyclophosphamide, methotrexate, and sirolimus. Recently, biologic agents such as anti-CD3 monoclonal antibodies have been used to stem acute rejection. Chronic rejection usually occurs months or even years after transplantation. It is characterized by thickening and fibrosis of the vasculature of the transplanted organ, involving both cellular and humoral immunity. Chronic rejection is treated with the same drugs as those used for acute rejection.

Allogeneic hematopoietic stem cell transplantation is a well-established treatment for many malignant and nonmalignant diseases. An HLA-matched donor, usually a family member, is located, patients are conditioned with high-dose chemotherapy or radiation therapy, and then donor stem cells are infused. The conditioning regimen is used not only to kill cancer cells in the case of malignant disease, but also to totally suppress the immune system so that the patient does not reject the donor stem cells. As patients' blood counts recover (after reduction by the conditioning regimen) they develop a new immune system that is created from the donor stem cells. Rejection of donor stem cells is uncommon, and can only be treated by infusion of more stem cells from the donor.

Graft-versus-host disease, however, is very common, occurring in the majority of patients who receive an allogeneic transplant. Graft-versus-host disease occurs as donor T cells fail to recognize the patient's skin, liver, and gut (usually) as self and attack those tissues. Although patients are given immunosuppressive therapy (cyclosporine, methotrexate, and others) early in the transplant course to help prevent this development, it usually occurs despite these medications. Acute graft-versus-host disease occurs within the first 100 days, and is usually manifested as a skin rash, severe diarrhea, or hepatotoxicity. Additional medications are added, invariably starting with high-dose corticosteroids, and adding drugs such as mycophenolate mofetil, sirolimus, tacrolimus, daclizumab, and others, with variable success rates. Patients generally progress to

chronic graft-versus-host disease (after 100 days) and require therapy for variable periods thereafter. Unlike solid organ transplant patients, however, most stem cell transplant patients are able to eventually discontinue immunosuppressive drugs as graft-versus-host disease resolves (usually 1–2 years after their transplant).

AUTOIMMUNE DISORDERS

The effectiveness of immunosuppressive drugs in autoimmune disorders varies widely. Nonetheless, with immunosuppressive therapy, remissions can be obtained in many instances of autoimmune hemolytic anemia, idiopathic thrombocytopenic purpura, type 1 diabetes, Hashimoto's thyroiditis, and temporal arteritis. Improvement is also often seen in patients with systemic lupus erythematosus, acute glomerulonephritis, acquired factor VIII inhibitors (antibodies), rheumatoid arthritis, inflammatory myopathy, scleroderma, and certain other autoimmune states.

Immunosuppressive therapy is utilized in chronic severe asthma, where cyclosporine is often effective and sirolimus is another alternative. Omalizumab (anti-IgE antibody) has been approved for the treatment of severe asthma (see previous section). Tacrolimus is currently under clinical investigation for the management of autoimmune chronic active hepatitis and of multiple sclerosis, where IFN-β has a definitive role.

IMMUNOMODULATION THERAPY

The development of agents that modulate the immune response rather than suppress it has become an important area of pharmacology. The rationale underlying this approach is that such drugs may increase the immune responsiveness of patients who have either selective or generalized immunodeficiency. The major potential uses are in immunodeficiency disorders, chronic infectious diseases, and cancer. The AIDS epidemic has greatly increased interest in developing more effective immunomodulating drugs.

Cytokines

The cytokines are a large and heterogeneous group of proteins with diverse functions. Some are immunoregulatory proteins synthesized within lymphoreticular cells and play numerous interacting roles in the function of the immune system and in the control of hematopoiesis. The cytokines that have been clearly identified are summarized in Table 55–2. In most instances, cytokines mediate their effects through receptors on relevant target cells and appear to act in a manner similar to the mechanism of action of hormones. In other instances, cytokines may have antiproliferative, antimicrobial, and antitumor effects.

The first group of cytokines discovered, the interferons (IFNs), were followed by the colony-stimulating factors (CSFs, discussed in Chapter 33). The latter regulate the proliferation and differentiation of bone marrow progenitor cells. Most of the more recently discovered cytokines have been classified as interleukins (ILs) and numbered in the order of their discovery. Cytokines are produced using gene cloning techniques.

TABLE 55–2 The cytokines.

Cytokine	Properties
Interferon-α (IFN-α)	Antiviral, oncostatic, activates NK cells
Interferon-β (IFN-β)	Antiviral, oncostatic, activates NK cells
Interferon-γ (IFN-γ)	Antiviral, oncostatic, secreted by and activates or up-regulates TH1 cells, NK cells, CTLs, and macrophages
Interleukin-1 (IL-1)	T-cell activation, B-cell proliferation and differentiation
Interleukin-2 (IL-2)	T-cell proliferation, TH1, NK, and LAK cell activation
Interleukin-3 (IL-3)	Hematopoietic precursor proliferation and differentiation
Interleukin-4 (IL-4)	TH2 and CTL activation, B-cell proliferation
Interleukin-5 (IL-5)	Eosinophil proliferation, B-cell proliferation and differentiation
Interleukin-6 (IL-6)	HCF, TH2, CTL, and B-cell proliferation
Interleukin- 7 (IL-7)	CTL, NK, LAK, and B-cell proliferation, thymic precursor stimulation
Interleukin-8 (IL-8)	Neutrophil chemotaxis, proinflammatory
Interleukin-9 (IL-9)	T-cell proliferation
Interleukin-10 (IL-10)	TH1 suppression, CTL activation, B-cell proliferation
Interleukin-11 (IL-11)	Megakaryocyte proliferation, B-cell differentiation
Interleukin-12 (IL-12)	TH1 and CTL proliferation and activation
Interleukin-13 (IL-13)	Macrophage function modulation, B cell proliferation
Interleukin-14 (IL-14)	B-cell proliferation and differentiation
Interleukin-15 (IL-15)	TH1, CTL, and NK/LAK activation, expansion of T-cell memory pools
Interleukin-16 (IL-16)	T-lymphocyte chemotaxis, suppresses HIV replication
Interleukin-17 (IL-17)	Stromal cell cytokine production
Interleukin-18 (IL-18)	Induces TH1 responses
Interleukin-19 (IL-19)	Proinflammatory
Interleukin-20 (IL-20)	Promotes skin differentiation
Interleukin-21 (IL-21)	Promotes proliferation of activated T cells, maturation of NK cells
Interleukin-22 (IL-22)	Regulator of TH2 cells
Interleukin-23 (IL-23)	Promotes proliferation of TH1 memory cells
Interleukin-24 (IL-24)	Induces tumor apoptosis, induces TH1 responses
Interleukin-27 (IL-27)	Stimulates naive CD4 cells to produce IFN-γ
Interleukin-28 and -29 (IL-28, IL-29)	Antiviral, interferon-like properties
Interleukin-30 (IL-30)	p28 subunit of IL-27
Interleukin-31 (IL-31)	Contributes to type I hypersensitivities and TH2 responses

(*continued*)

TABLE 55–2 The cytokines. (Continued)

Cytokine	Properties
Interleukin-32 (IL-32)	Involved in inflammation
Interleukin-34 (IL-34)	Stimulates monocyte proliferation via the CSF-1 receptor (CSF-1R)
Interleukin-35 (IL-35)	Induces regulatory T cells (iT_R35)
Tumor necrosis factor-α (TNF-α)	Oncostatic, macrophage activation, proinflammatory
Tumor necrosis factor-β (TNF-β)	Oncostatic, proinflammatory, chemotactic
Granulocyte colony-stimulating factor	Granulocyte production
Granulocyte-macrophage colony-stimulating factor	Granulocyte, monocyte, eosinophil production
Macrophage colony-stimulating factor	Monocyte production, activation
Erythropoietin (epoetin, EPO)	Red blood cell production
Thrombopoietin (TPO)	Platelet production

HCF, hematopoietic cofactor; LAK, lymphokine-activated killer cell.

Note: Many interleukin activities overlap and are influenced by each other.

Most cytokines (including TNF-α, IFN-γ, IL-2, granulocyte colony-stimulating factor [G-CSF], and granulocyte-macrophage colony-stimulating factor [GM-CSF]) have very short serum half-lives (minutes). The usual subcutaneous route of administration provides slower release into the circulation and a longer duration of action. Each cytokine has its own unique toxicity, but some toxicities are shared. For example, IFN-α, IFN-β, IFN-γ, IL-2, and TNF-α all induce fever, flu-like symptoms, anorexia, fatigue, and malaise.

Interferons are proteins that are currently grouped into three families: **IFN-α**, **IFN-β**, and **IFN-γ**. The IFN-α and IFN-β families comprise type I IFNs, ie, acid-stable proteins that act on the same receptor on target cells. IFN-γ, a type II IFN, is acid-labile and acts on a separate receptor on target cells. Type I IFNs are usually induced by virus infections, with leukocytes producing IFN-α. Fibroblasts and epithelial cells produce IFN-β. IFN-γ is usually the product of activated T lymphocytes.

IFNs interact with cell receptors to produce a wide variety of effects that depend on the cell and IFN types. IFNs, particularly IFN-γ, display immune-enhancing properties, which include increased antigen presentation and macrophage, NK cell, and cytotoxic T-lymphocyte activation. IFNs also inhibit cell proliferation. In this respect, IFN-α and IFN-β are more potent than IFN-γ. Another striking IFN action is increased expression of MHC molecules on cell surfaces. While all three types of IFN induce MHC class I molecules, only IFN-γ induces class II expression. In glial cells, IFN-β antagonizes this effect and may, in fact, decrease antigen presentation within the nervous system.

IFN-α is approved for the treatment of several neoplasms, including hairy cell leukemia, chronic myelogenous leukemia, malignant melanoma, and Kaposi's sarcoma, and for use in hepatitis B and C infections. It has also shown activity as an anticancer agent in renal cell carcinoma, carcinoid syndrome, and T-cell leukemia. IFN-β is approved for use in relapsing-type multiple sclerosis. IFN-γ is approved for the treatment of chronic granulomatous disease and IL-2, for metastatic renal cell carcinoma and malignant melanoma. Clinical investigations of other cytokines, including IL-1, -3, -4, -6, -10, -11, and -12, are ongoing. Toxicities of IFNs, which include fever, chills, malaise, myalgias, myelosuppression, headache, and depression, can severely restrict their clinical use.

TNF-α has been extensively tested in the therapy of various malignancies, but results have been disappointing due to dose-limiting toxicities. One exception is the use of intra-arterial high-dose TNF-α for malignant melanoma and soft tissue sarcoma of the extremities. In these settings, response rates greater than 80% have been noted.

Cytokines have been under clinical investigation as adjuvants to vaccines, and IFNs and IL-2 have shown some positive effects in the response of human subjects to hepatitis B vaccine. Denileukin diftitox is IL-2 fused to diphtheria toxin, used for the treatment of patients with CD25+ cutaneous T-cell lymphomas. IL-12 and GM-CSF have also shown adjuvant effects with vaccines. GM-CSF is of particular interest because it promotes recruitment of professional antigen-presenting cells such as the dendritic cells required for priming naive antigen-specific T-lymphocyte responses. There are some claims that GM-CSF can itself stimulate an antitumor immune response, resulting in tumor regression in melanoma and prostate cancer.

It is important to emphasize that cytokine interactions with target cells often result in the release of a cascade of different endogenous cytokines, which exert their effects sequentially or simultaneously. For example, IFN-γ exposure increases the number of cell-surface receptors on target cells for TNF-α. Therapy with IL-2 induces the production of TNF-α, while therapy with IL-12 induces the production of IFN-γ.

Cytokine Inhibitors

A more recent application of immunomodulation therapy involves the use of cytokine inhibitors for inflammatory diseases and septic shock, conditions in which cytokines such as IL-1 and TNF-α (see above) are involved in the pathogenesis. Drugs now in use or under investigation include anticytokine antibodies and soluble cytokine receptors. **Anakinra** is a recombinant form of the naturally occurring IL-1 receptor antagonist that prevents IL-1 from binding to its receptor, stemming the cascade of cytokines that would otherwise be released. Anakinra is approved for use in adult rheumatoid arthritis patients who have failed treatment with one or more disease-modifying antirheumatic drugs. **Canakinumab** is a recombinant human anti-IL-1β monoclonal antibody. It binds to human IL-1β and prevents it from binding to IL-1 receptors. **Rilonacept** is a dimeric fusion protein consisting of the ligand-binding domains of the extracellular portions of the human interleukin-1 receptor component (IL-1RI) and IL-1 receptor accessory protein (IL-1RAcP) fused to the Fc portion of human IgG1. These molecules are indicated for treatment of cryopyrin-associated periodic syndromes.

Patients must be carefully monitored for serious infections or malignancies if they are also taking an anti-TNF-α drug, have chronic infections, or are otherwise immunosuppressed.

IMMUNOLOGIC REACTIONS TO DRUGS & DRUG ALLERGY

The basic immune mechanism and the ways in which it can be suppressed or stimulated by drugs have been discussed in previous sections of this chapter. Drugs also activate the immune system in undesirable ways that are manifested as adverse drug reactions. These reactions are generally grouped in a broad classification as "drug allergy." Indeed, many drug reactions such as those to penicillin, iodides, phenytoin, and sulfonamides are allergic in nature. These drug reactions are manifested as skin eruptions, edema, anaphylactoid reactions, glomerulonephritis, fever, and eosinophilia.

Drug reactions mediated by immune responses can have several different mechanisms. Thus, any of the four major types of hypersensitivity discussed earlier in this chapter (pages 981-982) can be associated with allergic drug reactions:

- **Type I:** IgE-mediated acute allergic reactions to stings, pollens, and drugs, including anaphylaxis, urticaria, and angioedema. IgE is fixed to tissue mast cells and blood basophils, and after interaction with antigen the cells release potent mediators.
- **Type II:** Drugs often modify host proteins, thereby eliciting antibody responses to the modified protein. These allergic responses involve IgG or IgM in which the antibody becomes fixed to a host cell, which is then subject to complement-dependent lysis or to antibody-dependent cellular cytotoxicity.
- **Type III:** Drugs may cause serum sickness, which involves immune complexes containing IgG complexed with a foreign antigen and is a multisystem complement-dependent vasculitis that may also result in urticaria.
- **Type IV:** Cell-mediated allergy is the mechanism involved in allergic contact dermatitis from topically applied drugs or induration of the skin at the site of an antigen injected intradermally.

In some drug reactions, several of these hypersensitivity responses may occur simultaneously. Some adverse reactions to drugs may be mistakenly classified as allergic or immune when they are actually genetic deficiency states or are idiosyncratic and not mediated by immune mechanisms (eg, hemolysis due to primaquine in glucose-6-phosphate dehydrogenase deficiency, or aplastic anemia caused by chloramphenicol).

IMMEDIATE (TYPE I) DRUG ALLERGY

Type I (immediate) sensitivity allergy to certain drugs occurs when the drug, not capable of inducing an immune response by itself, covalently links to a host carrier protein (hapten). When this happens, the immune system detects the drug-hapten conjugate as "modified self" and responds by generating IgE antibodies specific for the drug-hapten. It is not known why some people mount an IgE response to a drug, while others mount IgG responses. Under the influence of IL-4, IL-5, and IL-13 secreted by TH2 cells, B cells specific for the drug secrete IgE antibody. The mechanism for IgE-mediated immediate hypersensitivity is diagrammed in Figure 55–5.

Fixation of the IgE antibody to high-affinity Fc receptors (FcεRs) on blood basophils or their tissue equivalent (mast cells) sets the stage for an acute allergic reaction. The most important sites for mast cell distribution are skin, nasal epithelium, lung, and gastrointestinal tract. When the offending drug is reintroduced into the body, it binds and cross-links basophil and mast cell-surface IgE to signal release of the mediators (eg, histamine, leukotrienes; see Chapters 16 and 18) from granules. Mediator release is associated with calcium influx and a fall in intracellular cAMP within the mast cell. Many of the drugs that block mediator release appear to act through the cAMP mechanism (eg, catecholamines, glucocorticoids, theophylline), others block histamine release, and still others block histamine receptors. Other vasoactive substances such as kinins may also be generated during histamine release. These mediators initiate immediate vascular smooth muscle relaxation, increased vascular permeability, hypotension, edema, and bronchoconstriction.

Drug Treatment of Immediate Allergy

One can test an individual for possible sensitivity to a drug by a simple scratch test, ie, by applying an extremely dilute solution of the drug to the skin and making a scratch with the tip of a needle. If allergy is present, an immediate (within 10–15 minutes) wheal (edema) and flare (increased blood flow) will occur. However, skin tests may be negative in spite of IgE hypersensitivity to a hapten or to a metabolic product of the drug, especially if the patient is taking steroids or antihistamines.

Drugs that modify allergic responses act at several links in this chain of events. Prednisone, often used in severe allergic reactions, is immunosuppressive; it blocks proliferation of the IgE-producing clones and inhibits IL-4 production by T helper cells in the IgE response, since glucocorticoids are generally toxic to lymphocytes. In the efferent limb of the allergic response, isoproterenol, epinephrine, and theophylline reduce the release of mediators from mast cells and basophils and produce bronchodilation. Epinephrine opposes histamine; it relaxes bronchiolar smooth muscle and contracts vascular muscle, relieving both bronchospasm and hypotension. The antihistamines competitively inhibit histamine, which would otherwise produce bronchoconstriction and increased capillary permeability in the end organ. Glucocorticoids may also act to reduce tissue injury and edema in the inflamed tissue, as well as facilitating the actions of catecholamines in cells that may have become refractory to epinephrine or isoproterenol. Several agents directed toward the inhibition of leukotrienes may be useful in acute allergic and inflammatory disorders (see Chapter 20).

Desensitization to Drugs

When reasonable alternatives are not available, certain drugs (eg, penicillin, insulin) must be used for life-threatening illnesses even in the presence of known allergic sensitivity. In such cases, desensitization (also called hyposensitization) can sometimes be accomplished by starting with very small doses of the drug and gradually

increasing the dose over a period of hours to the full therapeutic range (see Chapter 43). This practice is hazardous and must be performed under direct medical supervision, as anaphylaxis may occur before desensitization has been achieved. It is thought that slow and progressive administration of the drug gradually binds all available IgE on mast cells, triggering a gradual release of granules. Once all of the IgE on the mast cell surfaces has been bound and the cells have been degranulated, therapeutic doses of the offending drug may be given with minimal further immune reaction. Therefore, a patient is only desensitized during administration of the drug.

AUTOIMMUNE (TYPE II) REACTIONS TO DRUGS

Certain autoimmune syndromes can be induced by drugs. Examples include systemic lupus erythematosus following hydralazine or procainamide therapy, "lupoid hepatitis" due to cathartic sensitivity, autoimmune hemolytic anemia resulting from methyldopa administration, thrombocytopenic purpura due to quinidine, and agranulocytosis due to a variety of drugs. As indicated in other chapters of this book, a number of drugs are associated with type I and type II reactions. In these drug-induced autoimmune states, IgG antibodies bind to drug-modified tissue and are destroyed by the complement system or by phagocytic cells with Fc receptors. Fortunately, autoimmune reactions to drugs usually subside within several months after the offending drug is withdrawn. Immunosuppressive therapy is warranted only when the autoimmune response is unusually severe.

SERUM SICKNESS & VASCULITIC (TYPE III) REACTIONS

Immunologic reactions to drugs resulting in serum sickness are more common than immediate anaphylactic responses, but type II and type III hypersensitivities often overlap. The clinical features of serum sickness include urticarial and erythematous skin eruptions, arthralgia or arthritis, lymphadenopathy, glomerulonephritis, peripheral edema, and fever. The reactions generally last 6–12 days and usually subside once the offending drug is eliminated. Antibodies of the IgM or IgG class are usually involved. The mechanism of tissue injury is immune complex formation and deposition on basement membranes (eg, lung, kidney), followed by complement activation and infiltration of leukocytes, causing tissue destruction. Glucocorticoids are useful in attenuating severe serum sickness reactions to drugs. In severe cases plasmapheresis can be used to remove the offending drug and immune complexes from circulation.

Immune vasculitis can also be induced by drugs. The sulfonamides, penicillin, thiouracil, anticonvulsants, and iodides have all been implicated in the initiation of hypersensitivity angiitis. Erythema multiforme is a relatively mild vasculitic skin disorder that may be secondary to drug hypersensitivity. Stevens-Johnson syndrome is probably a more severe form of this hypersensitivity reaction and consists of erythema multiforme, arthritis, nephritis, central nervous system abnormalities, and myocarditis. It has frequently been associated with sulfonamide therapy. Administration of nonhuman monoclonal or polyclonal antibodies such as rattlesnake antivenin may cause serum sickness.

PREPARATIONS AVAILABLE*

Abatacept (Orencia)
Parenteral: 250 mg/vial lyophilized powder

Abciximab (ReoPro)
Parenteral: 2 mg/mL solution for IV injection

Adalimumab (Humira)
Parenteral: 20, 40 mg/vial for SC injection

Alefacept (Amevive)
Parenteral: 15 mg for IV injection

Alemtuzumab (Campath)
Parenteral: 30 mg/mL vial for IV injection

Anakinra (Kineret)
Parenteral: 100 mg/mL prefilled glass syringes for SC injection

Antithymocyte globulin (Thymoglobulin)
Parenteral: 25 mg/vial for IV injection

Azathioprine (generic, Imuran)
Oral: 50 mg tablets
Parenteral: 100 mg/vial for IV injection

Basiliximab (Simulect)
Parenteral: 20 mg powder; reconstitute for IV injection

Bevacizumab (Avastin)
Parenteral: 25 mg/mL for injection

Canakinumab (Ilaris)
Parenteral: 180 mg lyophilized powder for SC injection

Certolizumab (Cimzia)
Parenteral: 200 mg powder for SC injection

Cetuximab (Erbitux)
Parenteral: 2 mg/mL in 50 mL vials

Cyclosporine (Sandimmune, Neoral, SangCya)
Oral: 25, 100 mg capsules; 100 mg/mL solution
Parenteral: 50 mg/mL for IV administration

Daclizumab (Zenapax)
Parenteral: 25 mg/5 mL vial for IV infusion

Denileukin dititox (Ontak)
Parenteral: 150 mcg/mL for SC injection

Denosumab (Prolia)
Parenteral: 60 mg/mL for SC injection

Etanercept (Enbrel)
Parenteral: 25, 50 mg lyophilized powder for SC injection

Golimumab (Simponi)
Parenteral: 50 mg/0.5 mL prefilled syringes for SC injection

Ibritumomab tiuxetan (Zevalin)
Parenteral: 3.2 mg/2 mL for injection

Immune globulin intravenous [IGIV] (various)
Parenteral: 5, 10% solutions; 2.5, 5, 6, 10, 12 g powder for injection

Infliximab (Remicade)
Parenteral: 100 mg lyophilized powder for IV injection

Interferon alfa-2a (Roferon)
Parenteral: 3, 6, 9 million IU

Interferon alfa-2b (Intron-A)
Parenteral: 3–50 million units/vial

Interferon beta-1a (Avonex, Rebif)
Parenteral: 22, 33, 44 mcg powder for IV injection

Interferon beta-1b (Betaseron, Extavia)
Parenteral: 0.3 mg powder for SC injection

Interferon gamma-1b (Actimmune)
Parenteral: 100 mcg vials

Interleukin-2 [IL-2, aldesleukin] (Proleukin)
Parenteral: 22 million unit vials

Leflunomide (Arava)
Oral: 10, 20, 100 mg tablets

Lenalidomide (Revlimid)
Oral: 5, 10, 15, mg capsules

Lymphocyte immune globulin (Atgam)
Parenteral: 50 mg/mL for injection (in 5 mL ampules)

Muromonab-CD3 [OKT3] (Orthoclone OKT3)
Parenteral: 5 mg/5 mL ampule for injection

Mycophenolate mofetil (CellCept, Myfortic)
Oral: 250 mg capsules; 500 mg tablets; 200 mg powder for suspension; 180, 360 mg delayed-release tablets
Parenteral: 500 mg powder; reconstitute for injection

Natalizumab (Tysabri)
Parenteral: 300 mg/15 mL for dilution and IV infusion

Ofatumumab (Arzerra)
Parenteral: 100 mg/5 mL vial; dilute for IV infusion

Omalizumab (Xolair)
Parenteral: 150 mg powder for SC injection

Panitumumab (Vectibix)
Parenteral: single-use 20 mg/mL vials

Pegademase bovine (Adagen)
Parenteral: 250 units/mL for IM injection
Note: Pegademase is bovine adenosine deaminase.

Pegaptanib (Macugen)
Parenteral: 0.3 mL for intravitreal injection

Peginterferon alfa-2a (Pegasys)
Parenteral: 180 mcg/mL

Peginterferon alfa-2b (PEG-Intron)
Parenteral: 50, 80, 120, 150 mcg/0.5 mL

Ranibizumab (Lucentis)
Parenteral: 10 mg/mL for intravitreal injection

Rh_o(D) immune globulin micro-dose (RhoGam, others)
Parenteral: in single-dose and micro-dose vials

Rilonacept (Arcalyst)
Parenteral: 220 mg lyophilized powder for SC injection

Rituximab (Rituxan)
Parenteral: 10 mg/mL for IV infusion

Sirolimus (Rapamune)
Oral: 1, 2 mg tablets; 1 mg/mL solution

Tacrolimus [FK 506] (Prograf)
Oral: 0.5, 1, 5 mg capsules
Parenteral: 5 mg/mL
Topical (Protopic): 0.03%, 0.1% ointment

Thalidomide (Thalomid)
Oral: 50, 100, 200 mg capsules
Note: Thalidomide is labeled for use only in erythema nodosum leprosum in the USA.

Tocilizumab (Actemra)
Parenteral: 20 mg/mL vials for dilution and IV infusion

Trastuzumab (Herceptin)
Parenteral: 440 mg powder; reconstitute for IV infusion

Ustekinumab (Stelara)
Parenteral: 45 mg/0.5 mL, 90 mg/mL in prefilled syringes for SC injection

*Several drugs discussed in this chapter are available as orphan drugs but are not listed here. Other drugs not listed here will be found in other chapters (see Index).

REFERENCES

General Immunology

Bonneville M et al: γδ T cell effector functions: A blend of innate programming and acquired plasticity. Nat Rev Immunol 2010;10:467.

Kumar H, Kawai T, Akira S: Toll-like receptors and innate immunity. Biochem Biophys Res Comm 2009;388:621.

Levinson WE, Jawetz E: *Medical Microbiology and Immunology,* 7th ed. McGraw-Hill, 2008.

Murphy KM, Travers P, Walport M (editors): *Janeway's Immunobiology,* 7th ed. Garland Science, 2008.

Thornton AM et al: Expression of helios, an ikaros transcription factor family member, differentiates thymic-derived from peripherally induced Foxp3+ T regulatory cells. J Immunol 2010;184:3433.

Hypersensitivity

Hausmann O: Drug hypersensitivity reactions involving skin. Handbk Exper Pharmacol 2010;196:29.

Phillips EJ: Pharmacogenetics of drug hypersensitivity. Pharmacogenomics 2010;11:973.

Autoimmunity

Bousvaros A: Use of immunomodulators and biologic therapies in children with inflammatory bowel disease. Expert Rev Clin Immunol 2010;6:659.

Carroll WM: Clinical trials of multiple sclerosis therapies: Improvements to demonstrate long-term patient benefit. Mult Scler 2009;15:951.

Kircik LH et al: How and when to use biologics in psoriasis. J Drugs Dermatol 2010;9:s106.

La Cava A: Anticytokine therapies in systemic lupus erythematosus. Immunotherapy 2010;2:575.

Ma MH et al: Remission in early rheumatoid arthritis. J Rheumatol 2010;37:1444.

Immunodeficiency Diseases

Wood PM: Primary antibody deficiency syndromes. Curr Opin Hematol 2010;17:356.

Immunosuppressive Agents

Braun J: Optimal administration and dosage of methotrexate. Clin Exp Rheumatol 2010;28:S46.

Galustian C: The anticancer agents lenalidomide and pomalidomide inhibit the proliferation and function of T regulatory cells. Cancer Immunol Immunother 2009;58:1033.

Li S, Gill N, Lentzch S: Recent advances of IMiDs in cancer therapy. Curr Opin Oncol 2010;22:579.

Ponticelli C: Calcineurin inhibitors in renal transplantation still needed but in reduced doses: A review. Transplant Proc 2010;42:2205.

Vicari-Christensen M: Tacrolimus: Review of pharmacokinetics, pharmacodynamics, and pharmacogenetics to facilitate practitioners' understanding and offer strategies for educating patients and promoting adherence. Prog Transplant 2009;19:277.

Zhou H: Updates of mTOR inhibitors. Anticancer Agents Med Chem 2010;10:571.

Antilymphocyte Globulin & Monoclonal Antibodies

Cummings SR: Denosumab for prevention of fractures in postmenopausal women with osteoporosis. N Engl J Med 2009;361:756.

Gürcan HM: Information for healthcare providers on general features of IGIV with emphasis on differences between commercially available products. Autoimmunity Rev 2010;9:553.

Nelson AL: Development trends for human monoclonal antibody therapeutics. Nat Rev Drug Discov 2010;9:767.

Taylor PC: Pharmacology of TNF blockade in rheumatoid arthritis and other chronic inflammatory diseases. Curr Opin Pharmacol 2010;10:308.

Weiner LM: Monoclonal antibodies: Versatile platforms for cancer immunotherapy. Nat Rev Immunol 2010;10:317.

Cytokines

Foster GR: Pegylated interferons for the treatment of chronic hepatitis C: Pharmacological and clinical differences between peginterferon-alpha-2a and peginterferon-alpha-2b. Drugs 2010;70:147.

Gabay C: IL-1 pathways in inflammation and human diseases. Nat Rev Rheumatol 2010;6:232.

Drug Allergy

Hamilton RG: Human IgE antibody serology: A primer for the practicing North American allergist/immunologist. J Allergy Clin Immunol 2010;126:33.

Khan DA: Drug allergy. J Allergy Clin Immunol 2010;125:S126.

CASE STUDY ANSWER

Within 24–72 hours postpartum, the woman should be given a 2-mL intramuscular injection of 300 mcg anti-Rh_o(D) immune globulin. This will clear any fetal Rh-positive red cells from her circulation so she does not generate anti-Rh_o(D) B cells that might jeopardize any future pregnancy.