PART 11

Travel Medicine and Expeditions

CHAPTER 79

Travel Medicine

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International travelers, particularly those participating in wilderness and outdoors activities, have unique health needs based largely on their underlying health and specific geographic destination.[64] Exposure to unfamiliar cultures, poor sanitation, and harsh environments may have a deleterious effect on health and interfere with the purpose and enjoyment of the trip.

The multidisciplinary specialty of travel medicine shares principles with the fields of public health, infectious diseases, tropical medicine, environmental medicine, and wilderness medicine. Travel medicine integrates features of these disciplines with geographic and chronologic data to formulate an approach to health risk assessment for a given journey.[67]

SOURCES OF INFORMATION

As a basic introduction to travel medicine, this chapter focuses on advice for the healthy adult traveler from the United States. Closely related topics are covered extensively in other chapters. Children and unhealthy travelers are beyond the scope of this chapter. Excellent information about travel medicine–related vaccines for children has been published,[72,88] and reference tables for both drugs and vaccines can be found at http://www.istm.org. A published review on the approach to travelers with underlying medical conditions is available in the *International Journal of Antimicrobial Agents*.[44]

The U.S. Centers for Disease Control and Prevention (CDC) publishes several authoritative sources of information on travel medicine. *Health Information for International Travel,* commonly called the "Yellow Book," is updated annually. Two other periodicals, the weekly *Morbidity and Mortality Weekly Report* (or *MMWR*) and *Summary of Health Information for International Travel* (the "Blue Sheet," published biweekly), provide updated information on the status of immunization recommendations, worldwide disease outbreaks, and changes in health conditions.

A reliable way to obtain current travel health information, including vaccine requirements, malaria chemoprophylaxis, and disease outbreaks for various regions of the world, is to consult the CDC Database of Health Information for International Travel website (http://www.cdc.gov/travel/yb/index.htm). For nonmedical information of interest to the traveler, the U.S. Department of State can be accessed at http://travel.state.gov/. (See Resources for Travel Medicine Information, later.)

If an extended stay in a given country is planned, American travelers should register with the U.S. Smart Traveler Enrollment Program (STEP) before arriving in the foreign country. This will allow the traveler to receive important information from the embassy regarding safety conditions in the destination country, such as travel warnings and severe weather updates. It will also allow the U.S. embassy, family, and friends to contact a traveler in the event of an emergency. American travelers abroad who experience any emergency should contact the nearest U.S. consulate or embassy or call the U.S. Department of State, which can help provide additional assistance, information regarding logistics, and emergency planning.

Several months before departure, travelers should ascertain whether their health insurance policies cover the costs of hospitalization, treatment, and emergency evacuation back to the United States for illness or injuries occurring abroad. Travelers should obtain such a policy, particularly if their travel involves remote locations where medical care is marginal or nonexistent. For example, when trekking in the Himalayas, insurance that covers helicopter rescue evacuation is important. Air ambulance repatriation back to the United States for life-threatening emergencies may require a separate insurance policy. Depending on the insurer, chronic medical conditions may be excluded or covered only if they are certified to be under control for a period of time before departure. Elderly travelers may find it more difficult to obtain this type of medical insurance. Medicare generally only covers health care expenses arising in the United States and its territories. Some credit card services provide worldwide medical referrals and arrangements for emergency transportation for their cardholders, but do not actually cover the costs incurred. What the traveler needs is a short-term health insurance policy that specifically covers medical expenses and medical evacuation during foreign travel.

TRAVEL HEALTH RISK ASSESSMENT

Pretravel medical preparation should be individualized through review of the (1) geographic destination, duration, and purpose of the trip; (2) style of travel, including information about sanitation and environmental hazards; (3) underlying health of the traveler; and (4) available access to medical care during the trip (Box 79-1). Risk assessments should also include special considerations for environmental exposures, such as whether the traveler might be exposed to extreme weather conditions, high altitude, or aquatic activities.

In addition, discussions on immunizations, prevention of malaria, self-treatment of traveler's diarrhea, and prevention and treatment of common ailments, such as jet lag, motion sickness, sun exposure, altitude illness, and insect and animal bites, should be reviewed with the traveler when these issues are applicable. Some attention, at least in the form of patient education, should be given to address personal safety, sexually transmitted diseases, prevention of vehicular trauma, and emergency medical evacuation.

PRETRAVEL PREPARATIONS

Trips with multiple destinations and travel lasting longer than a few weeks increase the complexity of pretravel medical preparation. Extensive travel often mandates carrying travel medical kits that are more extensive, given that a traveler is more likely to become ill as time and number of destinations increase. Travelers who camp or live in small villages often have greater exposure to vectors of disease than do those staying in urban, air-conditioned hotels or resorts. If accommodations are deemed to be high risk for exposure to disease vectors, travelers should plan to take appropriate precautions. For example, portable bed nets and permethrin-containing sprays help protect against mosquitoes and other biting insects.

Teachers, students, missionaries, relief workers, agricultural consultants, field biologists, and adventure travelers are often considered high risk for exposure to endemic infectious diseases, such as hepatitis B, tuberculosis, and meningitis; insect-borne diseases, such as malaria, yellow fever, leishmaniasis, filariasis, plague, and typhus; and diseases associated with animal exposures, such as rabies, leptospirosis, and anthrax.

All travelers should be cautioned about blood-borne infections, such as those contracted through using contaminated needles, syringes, and other medical or dental devices or during

BOX 79-1 History for Travel Risk Assessment

Travel Details

Geographic itinerary
- Sequence of countries visited
- Urban versus rural travel

Duration and season of travel

Style of travel and accommodations
- Airline and resort hotel versus bus and camping

Reason for travel and planned activities
- Packaged tour versus business versus adventure

Access to competent medical care during travel

General and Special Personal Health Issues

General Health Status

Age and weight

Pregnant or lactating

History of routine immunizations

Allergies to drugs and vaccines

Medications taken on a regular basis

Special Medical Issues

History of travel immunizations

Impaired immunity from disease or treatment
- Human immunodeficiency virus (HIV)
- Transplantation
- Malignancy and its treatment
- Immunoglobulin A (IgA) deficiency
- Asplenia
- Use of immunocompromising drugs (e.g., corticosteroids)

Underlying medical or physical conditions
- Diabetes mellitus
- End-stage renal disease requiring dialysis
- Chronic obstructive pulmonary disease requiring oxygen therapy
- Heart disease, including recent myocardial infarction
- Gastrointestinal diseases, including cirrhosis
- Disability requiring special transport or accommodations

emergency medical or dental care, injections, tattoos, and transfusions. Travelers should be cautioned about sexually transmitted infections contracted during unprotected sexual encounters with new partners, especially with commercial sex workers. Gonorrhea and *Chlamydia* infection, common in the industrialized world, have worldwide distribution, including remote locations. Human immunodeficiency virus (HIV) infection, syphilis, chancroid, and lymphogranuloma venereum are more prevalent in the developing world.

Most international travelers should begin pretravel medical preparations 4 to 6 weeks before the date of departure so that multidose immunization schedules can be completed, protective immunity developed, and necessary medications and special supplies obtained. Medical preparations for an international trip that includes many tourist destinations are often uncomplicated for people in good health. However, advance planning and consultation with a travel medicine expert is recommended for people with allergies, special health needs (e.g., pregnancy, infancy, advanced age, disabilities), or chronic underlying health conditions (e.g., cardiovascular or respiratory disease, compromised immune system, diabetes, psychiatric disorder, renal failure, organ transplant, seizure disorder).

People who participate in global relief operations in regions affected by political unrest, war, terrorist activity, famine, or natural disaster should ideally prepare broadly for travel to any part of the world well in advance of possible deployment. These people often face unique exposures to diseases, in part because of impaired infrastructure at the destination. Health care workers traveling to West Africa to assist in caring for patients, such as those with Ebola virus disease, must plan to arrive with sufficient personal protective equipment to practice appropriate infection control precautions. Too frequently, volunteers anxious to help in the aftermath of a disaster, leave their home country poorly prepared to protect their own health.

Vaccine-preventable diseases (e.g., diphtheria, measles, polio, hepatitis, typhoid fever) and exotic infectious diseases (e.g., malaria, schistosomiasis, leishmaniasis, trichinosis) are important.[26,56] However, cardiovascular diseases and trauma account for more morbidity and mortality among American travelers and expatriates than do infectious diseases. This underscores the importance of not only addressing travel-specific health needs, but also seriously considering preparations to handle chronic illnesses.

Accident prevention is essential because injuries are the leading cause of preventable death among travelers. Road traffic accidents account for the majority of injury-related deaths.[122,123] If travelers consider driving an automobile while abroad, they must be aware of the possible differences in vehicle safety features, road conditions, and behavior of local drivers. Driving in even a developed country can be hazardous when signs cannot be read or the traffic patterns are reversed. If the traveler rides bicycles, mopeds, or motorcycles, he or she should wear a helmet. The traveler should avoid driving any vehicle at night and should never drink alcohol and drive. In addition to road traffic accidents, important causes of travel-related morbidity are injuries from falls, drowning, animal bites, fires, and poisonings.

Travelers should remain vigilant at all times to help guarantee personal safety. Even if statistical numbers are available for the incidence of certain illnesses or accidents during travel, it may be impossible to determine if the risk is high or low, because this may depend on the personal perception of the traveler.[56] People should consciously avoid risky situations that could lead to traumatic events such as sexual assault or kidnapping. Women traveling alone or under difficult circumstances must consider the possibility of sexual assault and plan to carry emergency contraception.[96] Up-to-date information on personal risk at specific destinations can be obtained from the U.S. Department of State website (http://www.state.gov).

Finally, travel advisers need to understand that culture shock generated by travel to remote areas might lead to psychological breakdown, especially if a person is traveling alone or with a person who has a psychiatric disorder.[56] Importantly, if travelers (before the trip) are made aware of the potential differences or absence of medical resources in a country, they may be more accepting, and they or their caregivers might cope more easily with the psychological impact of a medical emergency.

HAZARDS OF AIR TRAVEL

Changes in barometric pressure cause the majority of health-related problems during air travel. Although the cabin is pressurized to an altitude of approximately 1524 m (5000 feet), pilots can be authorized to climb to avoid threatening weather, resulting in an increase in cabin altitude to 2438 m (8000 feet). At this altitude, everyone is mildly hypoxic; however, a patient with underlying lung disease, such as chronic obstructive pulmonary disease (COPD), can become dangerously hypoxic. Pretravel assessments and trial exposures to lower fraction of inspired oxygen can help determine whether supplemental oxygen might be necessary during a flight. If that is the case, planning is needed because airlines often need several days to arrange supplemental O_2, and not all flights offer it. After a myocardial infarction, travelers are advised not to travel for at least 3 weeks.[44,101] Flying less than 12 to 18 hours after scuba diving may increase the risk of decompression sickness.[56]

Transmission of respiratory pathogens, such as *Mycobacterium tuberculosis*, is possible. However, because of the use of high-efficiency particulate air (HEPA) filters in passenger aircraft, the immediate risk is largely to travelers seated close to an infected person. Arthropods, such as mosquitoes, can transmit diseases such as malaria, dengue fever, and chikungunya virus infection during passenger airline travel, but such concerns are mitigated by disinfection practices followed by many airlines traveling in high-risk locations. Modern passenger airplanes are exposed to measurable cosmic radiation, which has been shown to pose a negligible risk to occasional travelers, but a potential risk to long-haul pilots and crew.[25]

JET LAG

Symptoms of fatigue, impaired concentration, performance, and sleep may occur when normal circadian rhythm is disrupted by travel across multiple (usually five or more) time zones.[25,128] In most people, more symptoms occur, and a longer period of adaptation is required, following eastward travel than with westward travel. The typical adjustment time is 1 day per hour of time zone change without intervention. Short-acting hypnotic medication, timed exposure to bright light, and melatonin have been used to shorten the period of adjustment.[25,128]

To avoid possible periods of amnesia associated with hypnotic agents,[85] these are best avoided during flight and should only be used when the traveler can schedule uninterrupted sleep during the time the drug is active. Any hypnotic, including benzodiazepines and the nonbenzodiazepine drugs zolpidem, zaleplon, and eszopiclone, should be used in the lowest effective dose. Such medications should probably be tried before travel to ensure tolerance. If desired, hypnotics should be taken for the first several nights after arrival in the new time zone and after return to the original time zone. Alcohol ingestion should be avoided because it interferes with rapid eye movement (REM) sleep.

Exposure to bright light on arrival to a new destination helps to "reset" the timing of melatonin production because the light suppresses melatonin production by the pineal gland. The specific recommendation is to seek exposure to bright sunlight in the evening after westward travel and in the morning after eastward travel. The recommendations become more complicated when travel exceeds eight time zones. Exposure too early to light might actually inhibit adaptation.[25,128]

To facilitate adaptation, melatonin may be taken at the new bedtime after eastward travel (and in the second half of the night after westward travel) in a dose as low as 0.5 mg until one becomes adapted to the new time.[57,107] In the United States, melatonin is a dietary supplement and may be contaminated with impurities, so its potency is not guaranteed.[103]

Based on a review of jet lag,[107] a summary of recommendations follows, depending on whether a person is traveling westward or eastward.

Before Travel

1. For a westward journey, shift the timing of sleep to 1 to 2 hours later for a few days before the trip; seek exposure to bright light in the evening.
2. For traveling eastward, shift the timing of sleep to 1 to 2 hours earlier for a few days before the trip; seek exposure to bright light in the morning.
3. Try to get an adequate amount of sleep.

In Flight

1. Try to be comfortable.
2. Drink plenty of water to stay hydrated.
3. Do not drink caffeine if you want to sleep.
4. Consider a short-acting sleep medication. Do not take sleep medication combined with alcohol, or if there is a risk for deep vein thrombosis.

On Arrival

1. Expect to have trouble sleeping until you become adjusted to local time.
2. If you are sleep deprived, take a nap after arrival. Continue to take daytime naps if you are sleepy, but keep them as short as possible to avoid ruining nighttime sleep.
3. Consider using sleep medication at bedtime for a few nights until you are adjusted to local time.
4. Melatonin may be taken at the new bedtime after eastward travel (and in the second half of the night after westward travel) in a dose as low as 0.5 mg until one becomes adapted to the new time.
5. Seek exposure to bright light in the evening if traveling westward. Seek exposure to bright light in the morning if traveling eastward.
   a. However, after westward travel across more than eight time zones, for the first 2 days after arrival, avoid bright light for 2 to 3 hours before dusk. Starting on the third day, seek exposure to bright light in the evening.
   b. After eastward travel exceeding eight time zones, for the first 2 days after arrival, avoid bright light for the first 2 to 3 hours after dawn, then starting on the third day, seek exposure to bright light in the morning.
6. Avoid caffeine after midday because it may interfere with sleep at night.

DEEP VEIN THROMBOSIS

Deep vein thrombosis (DVT) and its associated risk for pulmonary embolism are recognized as potential complications of flights that last for 6 or more hours.[111,112] DVT occurs more often in persons using oral contraceptives and in those with cardiovascular risk factors, active malignancy, or recent surgery.[20,51,79,81] Pulmonary embolism occurs in only 1 to 2 travelers per 1 million long-haul flights.[68] On the other hand, up to 10% of travelers who were not using support stockings sustained asymptomatic DVT in the calf after a flight of 8 hours or longer.[112]

As safety permits during long-haul flights, travelers should be encouraged to move frequently about the cabin. If this is not possible, isometric exercise is recommended. Using below-the-knee support stockings is encouraged; low-molecular-weight heparin may be used in high-risk travelers under the guidance of the traveler's primary care physician. Aspirin is not recommended because it does not appear to reduce the risk of DVT.[32]

IMMUNIZATIONS FOR TRAVEL

Immunizations may be divided into three categories: required, recommended, and routine. Table 79-1 details vaccine schedules and booster intervals for adult travelers who are assumed to have received the primary series of routine vaccines as children.[22,87,99] Vaccinations for traveling children can be found in tables referenced in Resources for Travel Medicine Information (see later). The international traveler should have all current immunizations recorded in a World Health Organization (WHO) International Certificate of Vaccination. This yellow document is recognized

TABLE 79-1 Vaccines and Immunoglobulin for Adult Travelers Who Completed Childhood Immunizations

Vaccine	Route (Dose)	Schedule	Side Effects, Precautions, and Contraindications*	Comments
Hepatitis A (Havrix and Vaqta)	IM (1.0 mL)	Primary: 2 doses Additional booster doses: not recommended	Local reactions: <56% Fever: <5% Headache: 16%	Prevaccine hepatitis A serology may be cost-effective for some travelers (see text).
Hepatitis B (Recombivax HB and Engerix-B)	IM (adult and pediatric formulations)	Primary: 1 dose at 0, 1, and 6 months Booster: not routinely recommended Accelerated schedules (see text)	Local reaction: 3%-29% Fever: 1%-6%	

TABLE 79-1 Vaccines and Immunoglobulin for Adult Travelers Who Completed Childhood Immunizations—cont'd

Vaccine	Route (Dose)	Schedule	Side Effects, Precautions, and Contraindications*	Comments
Hepatitis A and B antigens combined (Twinrix)	IM (1.0 mL)	Primary: 1 dose at 0, 1, and 6 months Booster: not routinely recommended Accelerated schedules (see text)	Local reactions: approximately 56% Systemic reactions: similar to single-antigen products	Give at least 2 doses of vaccine before departure to provide protection against hepatitis A.
Influenza	IM (0.5 mL)	One dose of current vaccine annually	Local reactions: <33% Systemic reactions: occasional Allergic reaction: rare Avoid in those with history of anaphylaxis to eggs.	
Influenza (FluMist)	Intranasal (0.5 mL)	Primary: 1 dose per season	Mild upper respiratory tract symptoms: occasional Avoid in those with history of anaphylaxis to eggs, Guillain-Barré syndrome, or immunosuppression.	Approved for persons 5 to 49 years old
Japanese B encephalitis (Ixiaro)	IM (0.5 mL) 2 months to 3 years: 0.25 mL >3 years: 0.5 mL	Primary: 1 dose at 0 and 28 days Booster: >1 year following primary series, booster if continued risk		Ixiaro is a Vero cell culture–derived formulation. A single booster >1 year after completion of primary series if ongoing risk
Measles (monovalent or combined with rubella and mumps, MMR)	SC (0.5 mL)	Primary: 2 doses separated by at least 1 year Booster: none (Unless born prior to 1956; then see CDC recommendation.)	Fever, 5-21 days after vaccination: 5%-15% Transient rash: 5% Local reaction among those who received killed vaccine (1963-1967): 4%-55% Severe allergic reactions, CNS complications, thrombocytopenia (MMR): rare Avoid in pregnancy, immunocompromised hosts, and those with history of anaphylaxis to eggs or neomycin.	Do not give immune globulin within 3 months of vaccine dose. If MMR and yellow fever vaccine are not given simultaneously, separate by 28 days or longer.
Meningococcal polysaccharide-protein conjugate quadrivalent vaccine (Menactra)	IM (0.5 mL)	Primary: single dose Booster: not recommended for routine use; every 5 years recommended for ongoing risk	Local reactions: 10%-60% Systemic reactions: occasional fever, headache, and malaise	Replaces quadrivalent polysaccharide vaccine (Menomune)
Mumps	SC (0.5 mL)	Primary: 1 dose (usually as MMR) Booster: none	Mild allergic reactions: uncommon Parotitis: rare Avoid in pregnancy, immunocompromised hosts, and those with history of anaphylaxis to eggs or neomycin.	Do not give immune globulin within 3 months of vaccine dose. If MMR and yellow fever vaccine are not given simultaneously, separate by 28 days or longer.
Pneumococcal polysaccharide Conjugate vaccine (PCV 13)	SC or IM (0.5 mL)	Primary: single dose at age 65 or age 60 if high risk Booster: high-risk patients after 5 years from initial dose	Mild local reactions: approximately 50% Systemic symptoms: <1% Arthus-like reaction with booster doses occurs. Avoid in those with moderate to severe acute illness.	Opportunity to update routine vaccination in older travelers
Poliomyelitis	SC or IM (0.5 mL)	Booster: one adult dose	Local reactions: occasional	Additional boosters not recommended. Access CDC or WHO databases for current regions with polio transmission.

Continued

TABLE 79-1 Vaccines and Immunoglobulin for Adult Travelers Who Completed Childhood Immunizations—cont'd

Vaccine	Route (Dose)	Schedule	Side Effects, Precautions, and Contraindications*	Comments
Rabies Human diploid cell vaccine (HDCV); purified chick embryo cell (PCEC); rabies vaccine adsorbed (RVA)	IM (1.0 mL)	Preexposure: 1 dose at 0, 7, and 21 or 28 days Booster doses depend on ongoing risk and results of serology (see text)	Mild local or systemic reactions: occasional Immune complex–like reactions after booster dose of HDCV (2-21 days after vaccination): 6%	Target children in endemic areas who might not tell parents about bites.
Rubella	SC (0.5 mL)	Primary: 1 dose (usually as MMR) Booster: none	Transient arthralgias in adult women beginning 3-25 days after vaccination: up to 25% Arthritis: <2% Avoid in pregnancy, immunocompromised hosts, and those with history of anaphylaxis to neomycin.	Do not give immune globulin within 3 months of vaccine dose. If MMR and yellow fever vaccine are not given simultaneously, separate by 28 days or longer.
Tetanus- diphtheria (Td)	IM (0.5 mL)	Booster dose every 10 years	Local reactions: common Systemic symptoms: occasional Anaphylaxis: rare Arthus-like reactions possible after multiple previous boosters Avoid if Guillain-Barré syndrome occurs 6 weeks or earlier after previous dose.	Consider booster at 5 years for travelers to remote areas or regions without adequate health care facilities when sustaining punctures or other significant wounds is possible.
Tetanus-diphtheria with acellular pertussis (Tdap)	IM (0.5 mL)	One-time dose (wait at least 2 years since last Td), then resume Td every 10 years.	Similar to Td	Do not confuse Tdap with the pediatric formulation (TDaP), which can cause adverse reactions in adults.
Typhoid Ty21a	Oral capsules	Primary: 1 capsule every other day for 4 doses Booster: every 5 years if ongoing risk	Gastrointestinal upset or rash: infrequent Avoid in pregnancy and in persons with febrile illness, taking antibiotics, or in immunocompromised state.	Refrigerate capsules. If already taking mefloquine, separate doses by 24 hours.
Typhoid Vi polysaccharide	IM (0.5 mL)	Primary: single dose Booster: every 2 years if ongoing risk	Local reaction: 7% Headache: 16% Fever: <1%	
Varicella	SC (0.5 mL)	Primary: 2 doses at 4-week interval or longer. No booster	Local reactions: 20% Fever: 15% Localized or mild systemic varicella rash: 6% Avoid in immunocompromised hosts, if severe allergic reactions to gelatin or neomycin, or if serum immune globulin within 5 months.	Rare transmission of vaccine strain to susceptible hosts; therefore, avoid if close contacts are immunosuppressed.
Varicella-zoster virus (VZV) vaccine	SC (0.5 mL)	One dose		Recommended for all adults over 60 years old, including those with previous history of zoster Decreases the incidence of postherpetic neuralgia
Yellow fever	SC (0.5 mL)	Primary: single dose Booster: every 10 years	Mild headache, myalgia, fever (5-10 days after vaccination): 25% Immediate hypersensitivity: rare Viscerotropic syndrome or neurotropic disease: rare (see text) Avoid if allergic to eggs. Contraindicated in immunocompromised hosts	If person can eat eggs without a reaction, person can take vaccine.

Modified from information in Centers for Disease Control and Prevention (CDC): *Health information for international travel*, 2014 (http://wwwnc.cdc.gov/travel/page/yellowbook-home-2014); and Hill DR, Ericsson CD, Pearson RD et al: Guidelines for the practice of travel medicine, *Clin Infect Dis* 43:1499, 2006.
IM, Intramuscularly; *SC*, subcutaneously.
*Moderate or severe acute illness with or without fever or a serious reaction to a previous dose is a contraindication to all vaccines.

BOX 79-2 Vaccination in HIV-Positive Adults

Generally Avoid
- Varicella-zoster virus (VZV) vaccine
- Bacille Calmette-Guérin (BCG) vaccine
- Oral polio vaccine
- Oral typhoid vaccine

Avoid if CD4+ Cells <200
- Yellow fever vaccine
- Measles vaccine

Give Routinely
- Tetanus/diphtheria (or Tdap) vaccine
- Hepatitis B vaccine
- *Streptococcus pneumoniae* vaccine
- *Haemophilus influenzae* type b (Hib) vaccine
- Influenza vaccine, yearly
- Hepatitis A vaccine

Give if Indicated for Travel
- Typhoid Vi vaccine
- Meningococcal vaccine
- Polio, IPV vaccine
- Rabies vaccine
- Japanese encephalitis
- Tick-borne encephalitis (JE) vaccine

worldwide and has a dedicated page for documentation of the yellow fever vaccine. Recent copies of the document do not contain a separate page for the cholera vaccine validation because the WHO officially removed cholera vaccination from the International Health Regulations in 1973. If given, cholera vaccination can be recorded in the space provided for "Other Vaccinations" in the newer booklets.

Contraindications to vaccinations are often overstated. In general, live-virus vaccines and attenuated bacterial vaccines are contraindicated during pregnancy and in persons with impaired immune systems due to medical conditions (e.g., HIV, asplenia, congenital immune deficiencies) or medical therapy (e.g., corticosteroids, cancer chemotherapy, radiation therapy, or immune suppression therapy in the organ transplant patient). Comprehensive review of contraindications to immunizations by underlying host deficiency is beyond the scope of this chapter; reviews are available.[44] Box 79-2 outlines vaccination practices for the patient with HIV, which is a reasonable approach to vaccination in most immunocompromised hosts, in whom live-virus and live-attenuated bacterial vaccines should generally be avoided.

REQUIRED TRAVEL VACCINES

"Required" immunizations are not only those regulated by WHO, but also those required by some countries. For example, yellow fever vaccine may be required for entry into some WHO member countries, whereas smallpox and cholera vaccinations are no longer required for international travel according to WHO regulations. However, some countries continue to "require" cholera vaccination in practice. Meningococcal vaccine is not required by WHO but is by certain countries; for example, Saudi Arabia requires meningococcal vaccination for persons arriving for the Hajj or Umrah pilgrimages.

Yellow Fever Vaccine

Yellow fever (YF) is a viral infection transmitted by mosquitoes in equatorial South America and Africa (Figure 79-1). YF vaccine is a live-attenuated viral vaccine that is highly protective.[83,131] It is given as a single dose for primary immunization; the booster interval is 10 years. According to WHO, a single dose of the vaccine is sufficient to confer lifelong immunity, but more data are needed documenting duration of immunity after vaccination. Because of age-related risk of encephalitis after immunization, most authorities agree that the YF vaccine is contraindicated in infants less than 6 months of age, and immunization should usually be delayed until the infant is 9 months or older.[33] The vaccine is generally not recommended for persons older than 60 years, immunocompromised, or pregnant. If the pregnant traveler cannot avoid or postpone travel to a highly endemic area, risk of the disease should be greater than the theoretical risk of adverse effects from the vaccine. A small case series demonstrated significant increase in relapse rates among travelers with multiple sclerosis (MS) who received YF vaccine, so unless there is a significant risk for YF, MS patients should not receive the vaccine.[45]

Three types of reactions to YF vaccine have been described. The most common is a general hypersensitivity or anaphylactic reaction to components of the vaccine. The vaccine includes proteins from chickens and eggs, because the virus is cultured in eggs. The vaccine is therefore contraindicated in persons with a history of anaphylactic reaction to chickens or eggs. If able to eat eggs without a reaction, the person can receive YF vaccine.

Vaccine-associated neurologic disease (YEL-AND) manifests as several distinct neurologic syndromes. These syndromes are caused either by virus entering the central nervous system (CNS) and causing infection, thereby resulting in neurotropic disease (i.e., meningoencephalitis), or by autoimmune damage to neuronal tissues causing syndromes such as Guillain-Barré or acute disseminated encephalomyelitis (ADEM).[116]

Vaccine-associated viscerotropic disease (YEL-AVD) has been reported in a small number of first-time recipients of YF vaccine.[29,116] This is a severe reaction that mimics fulminant YF infection, resulting in multiorgan failure and death. The disease is thought to be infection by the attenuated vaccine strain facilitated by an altered host response, rather than by a change in virulence of the vaccine strain. Persons who have successfully received a first dose of YF vaccine are unlikely to be at risk with a booster dose if they have remained immunocompetent hosts. Two potential risk factors for YEL-AVD are previous thymectomy and older age. Thymectomy was documented in four of the first 23 cases, but as of 2010 had not been documented in any subsequent case. The incidence of YEL-AVD in persons older than 60 is estimated at 1.4 to 1.8 cases per 100,000 doses, which is significantly higher than the estimated 0.3 to 0.4 cases per 100,000 doses in the general population.[116] Despite these two purported risks, the small number of cases makes accurate risk factor assessment difficult.[10,116]

Although complications from YF vaccine are rare, the potential lethality of YEL-AVD prompts careful risk assessment, especially when considering first-time vaccination in older travelers. Some countries may be listed as endemic for YF, but certain locations within the country may pose no risk. If a person for whom the vaccine is contraindicated (or not advised because the person is not truly at risk) must travel to a country where a YF vaccine is required for entry, then according to WHO regulations, a signed statement indicating that the YF vaccine could not be given because of medical contraindications should be acceptable in lieu of documented vaccination. The statement should be written on letterhead stationery and accompanied by authoritative stamps or seals. Contacting the embassy or consulate of the country may be necessary to help guarantee that the letter of waiver will be accepted.

Cholera Vaccine

Cholera is an intestinal infection caused by *Vibrio cholerae* that involves profuse secretory diarrhea. The injectable cholera vaccine is not very efficacious, even when the primary series of two doses given 1 week or more apart is received.[105] WHO no longer endorses a requirement for this vaccine before entry into any country. For countries that still require cholera vaccination for travelers arriving from cholera-endemic areas, recording a single cholera dose in the traveler's International Certificate of Vaccination should suffice to meet this regulation.

Travelers going to areas endemic or epidemic for cholera are encouraged to strictly follow food and water precautions intended to prevent all forms of travel-associated diarrhea. Oral killed and live-attenuated vaccines[97] are available in some countries, but at present, there are no standardized recommendations for use of cholera vaccines, although health care workers and relief workers traveling to higher-risk areas might be suitable candidates. Likewise, travelers to cholera-endemic areas who are achlorhydric or

have had a partial gastrectomy are logical candidates for the vaccine. Two oral, whole-cell killed vaccines are available. Dukoral (Crucell, The Netherlands), licensed in many European countries and Canada, is administered in two doses 1 to 6 weeks apart (three doses in children 2 to 6 years old). Shanchol (Shantha Biotechnics, India) is administered in two doses 2 weeks apart to persons more than 1 year old.[34]

Smallpox Vaccine

The requirement for smallpox vaccine for international travel was removed from WHO regulations in 1982. The CDC has embarked on an initiative to immunize health care providers, first responders, and others involved in bioterrorism preparedness, but the vaccine is not otherwise available, and travel is not considered a sufficient reason for vaccination.[113]

RECOMMENDED TRAVEL VACCINES

"Recommended" vaccines are those that are not routinely given during childhood in the United States but are advised for travelers based on the travel health risk assessment. Vaccines in this category include those for hepatitis A and B, typhoid fever, meningococcal meningitis, Japanese encephalitis virus, rabies, tick-borne encephalitis, varicella-zoster virus (VZV), influenza, and bacille Calmette-Guérin (BCG). The VZV vaccine is supposed to be used routinely in the United States, but for many adult U.S. travelers, it remains a vaccine that must be added. The influenza vaccine is often but not routinely used in children; it is recommended for many travelers. Although BCG vaccination is used in children in the developing world, it is not used in U.S. children. Some vaccines are now routinely recommended for children. These include hepatitis B (since 1991), hepatitis A (more recently in United States),[27] and meningococcal vaccine, which is recommended for all 11- to 12-year-olds and young adults before starting higher education. Because of these practices, in the future, more travelers will likely have been vaccinated with recommended vaccines.

Hepatitis A Vaccine

Hepatitis A is the second most common vaccine-preventable travel-associated infectious disease, after influenza, and hepatitis A virus (HAV) is the most common cause of viral hepatitis. In the absence of vaccination, HAV infection occurs in 6 to 30 persons per 100,000 travelers per month who visit high- and medium-endemic destinations.[132] Risk is high even among those residing in "first-class" accommodations. Adventure travelers who venture off usual tourist routes may be at increased risk compared with other groups of travelers. Although HAV infection is asymptomatic in young children and self-limited in most adults, it causes greater than 2% mortality in infected adults older than 40, considerable morbidity during travel, and lost productivity after travel. Vaccination against HAV should be considered for all travelers to regions with moderate to high endemicity.

Individuals who have a history of jaundice, who were born before 1950, or who were born or resided for lengthy periods in endemic regions are likely to have natural immunity to HAV.[120] They should be screened for immunoglobulin G (IgG) antibodies

FIGURE 79-1 **A**, Yellow fever vaccination recommendations in South America.

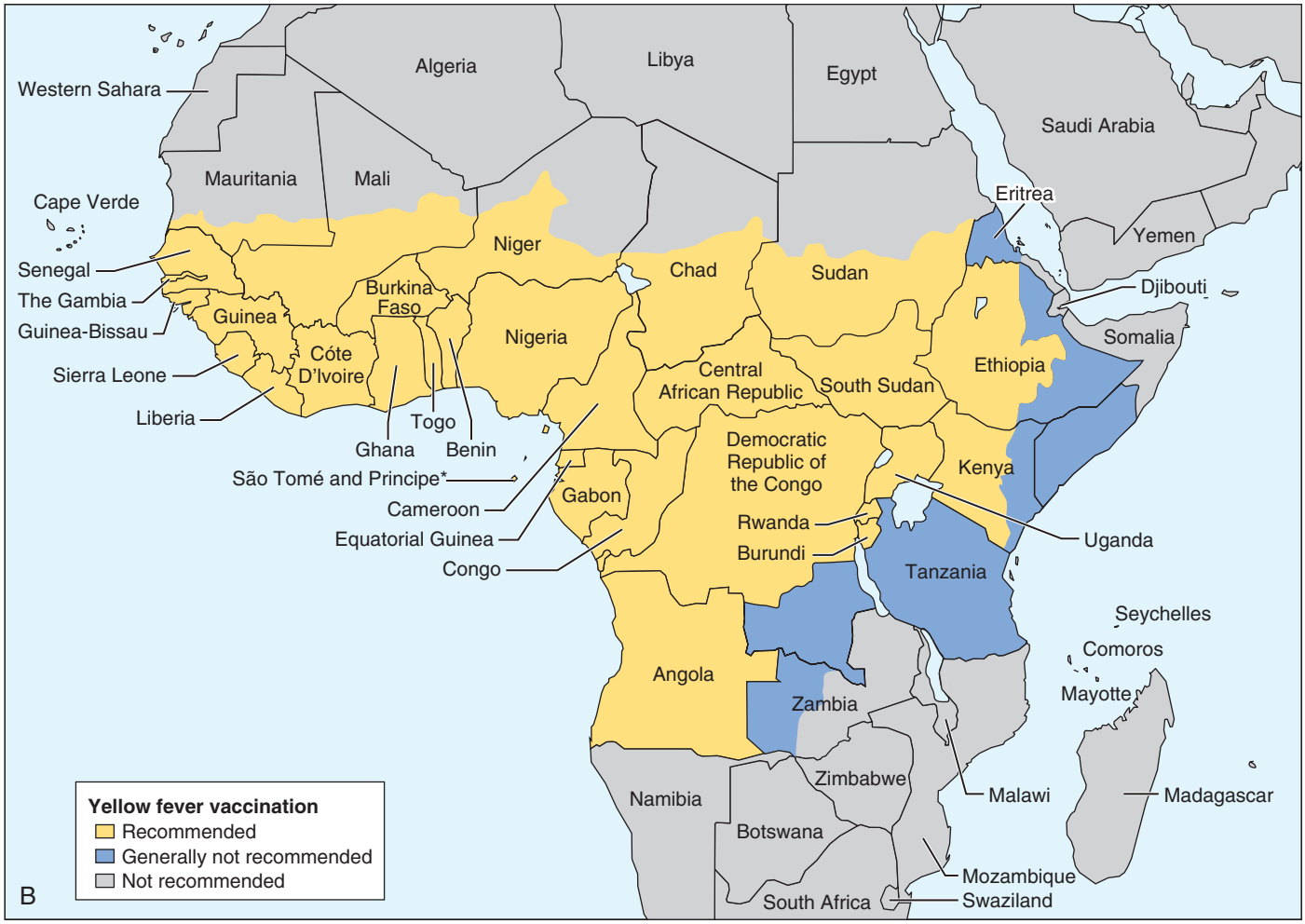

FIGURE 79-1, cont'd B, Yellow fever vaccination recommendations in Africa. *(From Centers for Disease Control and Prevention:* Health information for international travel, *2014.* http://wwwnc.cdc.gov/travel/yellowbook/2014/chapter-3-infectious-diseases-related-to-travel/yellow-fever.*)*

against HAV, because if these are present, it is possible to avoid the cost of vaccination, which is usually more expensive than serologic testing. However, because vaccination of HAV-immune persons is not associated with adverse consequences, a traveler who does not have time before departure to be tested should be vaccinated.

A single dose of monovalent hepatitis A vaccine leads to seroconversion of 80% by 2 weeks and 99% after 1 month following vaccination.[38,126,132] For most healthy people, one dose of the monovalent HAV vaccine administered at any time before departure should provide adequate protection. Immune globulin is seldom indicated, except in older individuals, in whom HAV infection is more life threatening, and persons who are immunocompromised and therefore might not respond to the vaccine.[38,132] Postexposure prophylaxis with immune globulin is recommended for nonimmunized persons who are exposed to HAV.[132]

The HAV vaccine products are thought to be interchangeable. After two full doses separated by 6 to 12 months, protection is likely lifelong, so booster doses are not recommended in immunocompetent travelers.[126] Travelers who fail to receive their second dose of HAV vaccine within 6 to 12 months should attempt to complete the series; however, protective antibody levels have been produced even when the second dose was given 8 years after the initial dose.[60]

Hepatitis B Vaccine

Hepatitis B vaccine was added to the list of vaccines recommended for routine immunization of U.S. children in 1991, and consideration should be given to vaccinating all U.S. adults regardless of travel. Risk to short-term travelers is low; however, travelers should be vaccinated when contact with body fluids or blood is possible (e.g., through sex or medical work), when it is anticipated that medical care might be received in a developing country, or if the person is a frequent short-term traveler. Long-term travelers and expatriates should be vaccinated.[58]

Two recombinant vaccines (Engerix-B and Recombivax HB) are thought to be interchangeable. A series started with one hepatitis B vaccine may be completed with another. The standard regimen for both vaccines is one dose at each of 0, 1, and 6 months. After any of the hepatitis B vaccination regimens, additional boosters are not recommended for normal hosts. Engerix-B is approved by the U.S. Food and Drug Administration (FDA) for an accelerated dosage schedule of 0, 1, and 2 months, with a booster dose at 12 months for long-lasting protection. Although a highly accelerated 3-week schedule is not FDA approved, literature supports dosing at 0, 7, and 21 days, with a 12-month booster with either licensed vaccine.[63,65] This regimen affords 65% protection at the end of 1 month and 100% seroconversion at 13 months. This is an attractive option for at-risk travelers who plan to depart in the next 3 to 4 weeks. An interrupted series can be completed without being restarted if the series cannot be completed before travel.

A combined hepatitis A and hepatitis B vaccine is dosed at 0, 1, and 6 months. Because a smaller dose of HAV antigen is used in this preparation, travelers must receive their second dose before travel for reliable protection. Literature supports a highly accelerated 3-week dosing regimen, with a 12-month booster using the combination vaccine.[89]

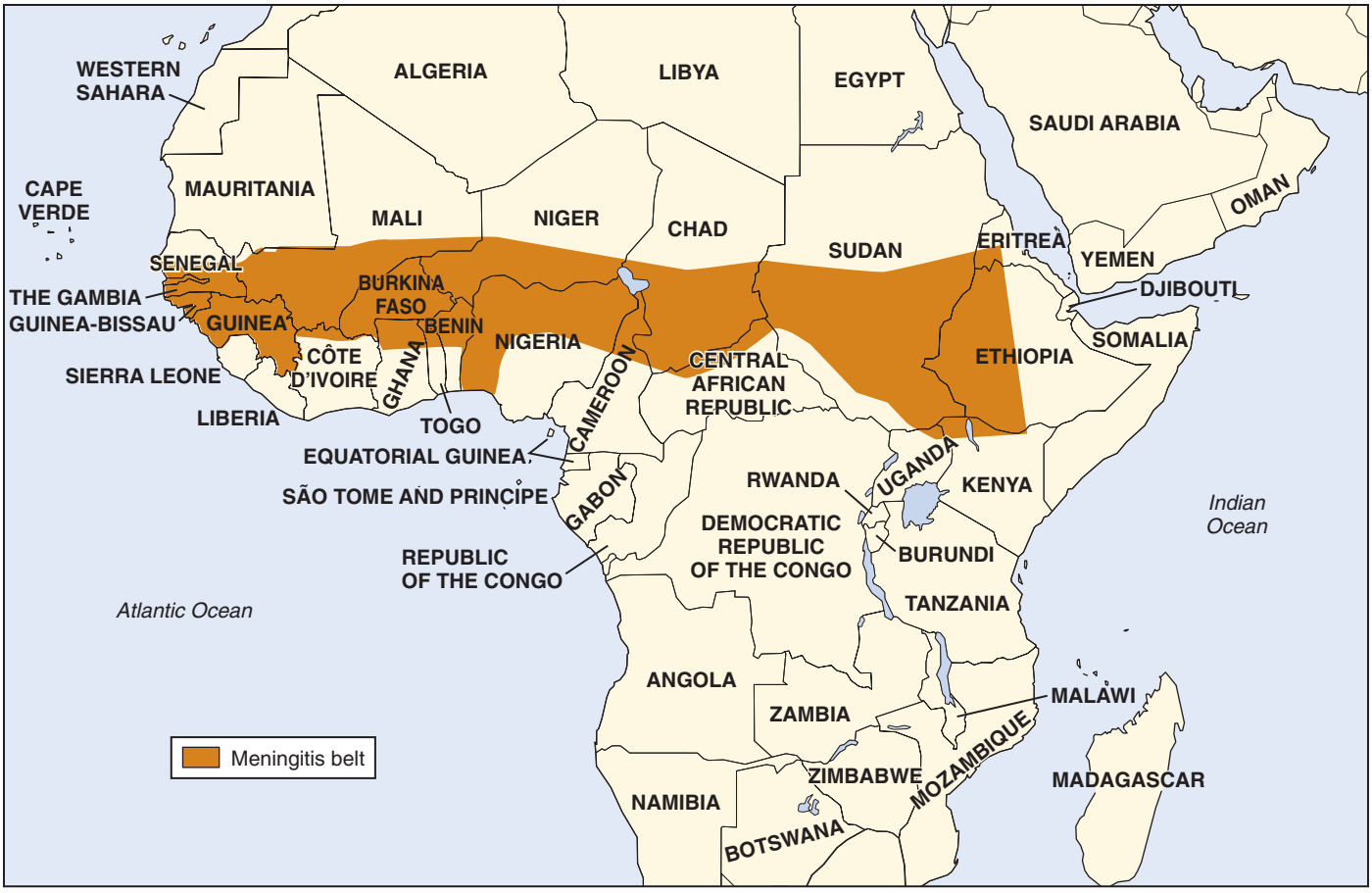

FIGURE 79-2 Meningitis belt. Consult details in the CDC Yellow Book for locations within each country where, and seasons when, pretravel vaccination is recommended. *(From Centers for Disease Control and Prevention:* Health information for international travel, *2014.* http://wwwnc.cdc.gov/travel/yellowbook/2014/chapter-3-infectious-diseases-related-to-travel/meningococcal-disease#3972.*)*

Typhoid Fever Vaccine

Typhoid is an insidious febrile illness caused by *Salmonella enterica* serotype Typhi. The incidence of typhoid fever among American travelers is estimated at 1 to 10 cases per 100,000 travelers.[95] Among reported cases in the United States., the majority were acquired during international travel.[71,75] The risk to travelers is highest among visitors to the Indian subcontinent, where the incidence is estimated at more than 100 cases per 100,000 native persons.[95] Travelers most at risk are those visiting friends and relatives (VFR). Visitors to Central and South America, Africa, and Asia should be considered for typhoid vaccination when they might be exposed to conditions of poor sanitation and hygiene, even for short periods.[23,118]

Increasing antibiotic resistance among *S. enterica* serotype Typhi infections is another reason to be vaccinated.[1,13] However, the current vaccines afford only 50% to 80% protection, and emergence of *S. enterica* serotype Paratyphi, against which protection is not afforded by current vaccines, underscores the importance of food and beverage hygiene among travelers.[75]

The two vaccines currently available offer a similar degree of protection. The parenteral purified Vi polysaccharide typhoid vaccine is administered as a single injection, with a booster recommended every 2 years. The oral Ty21a typhoid vaccine uses a live-attenuated strain of *S. enterica* serotype Typhi. One capsule is taken every other day for four doses (a three-dose regimen is recommended in Europe).[17] A booster regimen is recommended every 5 years.

Meningococcal Vaccine

Vaccine protection against meningococcal meningitis is recommended for long-term travelers to the sub-Saharan "meningitis belt"[27,36,100] (Figure 79-2). Short-term travelers to this region should receive vaccine if they will travel during the dry season (December to June) or have extensive contact with local people. The quadrivalent meningococcal vaccine is required for travel to Saudi Arabia for Umrah or the annual Hajj religious pilgrimages. Regardless of travel, the classic recommendation has been that young adults who will live in school dormitories and persons with complement deficiencies who will have prolonged contact with a local population, such as in a refugee camp, or with surgical or functional asplenia should be vaccinated. Travelers to regions where outbreaks are occurring should be vaccinated. Practitioners who do not subscribe to commercial information services that are routinely updated should check the CDC website (http://www.cdc.gov/travel) periodically to determine where epidemic disease of any causation is occurring.

Quadrivalent meningococcal polysaccharide vaccine induces immunity against serogroups A, C, Y, and W-135. A single dose appears to provide immunity for 5 years. However, a single-dose quadrivalent meningococcal polysaccharide-protein conjugate vaccine is the preferred vaccine for those older than 2 years, with a booster recommended every 5 years for ongoing risk.[37] Travelers who had previously been vaccinated with polysaccharide vaccine and need revaccination should receive a conjugate vaccine. However, neither the polysaccharide nor the conjugate vaccine provides immunity against serogroup B. The FDA recently approved a vaccine (Trumenba) active against four *Neisseria meningitidis* serogroup B strains prevalent in the United States, for use in adolescents and young adults age 10 to 25 years. It has not been recommended for travelers because *N. meningitides* serogroup B infections are rare in sub-Saharan Africa.[125]

Japanese Encephalitis Virus Vaccine

Japanese encephalitis (JE) is an arboviral infection transmitted by mosquitoes in Asia and Southeast Asia. Transmission is year-round in tropical and subtropical areas and during the late spring, summer, and early fall in temperate climates. JE virus is not considered a risk for short-term travelers visiting usual tourist destinations in urban and developed resort areas.[47]

Personal protective measures to prevent mosquito bites can greatly reduce risk of infection. The overall incidence of JE among people from nonendemic countries traveling to Asia is estimated at less than 1 case per 1 million travelers. However, travelers who stay for prolonged periods (including expatriates) in rural areas with active JE virus transmission are likely to be at a risk similar to that of the susceptible resident population (~5 to 50 cases per 100,000 children per year). Persons on short trips may be at risk if they are staying in rural areas or have high mosquito exposure.[47] Thus, vaccination should be offered to both long- and short-term visitors to rural areas when travel will occur during transmission season, particularly when mosquito exposure might be high and significant time will be spent outdoors.

Two vaccines (JE-Vax, Ixiaro) are FDA approved, but only Ixiaro, a Vero cell culture–derived formulation, is available. Previously recommended only for use in persons 17 years or older, Ixiaro is now approved by the FDA for use in children 2 months or older. A single dose of Ixiaro has been shown to effectively boost antibody levels in persons previously vaccinated with JE-Vax, but the duration of protection is unknown. The primary immunization schedule for Ixiaro is two doses, on days 0 and 28, with therapy completed 1 week or longer before travel. In patients receiving JE-Vax, fewer than 1% of patients reported redness, swelling, tenderness, and pain after injection.[47] Systemic adverse events reported included headache (26%), myalgias (21%), influenza-like illness (13%), and fatigue (13%).

The single-dose, live-attenuated SA 14-14-2 JE vaccine manufactured in Chengdu, China (available in destination countries such as Nepal) has been effectively used extensively in South and Southeast Asia for decades with an acceptable safety profile.

Rabies Vaccine

Rabies is an acute, progressive encephalomyelitis caused by neurotropic viruses in the family Rhabdoviridae[56] (see Chapter 31). Although rabies is endemic in much of the world, the risk of rabies for most travelers is very low.[55] Avoidance of dog bites eliminates much of the risk.[77] Other animal species important for transmission of rabies to travelers include monkeys, mongooses, bats, and foxes. Preexposure rabies immunization should be considered for rural travelers, particularly adventure travelers who go to remote areas, persons with occupational (veterinarians) or recreational (spelunkers) exposure, and expatriate workers, missionaries, and their families living in countries where rabies is a recognized risk. Children should be targeted for pre-exposure vaccination in high-risk regions, because they may not tell their parents when they have been bitten or exposed to rabies virus.

Any of the three tissue culture–derived inactivated virus rabies vaccines can be administered intramuscularly in the deltoid (not gluteal) muscle in a pre-exposure schedule of 0, 7, and 21 (or 28) days.[77] For persons who continue to be at risk of exposure, a booster can be given every 2 years, or less frequently based on annual serology testing. For persons engaging in high-risk activities (veterinarians, cavers, adventure travelers to Asia and Africa), serologic testing every 2 years and booster vaccine, if necessary, are recommended.

In the event of an exposure, the vaccinated traveler must understand how to clean the wound thoroughly and immediately seek two additional doses of vaccine. Pre-exposure vaccination obviates the need for postexposure administration of rabies immune globulin (RIG), which is an important consideration because RIG may be very difficult to obtain abroad.[77] Persons who are exposed without having had pre-exposure rabies vaccination require both RIG and a four-dose course of rabies vaccine given over 14 days, as recommended by the U.S. Advisory Committee on Immunization Practices.[104] Persons with immunosuppression should still receive five doses of the vaccine.[77]

Mild local reactions (pain at the injection site, redness, swelling, and induration) to rabies vaccine occur in 60% to 89% of persons receiving human diploid cell vaccine (HDCV) and 11% to 57% of persons receiving purified chick embryo cell vaccine (PCECV). Adverse reactions are self-limited, lasting a few days.[77] For persons receiving HDCV and PCECV, 6.8% to 55.6% and 0% to 31% of recipients, respectively, developed mild systemic symptoms that included low-grade fever, myalgia, headache, dizziness, and gastrointestinal (GI) upset. Systemic hypersensitivity reactions, characterized by urticarial rash, angioedema, and respiratory symptoms, occurred much less frequently in patients receiving HDCV and PCECV vaccination types. A serum sickness–like syndrome is possible after HDCV; sudden death and encephalomyelitis are very rare.[77]

Tick-Borne Encephalitis Vaccine

Tick-borne encephalitis (TBE) is a viral illness transmitted predominantly by bites of *Ixodes* ticks during spring and summer months in rural forested areas of central and eastern Europe, Scandinavia, Siberia, and northern Japan. Infection can lead to central nervous system (CNS) effects of meningitis, encephalitis, or meningoencephalitis in about 20% to 30% of infected persons.[56] Infection can occur after ingestion of unpasteurized dairy products from infected cows, goats, or sheep.[54]

There are no licensed vaccines for TBE in the United States.[6,46] The standard dosing regimen is three doses given over 1 year. Accelerated schedules exist, but doses would likely need to be administered in the destination country. Whereas expatriates can consider obtaining vaccine at their new location, it is much more practical for most travelers to at-risk areas to use stringent tick bite precautions (e.g., repellents and insecticides, protective clothing, frequent tick surveillance) and to avoid unpasteurized dairy products.

Bacille Calmette-Guérin Vaccine

The BCG vaccine is intended to prevent tuberculosis (TB). The vaccine is currently not recommended for most U.S. travelers, including expatriates. This is because it is believed to be of varying efficacy in preventing adult forms of TB.[56] Persons taking short trips for tourism or business to developing countries where TB is common among the indigenous population are not at great risk for contracting TB. However, expatriates or travelers who will live among foreign residents or work in foreign orphanages, schools, hospitals, or similar facilities are at significant risk of exposure to TB infection.[35] Such travelers should be tested with a purified protein derivative (PPD) skin test before the trip, and if the test is negative, they should be retested 3 months after their return to a developed country and yearly thereafter. In the setting of travel and exposure, persons who convert from a negative to a positive PPD skin test should be treated with isoniazid for 9 months, regardless of age. Interferon-γ release assays (IGRAs) are blood tests that measure host cell–mediated immune response to *Mycobacterium tuberculosis* antigen. IGRAs appear to have high specificity but variable sensitivity compared with the TB skin test. IGRAs may be most useful in BCG-vaccinated patients and in persons unlikely to return for reading of a skin test.[56]

Varicella-Zoster Virus (Chickenpox) Vaccine

Varicella-zoster virus (VZV) infections are common throughout the world. Primary infection with VZV is known as chickenpox. After primary infection with VZV, the virus often stays dormant. It can reemerge as shingles later in life.[56] A traveler with a history of chickenpox can be considered immune. Many adults have had exposure to VZV, so if time permits, serum immunity should be documented before considering vaccination. If a person is not immune, two doses of single-antigen varicella vaccine should be given 4 to 8 weeks apart.[78]

Influenza Vaccine

Each year, the influenza vaccine antigen composition is based on projections of winter influenza activity in North America (or South America). The vaccine differs depending on the hemisphere in which one lives, and therefore may not protect against

the precise influenza strains circulating elsewhere in the world. As a result of when the projections are made, the vaccination may not be available for at-risk travelers from the United States during late spring through early autumn.[21]

Travelers from the United States may be exposed to influenza when traveling during winter months in the northern hemisphere; between April and September in the southern hemisphere; and year-round in the tropics. Travelers from diverse locations may be brought together during cruises, resulting in an outbreak of influenza during periods when influenza transmission might otherwise not frequently occur.[124] Risk for acquiring influenza during long-haul flights exists if a person infected with influenza is seated close to a susceptible individual. For these reasons, influenza should be considered a travel-related infection, and influenza vaccine should be recommended to travelers.[21]

Other Vaccines

According to the CDC, anthrax vaccine is not recommended for travelers. A killed bacterial vaccine for plague exists, but the dosing schedule is long and protection is uncertain. An alternative for select persons at risk (e.g., field biologists) for plague is a daily 100-mg dose of doxycycline, which can double as protection against malaria. The protective efficacy of this regimen against plague is inferred from treatment recommendations.[56]

ROUTINE VACCINES

"Routine" immunizations are those customarily given in childhood and then updated in adult life, regardless of travel.[87] Visits to travel medicine clinics afford opportunities to update immunizations through booster doses of routine vaccines.

The routine vaccines currently recommended in childhood include those against tetanus, diphtheria, pertussis, measles, mumps, rubella, varicella, polio, *Haemophilus influenzae* type b (Hib), hepatitis A/B, pneumococcus (PCV), and rotavirus. Routine immunization schedules for children, including nuanced changes in routine schedules for traveling children, can be found in the CDC's Yellow Book.[56]

Diphtheria, Tetanus, and Pertussis Vaccine

Primary immunization in young children is accomplished with five doses of a combination vaccine containing full doses of tetanus/diphtheria toxoid combined with acellular pertussis antigen (DTaP). The diphtheria/tetanus vaccine (Td) classically used for booster doses in older children and adults has no pertussis component and a lower dose of diphtheria antigen. Absence of a pertussis booster for adults has led to waning immunity and susceptibility to the disease.[2,22] Therefore, adolescents (11 to 18 years) and adults (>19 years) should receive a single dose of tetanus/diphtheria with acellular pertussis (Tdap). The Td vaccine should then be used every 10 years or after an exposure to tetanus to maintain tetanus immunity.[87] Travelers to remote locations who might sustain open wounds and be unable to safely obtain a tetanus booster should be given a Td booster if it has been 5 or more years since the prior booster. This should particularly be considered when a person plans travel to areas of the world where diphtheria remains a risk (e.g., most countries of Africa, Asia, South Pacific, Middle East, eastern Europe, South America, Haiti, Dominican Republic.).

Poliomyelitis Vaccine

All traveling adults should have received a primary course of polio vaccine. Vaccination campaigns worldwide have been largely successful in making some regions (e.g., western hemisphere, Europe, western Pacific) polio-free.[31] However, some regions continue to have circulating wild poliovirus (WPV). This is often caused by political instability that interferes with vaccination programs, or because of regional reimportation of polio virus, or because the live oral polio vaccine (OPV) has replicated and regained some properties of WPVs, which leads to small outbreaks of vaccine-derived poliovirus (VDPV) infection that are clinically indistinguishable from WPV infection.[28,30] Travel medicine practitioners should routinely check the CDC or WHO websites for the latest information regarding recommendations for polio prevention. Adult travelers to at-risk regions should receive a one-time booster dose of inactivated polio vaccine (IPV).[56]

Measles, Mumps, and Rubella Vaccine

Measles is endemic in large portions of the world.[56] Travelers to developing countries are at risk for acquiring measles. Measles cases in the United States are largely caused by importation of measles from other countries, with the largest proportion of cases occurring in unvaccinated individuals.[50] If travelers have received two doses of a measles-containing vaccine, usually given in childhood as the measles, mumps, and rubella (MMR) vaccine or the MMR plus varicella vaccine (MMRV), they should be protected. Adults born after 1956 who have not received two doses of live measles vaccine and who do not have a physician-documented history of infection or laboratory evidence of immunity should receive two doses of MMR vaccine separated by at least 28 days.[80] The measles component of the combination vaccines distributed in the United States contains a live-attenuated virus. Measles-containing vaccines are therefore contraindicated in pregnancy and in all immunocompromised persons (except persons with HIV and CD4 counts ≥200 cells/μL, for whom measles vaccination is recommended).[80]

Haemophilus Influenzae Type B (Hib) Vaccine

The risk for *H. influenzae* type b disease is the same in traveling children as it is in children who reside in developed countries. Traveling children should be kept up to date according to standard pediatric vaccination schedules.

Pneumococcal Vaccine

The pneumococcal polysaccharide vaccines (PCV13 and PPSV23) should be offered routinely, regardless of travel, to people 65 and older and those 19 and older with significant comorbidities, as recommended by the CDC. Many older travelers as well as high-risk individuals may not have been vaccinated, so a visit to the travel clinic is an ideal opportunity to bring these people up to date.[121]

MALARIA

Malaria is a mosquito-transmitted, blood-borne, parasitic infection present throughout tropical and developing areas of the world (Figure 79-3) (see Chapters 39 and 40). In the United States, 1500 to 2000 cases of malaria are reported annually to the CDC. Almost all of these cases are in returning travelers. Although the risk to travelers is relatively low compared with other medical problems (e.g., diarrhea, respiratory problems), malaria is the most common preventable infectious cause of death among travelers and one of the most common causes of fever in the returning traveler. Most travelers who develop malaria have not used chemoprophylaxis, were prescribed inappropriate chemoprophylaxis, or were not compliant with their medication regimen.[52,110]

Travelers often fail to use appropriate personal protective measures (PPMs). Visitors to friends and relatives (VFR) are now recognized as a group that disproportionally accounts for malaria occurring among travelers.[4] These persons typically grow up in a malaria-endemic region, immigrate to a malaria nonendemic region (subsequently losing much of their protective immunity), and then return to a malaria-endemic region to visit friends and relatives. This population needs to be counseled to practice the same PPMs and chemoprophylaxis as should other travelers to malaria-endemic regions. Although newer medications for malaria chemoprophylaxis have been introduced, rising drug resistance, breakdown in malaria control, and continuing reports of real or perceived adverse effects from antimalarial medications contribute to difficulties in protecting travelers against malaria.

MALARIA RISK ASSESSMENT

Assessment of risk for malaria requires knowing the details of a traveler's itinerary, including specifics of travel within a country. For instance, a geographic area may be listed as endemic for malaria, whereas urban travel may represent no appreciable risk,

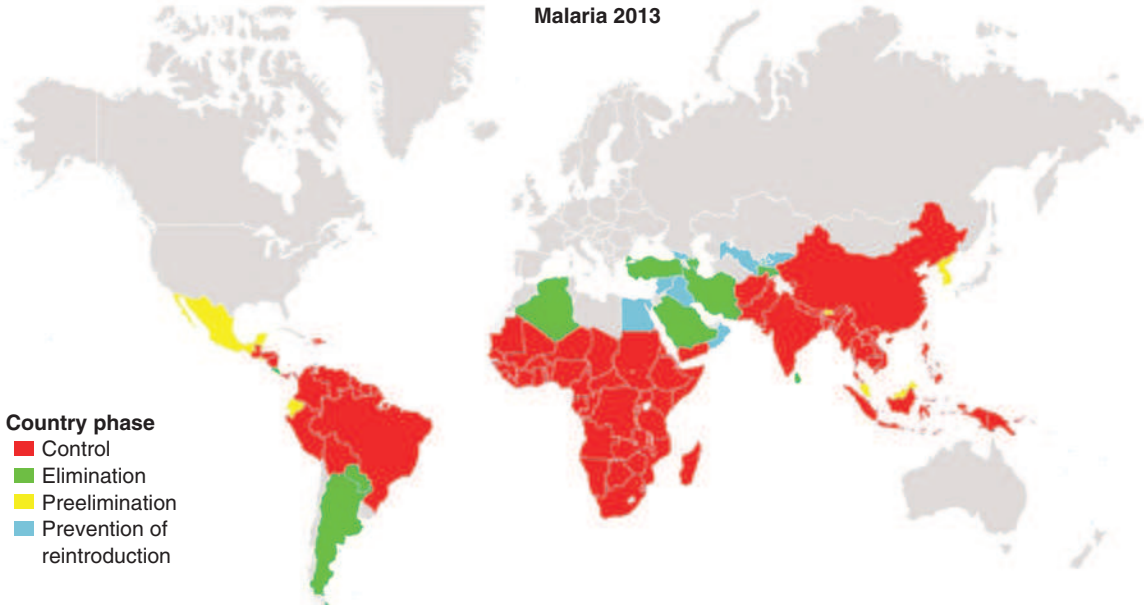

FIGURE 79-3 Worldwide distribution of malaria based on data from the WHO 2013 World Malaria Report. *(From* http://worldmalariareport.org.*)*

so chemoprophylaxis might be delayed until rural travel begins. When health facilities in the area are reliable, the traveler might need only to practice PPMs and perhaps take along standby therapy if duration of travel exceeds the minimum incubation time (~1 week) for malaria.

Season of travel (dry vs. rainy) and elevation of a destination influence risk, although climate change is altering our general understanding of these patterns.[84] Type of accommodation (e.g., camping vs. sleeping in air-conditioned well-screened room) influences whether to recommend permethrin-coated products such as bed nets. Location and duration of stay impact the amount and type of chemoprophylaxis (e.g., weekly mefloquine vs. daily doxycycline or atovaquone/proguanil for long-term travel) providers should recommend. A medical history must address the possibility of known intolerance of an antimalarial medication, drug-drug interactions, and contraindications (e.g., mefloquine and depression).

Any traveler determined to be at risk for malaria should be educated about the serious nature of malaria; risks posed by itineraries; how to avoid mosquito bites; antimalarial drug compliance; and how to seek medical care expeditiously in the event that fever occurs during or after travel. Up to 20% of cases of *Plasmodium vivax* malaria in travelers may have onset more than 6 months after travel. A helpful pneumonic for travelers is the ABCD of malaria prevention: awareness of risk, bite avoidance, compliance with drugs, and diagnose promptly.

Health departments in other countries may offer differing recommendations regarding malaria prophylaxis, thereby confusing the traveler. The advising provider must take the traveler's medical history, itinerary, and individual risk into account to create an individualized plan based on relevant information.

PRECAUTIONS AGAINST INSECTS
(see Chapter 45)

No drug completely prevents malaria. Many chemoprophylactic regimens do not absolutely prevent the liver phase of *P. vivax* infection. At the outset, travelers should be told to practice PPMs against malaria in addition to taking prophylactic medication.[49] Only perfect avoidance of mosquito bites can successfully prevent mosquito-borne diseases, such as malaria, chikungunya virus infection, or dengue fever.[48,59] Resistance to antimalarial compounds is increasing in some malaria-endemic regions.

The female *Anopheles* mosquito transmits malaria parasites. Depending on the species of mosquito, bites most frequently occur between dusk and dawn, during which travelers should take appropriate precautions or limit time outdoors. At-risk persons should wear protective clothing and apply insect repellents to exposed areas of skin. They should sleep in well-screened or air-conditioned rooms or within bed nets, the protective efficacy of which can be increased by application of insecticide (e.g., permethrin). Treated bed nets and clothing retain residual insecticide activity for weeks (sprayed) to months (soaked).[84] In addition to repelling mosquitoes, permethrin insecticides are effective against gnats, ticks, chiggers, bedbugs, scorpions, centipedes, beetles, and flies. Permethrin is a chemical derivative of alkaloids (pyrethrums) naturally occurring in the chrysanthemum plant family. When permethrin is allowed to air-dry before treated items are used, it is relatively nontoxic and suitable for treatment of external clothing and mosquito nets (Figure 79-4). It is not recommended for direct skin application, because skin hypersensitivity reactions may occur.[84]

The three most highly recommended repellents for disease prevention are the synthetic repellent *N,N*-dimethyl-*m*-toluamide (DEET); the plant-derived terpene repellent *p*-menthane-3,8-diol (PMD) from lemon eucalyptus; and the piperidine icaradin (also known as picaridin).[84] Picaridin appears to be better tolerated on skin than DEET and should not damage fabric or plastics.

In the United States, according to the Environmental Protection Agency (EPA), DEET-containing repellents are the most commonly used. Concentrations of DEET that afford a reasonable duration of protection are in the range of 30% to 40%. Higher concentrations of DEET do not protect better; rather, protection lasts longer. Particularly in concentrations of less than 30%, DEET appears to be safe for use on infants and children older than 2 months. DEET repels not only mosquitoes but also ticks, chiggers, fleas, gnats, and flies. Care should be taken in its application to avoid applying it to the eyes or mouth. When sunscreen and insect repellent need to be used simultaneously, the sunscreen should be applied first to avoid increasing absorption of DEET.[84]

MALARIA CHEMOPROPHYLAXIS
(see Chapter 40)

Selection of a malaria chemoprophylaxis agent is determined by the geographic destination and pattern of drug resistance among malaria strains transmitted at the destination. As shown in Table 79-2, chloroquine is still appropriate for chemoprophylaxis in some regions of the world (Caribbean, Central America west of Panama Canal, some Middle East countries). For much of the

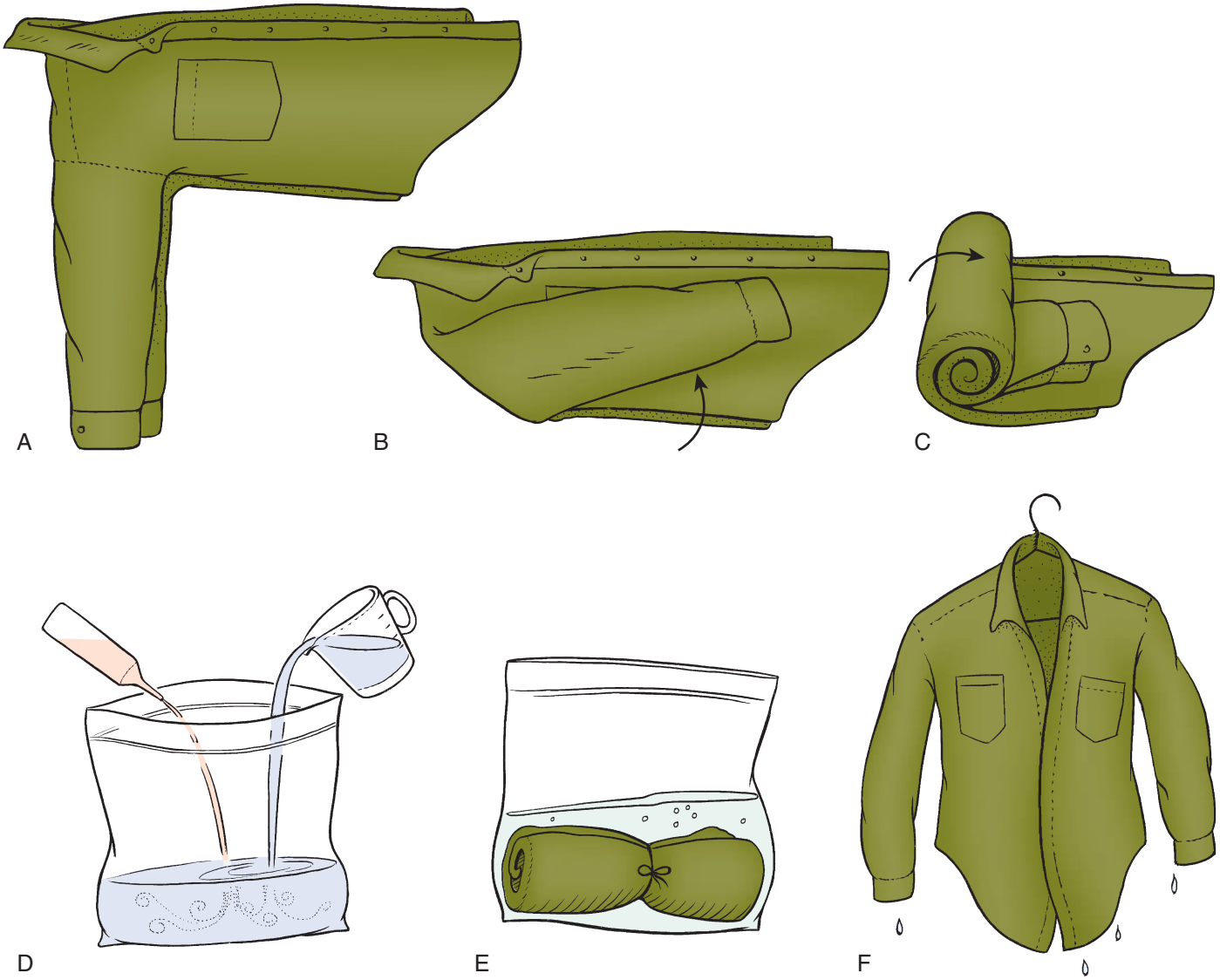

FIGURE 79-4 Technique for impregnating clothing or mosquito netting with permethrin solution. **A** to **C,** Lay jacket flat and fold it shoulder to shoulder. Fold sleeves to inside, roll tightly, and tie middle with string. For mosquito net, roll tightly and tie. **D,** Pour 60 mL (2 oz) of permethrin into plastic bag. Add 1 L (1 quart) water. Mix. Solution will turn milky white. **E,** Place garment or mosquito netting in bag. Shut or tie tightly. Let rest 10 minutes. **F,** Hang garment or netting for 2 to 3 hours to dry. Fabric can also be laid on a clean surface to dry. *(Redrawn from Rose S:* International travel health guide, *North Hampton, Mass, 1993, Travel Medicine, with permission.)*

TABLE 79-2 Chemoprophylaxis Drugs by Regions of Drug Resistance

Malaria Drug Resistance	Country or Region	Drugs	
		Preferred	Alternatives
Chloroquine-sensitive	Central America (west of Panama); parts of Mexico; Haiti/Dominican Republic; most of the Middle East; states of the former Soviet Union; northern Africa; Argentina and Paraguay; parts of China	Chloroquine	Atovaquone/proguanil Doxycycline Mefloquine Primaquine Hydroxychloroquine
Chloroquine-resistant	Most of malarious South America, including Panama, west of the former Panama Canal Zone; most of Asia and Southeast Asia; sub-Saharan Africa; Oceania; parts of Iran, Oman, Saudi Arabia, and Yemen	Atovaquone/proguanil Doxycycline Mefloquine	Primaquine
Chloroquine-, mefloquine-, and sulfonamide-resistant	Thailand borders with Myanmar and Cambodia	Doxycycline Atovaquone/proguanil	

TABLE 79-3 Malaria Chemoprophylaxis Drug Regimens for Adults

Drug	Dose	Regimen	Comments and Adverse Effects
Chloroquine	500 mg/wk	Begin 1-2 weeks before arrival in malarious area; continue drug weekly while in, and for 4 weeks after leaving, the malarious area.	May exacerbate psoriasis Pruritus (persons of African descent), headache, bitter taste: common Transient visual blurring, partial alopecia skin eruptions, reversible corneal opacity: occasional
Hydroxychloroquine	200 mg/wk	As with chloroquine	As with chloroquine
Mefloquine	250 mg/wk	As with chloroquine	Take with food. Avoid concurrent alcohol. Avoid if history of depression, psychosis, seizures, or cardiac conduction abnormality. Dizziness, nausea, diarrhea, nightmares, insomnia, mood alteration, headache: common
Doxycycline	100 mg daily	Begin 1-2 days before arrival in malarious area; continue drug daily while in, and for 4 weeks after leaving, the malarious area.	Use sunscreen. Stains teeth (fetuses and children age <8 yr) GI upset, photosensitivity, *Candida* vaginitis: common
Atovaquone/proguanil	250 mg/100 mg daily	Begin 1-2 days before arrival in malarious area; continue drug daily while in, and for 7 days after leaving, the malarious area.	Take with food. Avoid if CLcr <30 mL/min. Nausea, abdominal pain, headache: common Transient increase in transaminases: occasional
Primaquine	30 mg base daily	Begin 1-2 days before arrival in malarious area; continue drug daily while in, and for 2 days after leaving, the malarious area.	Take with food. Avoid if G6PD deficiency. GI upset: common

CLcr, Creatinine clearance; *GI*, gastrointestinal; *G6PD*, Glucose-6-phosphate dehydrogenase.

malaria-endemic world, chloroquine-resistant *Plasmodium falciparum* malaria (CRPF) dictates the drug of choice. In a limited area of the world, chloroquine-, mefloquine-, and sulfonamide-resistant malaria is a concern. Where chloroquine-resistant *P. vivax* (CRPV) is a concern, recommendations for CRPF, which is also present in these regions, suffices for CRPV as well. Table 79-3 provides doses and schedules for drugs typically used in malaria chemoprophylaxis.[56]

Travelers should start taking drugs with a weekly dosing regimen (chloroquine or mefloquine[56]) 1 to 2 weeks before departure. This allows time for familiarity with the side effects of the drug while the drug attains steady-state levels in the body, enables the traveler to habituate to the timing of doses, and gives the traveler time, while at home, to switch to an alternative drug in the event of intolerable side effects. Antimalarial drugs with a daily dosing schedule (doxycycline, atovaquone/proguanil, or primaquine phosphate[5,52]) are started 1 to 2 days before entering the malaria-endemic area.[56] Doxycycline, chloroquine, and mefloquine chemoprophylactic regimens should be continued for 4 weeks after the traveler leaves a malaria endemic area to prevent malaria in the immediate post-travel period. Atovaquone/proguanil should be continued for 7 days, and primaquine for 2 days, after leaving a malaria endemic area.[56] Travelers should be warned not to stop or switch the antimalarial regimen during the trip without the advice of a knowledgeable health care provider.

In addition to geographic considerations, convenience of dosing regimen, cost, and adverse effect profile of the malaria chemoprophylaxis agents combine to play an important role in choice and traveler compliance when taking the medication. Although inexpensive, doxycycline is associated with sun sensitivity rash.[56] Mefloquine has the greatest purported neuropsychiatric side effects.[56,109] Studies indicate that doxycycline and atovaquone/proguanil have relatively advantageous side effect profiles, are well tolerated, and are therefore often the most popular agents.[109]

Some travelers may not be able to take an optimal chemoprophylactic regimen. During pregnancy, doxycycline (category D), atovaquone/proguanil (category C), and primaquine (potential risk of hemolysis in the fetus) are contraindicated. The most recent data suggest that mefloquine (category B as of 2011) is probably safe for use during pregnancy.[56] Doxycycline is contraindicated in children younger than 8 years.

STANDBY SELF-DIAGNOSIS AND DRUG TREATMENT

For travelers who spend prolonged time in very-low-risk areas, where risks of chemoprophylaxis might exceed the risk of malaria, the approach of self-diagnosis[61,90,129] and self-treatment,[93] instead of malaria chemoprophylaxis, is an option. This may also be appropriate for persons taking suboptimal chemoprophylaxis or for those taking appropriate chemoprophylaxis who travel to remote areas where the risk of breakthrough clinical illness due to resistant malaria is high. This approach mandates that the traveler who develops a febrile illness and begins antimalarial treatment also seeks rapid, definitive medical care.

Self-diagnosis of malaria using rapid diagnostic tests (RDTs) by travelers in the field can be accompanied by a high false-negative rate depending on the test, species of malaria, and presence of other infectious agents.[76] When travelers who develop a febrile illness elect to self-treat and are subsequently evaluated medically, they often are found not to have had malaria. Recent expert consensus concludes that self-diagnosis and self-treatment cannot routinely be recommended and should be considered only after expert consultation.[56] In the United States, the currently preferred recommendation for self-treatment of suspected malaria is either atovaquone/proguanil (four 250-mg tablets taken as a single daily dose for 3 days) or artemether/lumefantrine (3-day treatment based on weight).[56]

In addition to malaria, enteric fever, scrub typhus, leptospirosis, and dengue are common causes of undifferentiated febrile illness that travelers may acquire in the tropics. If empirical drug self-treatment is started for presumed malaria and then malaria is ruled out, empirical antibiotic therapy for another presumed cause may need to be started. Oral azithromycin may be an option for the empirical treatment of enteric fever, scrub typhus, and leptospirosis while the medical workup is underway.[12,95,98]

TRAVELER'S DIARRHEA
(see Chapter 82)

The term *traveler's diarrhea* (TD) usually refers to abrupt onset of loose stools accompanied by abdominal cramps. Other symptoms often include nausea, vomiting, fever, and malaise. Tenesmus and bloody stools are uncommon features. According to the

CDC, it is estimated that 30% to 70% of international travelers develop travel-related diarrhea, depending on the destination and season of travel.[56] Most cases of TD are self-limited and resolve within 1 to 2 days; 90% of cases resolve by 7 days.[56] Despite this, a substantial percentage of travelers change activities because of symptoms, which can severely impact a trip. Current evidence indicates that 4% to 32% of patients with bacterial gastroenteritis may develop postinfectious irritable bowel syndrome (IBS), leading to chronic, episodic symptoms of IBS.[41]

Diarrhea associated with travel can result from multiple causes, including a change in normal diet, food poisoning (toxins), viral infections (e.g., rotavirus, norovirus), and parasites (e.g., *Giardia lamblia*, *Entamoeba histolytica*, *Cryptosporidium*). However, bacteria such as enterotoxigenic (ETEC) and enteroaggregative (EAEC) *Escherichia coli*, *Shigella*, *Campylobacter*, *Aeromonas*, *Salmonella*, noncholera *Vibrio*, and *Plesiomonas* account for the majority of cases.[39,66] The major causal role of bacteria explains the benefits of antimicrobial agents for treatment and prevention of the syndrome.[39]

The world can be divided into high-, intermediate-, and low-risk regions for TD[66,127] (Figure 79-5). The risk of TD is highest during the first week of travel. The style of travel may confer increased risk of disease (e.g., backpacking seems to carry a higher risk for TD than staying at resorts).[66] Although strict adherence to food hygiene when traveling is still recommended, the advice to "cook it, peel it, boil it, or forget it" has been shown to have marginal benefit in preventing TD.[66] Nevertheless, thoroughly cooked food, dry food, and fruits and vegetables that can be peeled by the traveler are generally considered safe, whereas tap water, ice cubes, fruit juices, fresh salads, unpasteurized dairy products, cold sauces and toppings, open buffets, and undercooked or incompletely reheated foods should be avoided.

TABLE 79-4 Recommended Agents for Traveler's Diarrhea Chemoprophylaxis

Agent	Dosage	Comments and Adverse Effects
Bismuth subsalicylate (Pepto-Bismol)	Two tablets chewed four times daily	Avoid in persons who should not take aspirin or who are taking anticoagulants. Black stool and tongue may occur.
Fluoroquinolones*		Occasional gastrointestinal upset, rash, and allergic reaction
Norfloxacin	400 mg PO daily	
Ciprofloxacin	500 mg PO daily	
Rifaximin	200 mg PO daily	Well tolerated because rifaximin is not absorbed

*Other fluoroquinolones can be predicted to be effective but have not been studied in prophylaxis; *PO*, orally.

CHEMOPROPHYLAXIS

Bismuth subsalicylate (BSS)–containing compounds and antimicrobial agents are successful for prevention of TD (Table 79-4).[66] Antimicrobial prophylaxis for TD is not recommended for most travelers.[56] Antimicrobial prophylaxis might be a reasonable strategy for a traveler who is taking a brief trip to a high-risk area and cannot afford even a brief illness. According to current

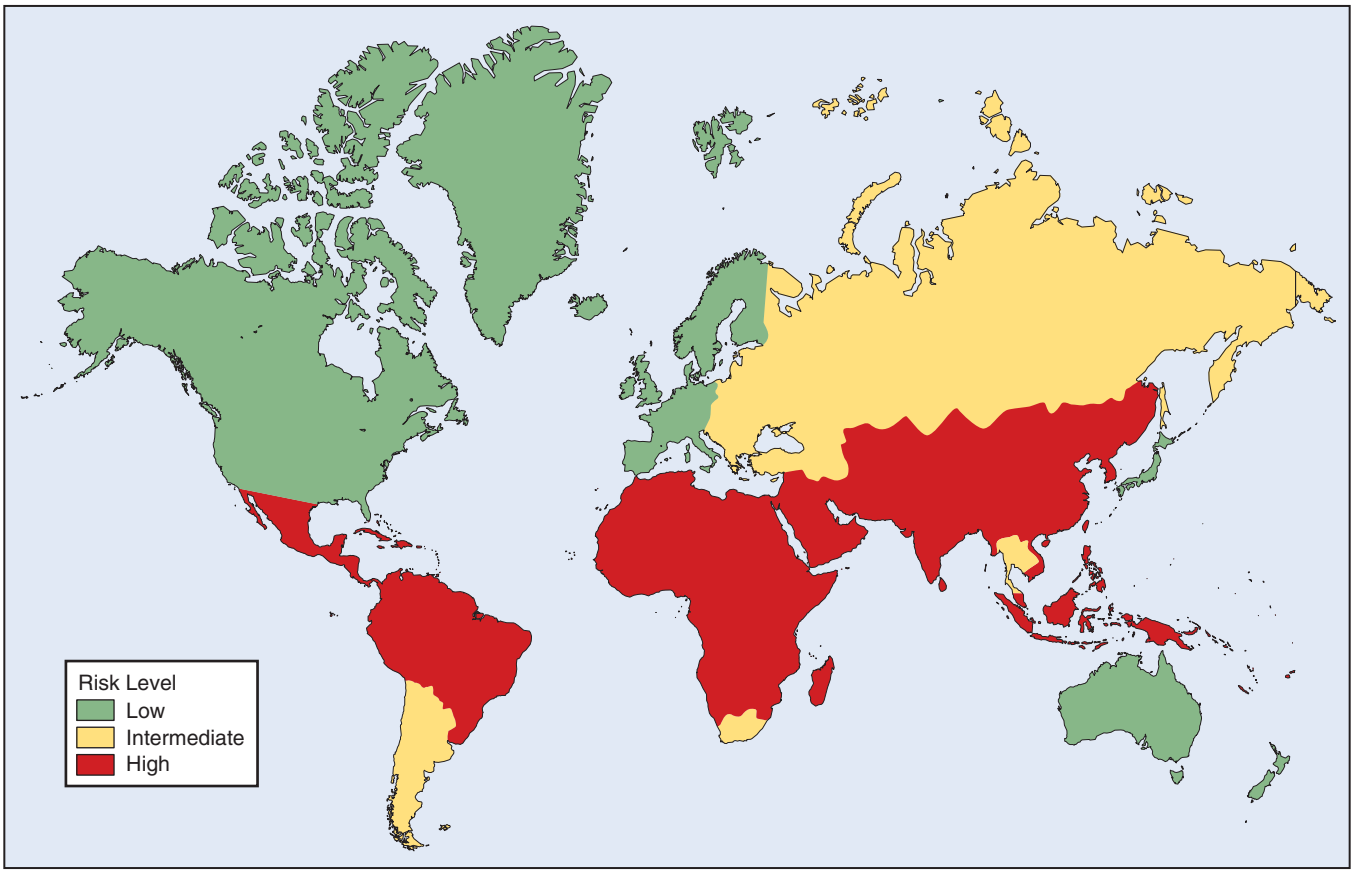

FIGURE 79-5 Risk areas for traveler's diarrhea: low risk, less than 4%; intermediate risk, approximately 8% to 15%; high risk, approximately 40%. Thailand has recently been reclassified as intermediate risk, based on data from Bangkok, Phuket, and Chiang Mai. *(Courtesy R. Steffen, MD.)*

guidelines, travelers who are competitive athletes, politicians, on essential business, or going to special events or who have significant underlying comorbidities can be considered for antimicrobial prophylaxis. Confirmation that between 4% and 32% of patients with bacterial gastroenteritis may develop postinfectious IBS[41] and the availability of rifaximin[66] have rekindled interest in chemoprophylaxis of TD.

Using probiotics to prevent TD cannot be recommended at this time because of inconclusive evidence.[56,66] *Lactobacillus* GC, *Saccharomyces boulardii*, and other combination probiotics have been studied with inconclusive results regarding prevention of TD.[66] Anecdotal reports exist favoring use of probiotics for prevention of TD, but direct evidence is lacking.

Bismuth subsalicylate, which is active in large part because of its antimicrobial properties, can successfully prevent approximately 65% of cases of traveler's diarrhea.[66] Disadvantages include cost and dosing regimen, risk of salicylate toxicity, and adverse effects of tongue and stool blackening.

Trimethoprim-sulfamethoxazole (TMP-SMX) and doxycycline are no longer recommended for prevention of TD because of increasing worldwide bacterial resistance. Fluoroquinolones successfully prevent up to 90% of TD cases.[66] Rifaximin is a nonabsorbed antimicrobial agent with an excellent safety profile and usefulness only in the management of enteric diseases. A daily dose of rifaximin may prevent 58% to 70% of cases of TD,[43,66] but it should only be offered as prophylaxis in patients deemed high risk by current guidelines.

SYMPTOMATIC TREATMENT

Fluid replacement has long been the cornerstone of therapy for TD. Dehydration and decreased oral intake are the greatest risks to health in patients with TD. However, when loperamide is used to treat TD, addition of oral rehydration solution (ORS) has not been demonstrated to add to the clinical benefit of loperamide alone.[24] Despite this, dilute fruit juices or flavored mineral water are typically adequate when used for oral rehydration during most episodes of TD. Packets of oral rehydration salts, which can be reconstituted with clean water to make ORS, are available in pharmacies globally.

Table 79-5 lists medications and their doses for symptomatic relief of TD. Agents that offer insufficient or no relief include anticholinergics, adsorbents such as kaolin-pectin preparations, and probiotics (e.g., *Lactobacillus*). Because of insufficient information or lack of availability, calmodulin and enkephalinase inhibitors (zaldaride and racecadotril, respectively) cannot be recommended.

TABLE 79-5 Recommended Agents for Symptomatic Treatment of Traveler's Diarrhea

Agent*	Dosage	Comments and Adverse Effects
Bismuth subsalicylate (Pepto-Bismol)	1 oz PO every 30 minutes for 8 doses	Delayed onset of action. Avoid in persons who should not take aspirin or who are taking anticoagulants. May interfere with absorption of other antimicrobials, notably fluoroquinolones and doxycycline. Black stools and tongue may occur.
Loperamide (Imodium)	4 mg PO, then 2 mg after each loose stool, not to exceed 8 mg daily	Rapid onset of action. Best results occur with loperamide plus an antimicrobial agent. Very well tolerated.

*See text for discussion of other agents; *PO*, orally.

Bismuth subsalicylate reduces the number of stools passed in traveler's diarrhea by approximately 50%.[66] Although BSS can be recommended for mild diarrhea, for moderate to severe disease, loperamide works better and with a faster onset of action.[62] Opiates and diphenoxylate are effective, but CNS and other side effects, plus poor tolerance among elderly persons, limit their usefulness.[66] Because it is safe and efficacious, loperamide has become the symptomatic treatment agent of choice.[66]

The combination of loperamide and an antimicrobial agent is the treatment of choice for TD.[3,66] Loperamide appears to be safe,[24] even in children, as long as doses are kept in the recommended range and the drug is stopped if diarrhea persists despite several days of treatment. Most experts prefer, however, to avoid using loperamide in children under 6 years of age.[56] Although the combination of loperamide and an antibiotic was more efficacious than an antibiotic alone in the treatment of *Shigella* dysentery,[86] most experts prefer not to use loperamide when the patient has high fever or grossly bloody stools, which are usually not present in TD[56] (Figure 79-6).[66]

Traveler's diarrhea can also be treated with empirical antibiotic therapy. An antibiotic with concurrent use of loperamide often leads to relief in a few hours. A fluoroquinolone is the empirical antimicrobial of choice for the treatment of TD for travelers in most parts of the world. Because of increased resistance, specifically found in *Campylobacter jejuni* and *Shigella* strains from patient with TD in South and Southeast Asia, the preferred agent for empirical treatment of TD in these areas is azithromycin. In addition, azithromycin can be used in pregnant women and children (10 mg/kg/day for 3 days) and in patients who do not respond to a fluoroquinolone within 48 hours.[3,27,66] Given resistance patterns worldwide,[66,127] TMP-SMX can no longer be recommended for empirical treatment of TD.[66]

Rifaximin, a nonabsorbed antimicrobial agent with broad activity against enteric pathogens, is effective in treatment of TD in regions of the world where enterotoxigenic *E. coli* is the predominant pathogen.[42,66,117] Rifaximin is not recommended for treating bloody diarrhea or when an invasive pathogen is suspected, limiting its usefulness as a therapeutic agent.

Either a fluoroquinolone or azithromycin can be used for treatment of TD that occurs despite prophylaxis. Table 79-6 provides recommended dosages of antimicrobial agents. A 3-day treatment course has been shown to be as effective as a single dose for the treatment of TD.[66] Travelers who do not respond to empirical antibiotic treatment or who have persistent diarrhea for more than 1 week should seek medical attention.

In the wilderness, *Giardia lamblia* can be an important cause of ongoing diarrhea that is unresponsive to antibiotics. Metronidazole (250 mg three times daily for 5 days), tinidazole (2 g once), or nitazoxanide (500 mg twice daily for 3 days) can be used for empirical treatment of infection with *Giardia*.[56,94]

HIGH-ALTITUDE ILLNESS
(see Chapter 2)

High-altitude illness is generally considered to exist as one of three syndromes: acute mountain sickness (AMS),[19] high-altitude cerebral edema (HACE),[130] or high-altitude pulmonary edema (HAPE).[119] High-altitude illness can occur when travelers ascend rapidly to altitudes greater than 3000 m (9850 feet), particularly if the traveler fails to acclimatize as higher altitudes are reached.[19,69] Of persons who ascend rapidly to moderate altitude (1900 to 3000 m [6250 to 9850 feet]), approximately 25% develop at least mild AMS. Symptoms of AMS are usually experienced within 6 to 12 hours of arrival at altitude and are characterized by headache, fatigue, sleep disturbance, dizziness, and anorexia.[7,18,53,69] These symptoms typically resolve spontaneously over 1 to 3 days, as long as the traveler does not ascend further. The risk of AMS in the individual traveler is uncertain, although travelers with preexisting medical conditions, such as lung disease, kidney disease, hypertension, eye problems, epilepsy, and coronary artery disease, benefit from consulting an altitude medicine expert before travel.[70,73,82]

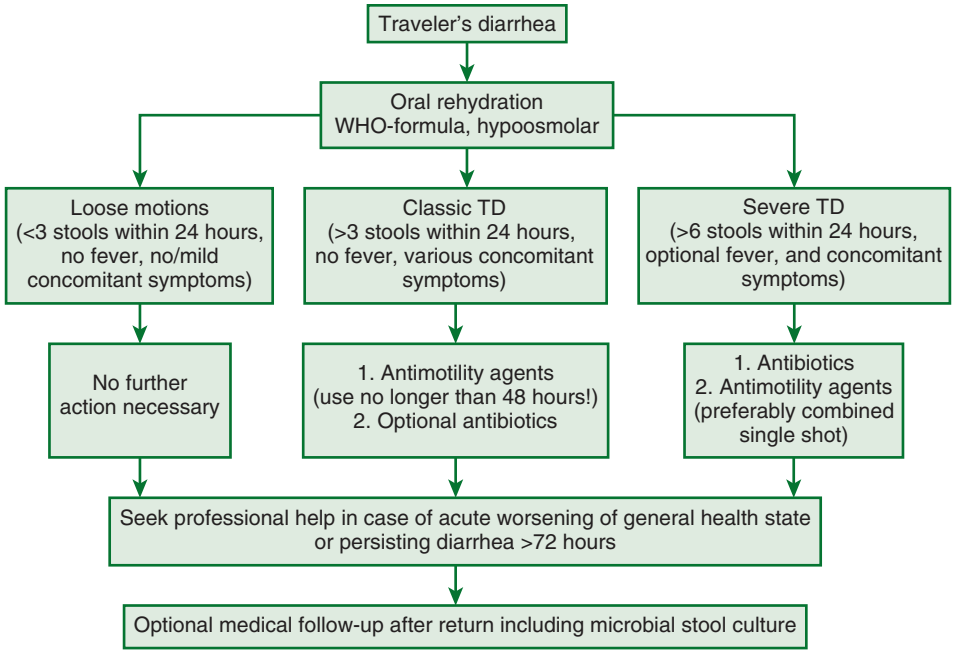

FIGURE 79-6 Management of acute traveler's diarrhea. *WHO,* World Health Organization. *(Modified from Kollaritsch H, Paulke-Korinek M: Durchfallerkrankungen. In Löscher T, Burchard GD, editors:* Tropenmedizin in Klinik und Praxis mit Reise- und Migrationsmedizin, *4th ed, New York, Stuttgart, 2010, Georg Thieme Verlag.)*

Acclimatization is the best way to prevent altitude illness. Gradual ascent is critical. Ideally, travelers should spend a few days ascending to 3000 m (9850 feet), then gradually ascend above 3000 m so that the elevation at which they sleep does not increase more than 300 to 500 m (990 to 1640 feet) per night.[69] The carbonic anhydrase inhibitor acetazolamide (Diamox) hastens acclimatization by increasing ventilation, bicarbonate diuresis, and arterial oxygen levels.[40] A dose of 125 mg twice daily can be taken 1 day before ascent and continued for at least 2 days once the highest altitude is reached.[16,69] Acetazolamide is contraindicated in persons who have had a life-threatening reaction to sulfa drugs. Extremity and circumoral paresthesias occur in 35% to 90% of persons taking acetazolamide, which can be very bothersome for some people, so the trekker should be warned about this potential side effect.[9]

Although dexamethasone has been used for prevention of all three major syndromes of high-altitude illness, it does not hasten acclimatization. Given the potential adverse effects of dexamethasone, which include glucocorticoid toxicity and adrenal suppression, it should only be used for prevention of altitude illness if the patient cannot take another agent.[9,53,69] However, dexamethasone should be used for treatment of AMS/HACE in conjunction with descent.[69]

For climbers who have previously developed HAPE and want prophylaxis for subsequent travel to altitude, nifedipine, 30 mg (extended-release preparation) every 12 hours, can be prescribed.[8,69] Although acetazolamide speeds acclimatization, no data support its role specifically in HAPE prevention.[69] In accordance with Wilderness Medical Society practice guidelines, salmeterol (125 mcg inhaled twice daily),[108] tadalafil (10 mg twice daily), and dexamethasone (8 mg twice daily) are also effective for prevention of HAPE.[69,74] Oxygen and nifedipine are used as adjuncts combined with descent for treatment of HAPE.[92,119]

If AMS symptoms do not resolve or symptoms worsen with evidence of HACE or HAPE, descent is imperative. Descending only 500 to 1000 m (1640 to 3280 feet) can be lifesaving. Acetazolamide (250 mg twice daily) can also be added for treatment of AMS.[69]

Treatment of the symptoms of AMS is also important. Antiemetics such as ondansetron, a serotonin antagonist, can be

TABLE 79-6 Recommended Antimicrobial Agents for the Treatment of Traveler's Diarrhea

Agent	Dosage	Comments
Fluoroquinolones		
Norfloxacin	400 mg PO bid for 3 days	Occasional gastrointestinal upset, rash, and allergic reactions. After 24 hours, patients can reevaluate themselves before taking next dose. If diarrhea persists, or if fever or passage of bloody stools was present, finish 3 days of therapy.
Ciprofloxacin	500 mg PO bid for 3 days	
Ofloxacin	200 mg PO bid for 3 days*	
Levofloxacin	500 mg PO qd for 3 days*	
Azithromycin	1000 mg PO once, *or* 500 mg daily for 3 days	A single 500-mg dose suffices when *Escherichia coli* is the predominant enteropathogen; agent of choice for diarrhea occurring in Southeast Asia.
Rifaximin	200 mg PO tid for 3 days†	Should not be used to treat persons with fever, grossly bloody stools or in whom an invasive enteropathogen is otherwise suspected.

PO, Orally; *bid,* twice daily; *qd,* once daily; *tid,* three times daily.
*Single doses of ofloxacin and levofloxacin have been studied and appear equivalent to 3-day regimens. A single dose of any fluoroquinolone likely will suffice.
†400 mg PO bid for 3 days was also efficacious in one study.

FIGURE 79-7 Pilgrims going to Muktinath sacred temple at approximately 3700 m (12,139 feet) in the Mustang region of Nepal.

effective to treat nausea caused by AMS.[69] Another beneficial effect of acetazolamide (125 mg taken before dinner) is stabilization of periodic breathing, which leads to hypoxemia during sleep. It is important to note that because not all medical problems at high altitude are caused by altitude-related illness, a differential diagnosis must be formulated.[15]

Older travelers and other groups, such as pilgrims traveling to remote, sacred areas at high altitude, may have comorbidities that require prior attention[11,14] (Figure 79-7). Porters may be sojourning to high altitude without adequate clothing or equipment, predisposing them, for example, to hypothermia and frostbite. Trekkers and travelers could check with the trekking agency to ensure that the porters who will accompany them on their wilderness trip are adequately equipped.

RADIATION FROM THE SUN
(see Chapter 16)

Sunscreens should be applied in sufficient quantities to achieve protection from solar radiation.[102] At least 1 oz is required to adequately protect an adult who is average size and wearing a small bathing suit. Sunscreen should be applied at least 20 minutes before sun exposure (or as directed by the manufacturer). Care must be taken to apply sunscreen under the chin and to other skin that might be burned because of reflected ultraviolet (UV) rays. A sun protection factor (SPF) of at least 15 is preferred, but SPF relates mainly to protection against ultraviolet B (UVB) rays. Ultraviolet A (UVA) radiation is also deleterious to skin. Only sunscreens with specific added ingredients offer protection against UVA rays. The consumer should purchase "broad-spectrum" sunscreens with UVA/UVB protection. Although products vary somewhat in their ability to withstand water exposure, any sunscreen should be reapplied at regular intervals after swimming, profuse sweating, or ongoing exposure to the sun. Sunblocks containing emulsified titanium dioxide are useful to protect especially sensitive skin or to block UV exposure in persons taking doxycycline for malaria prophylaxis.[102]

MOTION SICKNESS

Oral scopolamine preparations to prevent motion sickness are convenient for short-duration travel.[114] For longer-duration travel (e.g., cruises, prolonged or frequent automobile or bus trips), transdermal sustained-release scopolamine may be employed. Scopolamine is contraindicated in persons with urinary tract obstruction or glaucoma and can cause dry mucous membranes and drowsiness.[114] Other medications for motion sickness prevention are meclizine and dimenhydrinate, but sedation can be a limiting factor because both cause sleepiness.

TRAVEL MEDICAL KIT

Travelers are advised to prepare a travel medicine kit appropriate for their itinerary. Such a kit should contain adequate supplies of all prescription medications normally taken, medications for malaria and diarrhea, and remedies for common problems such as headache, musculoskeletal pain, allergies, nasal and sinus congestion, cough, jet lag, and constipation. Travelers should be instructed to carry prescription medications in their handheld luggage and copies of their prescriptions, because finding exact replacements for medications can be very difficult in certain parts of the world. A second supply of critically necessary medications might be placed in checked luggage to guard against loss in the event that hand luggage is stolen or misplaced.

Depending on the individual and itinerary, insect repellent, sunscreen, topical antiseptic ointment, antifungal cream or powder, and medications for motion sickness, allergic reactions, and high-altitude illness should be included. Female travelers should be reminded to carry personal sanitary supplies, because disposable tampons and pads may be difficult to obtain in developing countries. Sexually active travelers of both genders should take along a supply of high-quality latex condoms. Kits carried by medical professionals on trips to remote areas (e.g., trekking and climbing expeditions in the Andes or Himalayas) should include equipment for a wider variety of injuries, infections, and medical conditions.

POST-TRAVEL MEDICAL CARE AND SCREENING

Although travel medicine practitioners generally focus on pretravel advice, prevention, and self-treatment of disease, they may be called for advice by returned travelers who are ill. They should be generally familiar with common and life-threatening conditions after travel and how to triage post-travel complaints.[115] Particularly when a traveler presents only with constitutional symptoms, the differential diagnosis may be broad. It can often be narrowed by considering incubation time, geographic area of disease acquisition, immunizations, malaria chemoprophylaxis, dietary habits, insect and rodent exposure, animal bites, and intimate or sexual contact with foreign residents or fellow travelers.

The approach to post-travel illness has been extensively reviewed.[91,106,115] In a traveler who develops high fever weeks, months, or even years after travel in a malarious area, malaria should be actively sought and treated. Many physicians practicing in developed countries are unfamiliar with the clinical presentation of malaria and may fail to include malaria in the differential diagnosis. This holds true for typhoid, typhus, dengue, leptospirosis, and other causes of febrile illness in the traveler recently returned from a developing country. When empirical treatment needs to be started for a returned traveler for a febrile illness without any particular focus and malaria is ruled out, ceftriaxone (for enteric fever) and doxycycline (for rickettsial illnesses and leptospirosis) are good choices.

Diarrhea that develops within approximately the first week after travel can be assumed to be TD and treated empirically. Persistent or remittent diarrhea should prompt a diagnostic workup. Antibiotic-resistant bacterial enteropathogens, intestinal parasites, or even hepatitis may account for prolonged symptoms. TD may unmask inflammatory bowel disease; persistent symptoms raise concern for coincidental biliary tract disease or even intestinal malignancy.

Returned travelers may complain of unusual skin lesions or rashes. Tropical infections that might present with cutaneous manifestations include cutaneous myiasis, cutaneous larva migrans, larva currens, and cutaneous or mucocutaneous leishmaniasis. Because secondary bacterial infection can occur with these conditions, the skin lesion may initially improve with therapy for bacterial skin infections. If the lesion fails to resolve completely, however, consultation with a tropical medicine specialist is recommended.

Many parasitic infections may have unfamiliar signs and symptoms. Eosinophilia may be a clue to some parasitic diseases.

Nonspecific symptoms in a recently returned traveler, in whom common, non–travel-related illness has been excluded, probably should be referred for expert evaluation.

RESOURCES FOR TRAVEL MEDICINE INFORMATION

Telephone Information

Centers for Disease Control and Prevention (CDC) Traveler's Health Hotline: +1-800 CDC-INFO (+1-800-232-4636).

U.S. Department of State Overseas Citizens' Services: U.S.-based telephone number, 888-407-4747, and from overseas, +1-202-501-4444.

Official References

Centers for Disease Control and Prevention (CDC): *Health information for international travel,* New York, 2015, Oxford University Press (revised annually).

Morbidity and Mortality Weekly Report, Centers for Disease Control and Prevention, 1600 Clifton Rd, MS E-90. Atlanta, GA 30333. Telephone: +1-404-498-1150. Subscriptions are available at the website: http://www.cdc.gov.

World Health Organization (WHO): *International travel and health, vaccination requirements and health advice,* 2012, World Health Organization Publications Center USA, 49 Sheridan Avenue, Albany, NY 12215 (revised frequently).

Pretravel Clinic Directories

American Society of Tropical Medicine and Hygiene: http://www.astmh.org.

International Society of Travel Medicine: http://www.istm.org.

Travelers' Clinic Directory

English-Speaking Physicians: International Association for Medical Assistance to Travelers (IAMAT): https://www.iamat.org.

Locations:

1623 Military Rd #279, Niagara Falls, NY, USA, 14304-1745. Telephone: 716-754-4883.

67 Mowat Ave, Suite 036, Toronto, Ontario, M3K 3E3 Canada. Telephone: 416-652 0137.

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Complete references used in this text are available online at expertconsult.inkling.com.

CHAPTER 80

Expedition Medicine

JON DALLIMORE, NICHOLAS P. MASON, AND JAMES MOORE

HISTORICAL BACKGROUND

The desire for exploration runs deep in the human spirit. "The Journey" appears as a recurring theme in historical, religious, and literary records of numerous societies. It is used as a vehicle to describe and understand the mystery of human existence: the Exodus of the Israelites from Egypt and their wandering in the wilderness for 40 years, recorded in the Pentateuch books of the Old Testament; Homer's *Odyssey*, describing the journey of Odysseus home from the Trojan Wars; and the voyage of Marlow along an African river in Conrad's *Heart of Darkness*.

The *Oxford English Dictionary* defines an expedition as "a journey undertaken by a group of people with a particular purpose, especially that of exploration, research or war."[55]

A history of expeditions is beyond the scope of this chapter. Readers are referred to excellent works published on this topic.[1,19] The first clearly documented expeditions are those of Harkhuf, who was the governor of Upper Egypt during the 23rd century BC and whose three explorations along the Nile are recorded on his tomb at Aswan. In modern times, the golden age of expeditions and exploration stretches from the middle of the 19th century to the middle of the 20th century, although it has been mentioned that many of those who occupy a prominent place in the Western imagination were merely recorders of preexisting civilizations, rather than genuine explorers of untrodden ground.[1] Despite this observation, many expeditions that took place during this period illustrate both the varied environments and the recurring controversies that surrounded expeditions then and continue to do so today:

- The jungle explorations of David Livingstone during his 6-year search for the origin of the Nile and the subsequent search for Livingstone by the journalist Henry Stanley[63] were sponsored by the *New York Herald* to further boost the newspaper's circulation.
- The disputed claims of Robert Cook and of the celebrity-obsessed Robert Peary as to who, if either, may have reached the North Pole.[32]
- The ill-fated journey of Robert Falcon Scott to the South Pole, who discovered that he had been beaten by Roald Amundsen by 5 weeks, and then died with the rest of his team on the return journey only 11 miles from the food cache that might have saved them.[20]
- Charles Darwin's scientific voyages[14] to the southern hemisphere in *The Beagle*, which revolutionized our understanding of humans' place on the planet.
- Sven Hedin's expeditions[30] to the deserts of Central Asia.
- Early British attempts on the north side of Mt Everest during the 1920s and 1930s;[67] Charles Houston's expeditions to K2;[37] the first ascent of an 8000-m (26,247-foot) peak by Maurice Herzog;[33] and the ascent of Mt Everest by Sir Edmund Hillary and Tenzing Norgay.[39]

EXPEDITION DEMOGRAPHICS

In the six decades since Hillary and Tenzing stood on the summit of Mt Everest, the demographics of expeditions, particularly mountaineering expeditions to the Great Ranges, have changed dramatically. Although audacious, groundbreaking ascents continue to be made,[11,23] mountains that were once the domain of only an elite group of climbers, who served long apprenticeships to gain the skills necessary to survive in hostile surroundings, now are frequently attempted by less experienced mountaineers.

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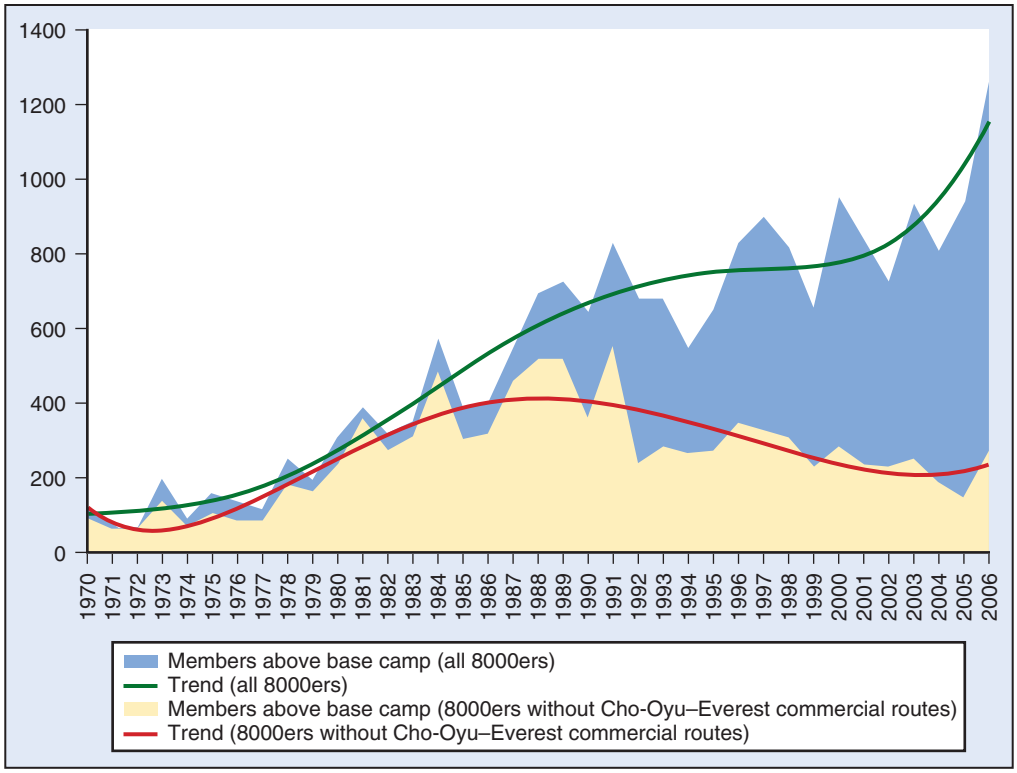

FIGURE 80-1 Climbing activity (members above base camp) for all 8000-m (26,247-foot) peaks between 1970 and 2006, with the Mt Everest and Mt Cho Oyu commercial routes shown separately. *(Data from Salisbury R, Hawley E: The Himalaya by the Numbers, Golden, CO, 2007, The American Alpine Club.)*

Where once expedition members were chosen for their experience and ability to function autonomously, many now utilize the infrastructure of a commercial expedition and purchase the services of highly experienced guides to fulfill their summit dreams. There has also been an explosion in charity treks over the last 20 years, which has contributed to large numbers of unfit wilderness- and altitude-naive individuals being led into an environment for which they may be totally unprepared.

Many accounts from leaders, guides, physicians, and a growing number of books recount expeditions in the commercial era in an unfavorable light.[7,15,31,45,46,61] Figure 80-1, from the Himalayan Database, shows climbing activity on all the 8000-m (26,247-foot) peaks between 1970 and 2006, separating out the commercial routes on Mt Everest and Mt Cho Oyu. This demonstrates the large increase in the number of people attempting these routes. The increased popularity of the highest peaks has been mirrored on lower peaks and by nonclimbing trekkers. Figure 80-2 illustrates the numbers of climbers with permits issued for the 18 Nepalese group B climbing peaks, which includes the most popular peaks below 7000 m (22,966 feet), formerly known as "trekking peaks," between 1996 and 2009. The number of visitors to Sagarmatha National Park of Nepal has increased massively over the last 35 years. Between 1972 and 1973 there were approximately 1400 visitors; 7492 persons visited in 1989 and 25,925 in 2001. Visitor numbers fell during the recent civil unrest but were reported at more than 20,000 in 2004, increased to 30,599 in 2008, and exceeded 37,000 in 2014.[58]

The increase in popularity and accessibility of expeditions has, in all likelihood, been accompanied by a decrease in the experience and wilderness skills of expedition participants. There is certainly a need for data to substantiate the anecdotal accounts of the guides and medical professionals who provide medical cover for these trips or who work at high-altitude rescue posts in Nepal. Increasing familiarity of the general public with wilderness environments and "extreme sports" via the media has resulted in an exponential growth in adventure tourism. The better commercial companies vet participants for appropriate experience. However, many do not. Strangers, whose primary motivation is completing a trek or climb, are often grouped together. Individuals acclimatize to their environments at differing rates, which presents significant challenges for group leaders adhering to tight schedules. Members are frequently unaccustomed to adapting goals to weather, terrain, or the needs of other team members.

Recently, many countries have seen development of the "charity trek" business, in which supporters of charities attempt

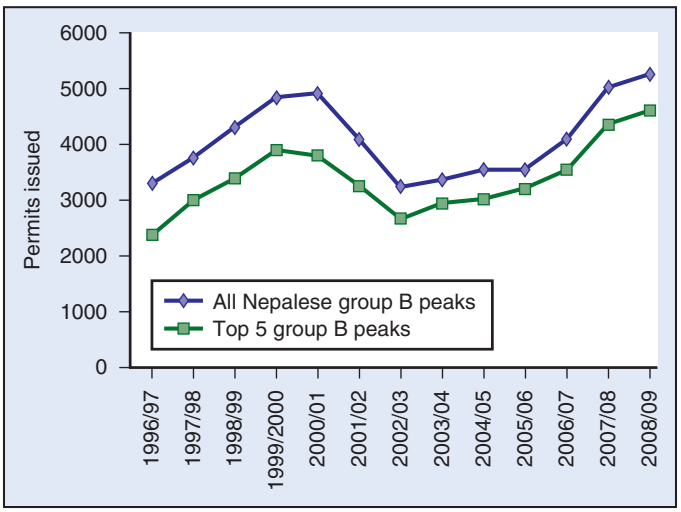

FIGURE 80-2 Permits issued by the Nepal Mountaineering Association for the 18 Nepalese group B climbing peaks, formerly known as "trekking peaks," between 1996 and 2009. The five most popular peaks—Mera, Island Peak (Imja Tse), Pharchamo, Lobuche, and Pokhalde—are grouped separately. *(From Nepal Mountaineering Association.)*

endurance events such as treks, long-distance cycle rides, or summit climbs to raise money through individual sponsorship of these efforts. These have been further popularized by widely publicized "celebrity treks" that make light of the risks.[41,43] Inexperienced participants entirely depend for their safety on the advice, guidance, and care provided by the trek organizers. When this guidance is misplaced, the results can be catastrophic, as the tragic events on the Thorung La in October 2014 illustrate. Despite a well-recognized weather pattern in the Bay of Bengal resulting in unseasonably high snowfalls over the Annapurna region of Nepal, the rapidly deteriorating conditions were ignored, and poorly equipped groups lacking in mountaineering experience and knowledge were led from the safety of shelter to their deaths. More than 50 people died, although the number of Nepalese trekking staff who died has never been finalized, and more than 500 people were rescued by helicopter.[16]

Three very popular destinations are Mt Kilimanjaro in Tanzania, Mt Everest Base Camp in Nepal, and Mt Aconcagua in South America. Mt Kilimanjaro at 5895 m (19,341 feet) attracts more than 50,000 climbers per year, fewer than 70% of whom reach the summit. Between 1996 and 2003, 25 tourists died attempting to reach the summit.[29] Sensible ascent profiles of Mt Kilimanjaro would suggest that trekkers require 7 to 9 days above 2500 m (8202 feet) to ascend safely and maximize their chances of summit success. A comparative study of commercial charity treks found that 15 of 20 treks planned only 4 nights above 2500 m (8202 feet).[38,53] There are many reasons for this. The Tanzanian government levies a charge in excess of $70 per day for each day tourists spend in the national park, and as a result, in an attempt to maximize profits, trekkers are encouraged to climb the mountain as quickly as possible, thereby putting lives at risk. None of the charity groups surveyed offered the option of an acclimatization ascent of Mt Meru (4566 m [14,980 feet]) before attempting Kilimanjaro.

Tourists may choose to ignore sensible ascent profiles, but this is not the case for their employed porters, without whom they would be unable to make an attempt on the mountain. No formal statistics are available, but porters die as a result of altitude illness or from hypothermia when guides push on in bad weather.[44] The difficulties faced by mountain porters are discussed in more detail later.

PREEXISTING MEDICAL CONDITIONS

More participants with complex medical problems are attempting expeditions. There is once again need for international data. The medical advisor to a major British commercial expedition company has described his experience of clients who successfully completed mountaineering trips with Hodgkin's lymphoma; epilepsy; insulin-dependent diabetes; a cardiac pacemaker; post–coronary angioplasty, or post–renal transplant.[35] It is increasingly common for prospective clients to have a history of depression, anxiety, hypertension, asthma, or diabetes.[36] Comparatively little is known about the effects of altitude on the majority of common medical problems.[27] Most published recommendations deal with cardiopulmonary pathologic conditions at altitude but are frequently based on theoretical considerations rather than documented experience.[10,34,47,52,56] The result of this lack of documented experience with preexisting medical conditions is that advice given to potential expedition participants may be unduly conservative and prohibitive. It is apparent that, with appropriate motivation, care, and planning, people with significant comorbidities can trek and climb successfully and safely in remote, hostile wilderness environments.[35] The approach to preexpedition screening is discussed later.

It is not our intention to criticize those who take part in commercial expeditions and treks. Many experienced mountaineers and travelers use commercial organizations to facilitate trips. However, the days of the ad hoc expedition physician, who often learned his or her trade extemporaneously while caring for friends while climbing, are receding. It is in the context of these demographic changes that the 21st-century expedition medical officer (EMO) is expected to operate.

THE EXPEDITION MEDICAL OFFICER

Providing health care in an expedition setting is a specialist area of practice, requiring not only medical skills, but also the ability to live and work in a potentially austere or hostile environment. This distinctive area of practice demands a set of skills and qualities seldom found in other disciplines. The attributes of an experienced EMO may be divided into three main categories that will be required simultaneously during an expedition, but not necessarily in equal measure. These categories are clinical skills, expedition skills, and personal skills.

CLINICAL SKILLS

An EMO's clinical skills can be considered in three further categories, depending on the expedition phase.

Preexpedition Phase

Preexpedition clinical skills are crucial to successful preparation of a team for an expedition:

- Distribution and evaluation of pretrip medical questionnaires for all team members
- Advice on travel vaccinations and, when appropriate, antimalarial medication
- Medical risk assessment and contingency planning
- Developing the expedition's policy for treating indigenous peoples
- Preexpedition medical briefing and training
- Medical kit preparation

Expedition Phase

The EMO needs to have broad-based clinical skills. As in nonexpedition clinical practice, the EMO typically has a specialist interest, such as tropical medicine, envenomation, or high-altitude medicine. However, other than for the situation of the high-altitude environment, this is unlikely to provide the majority of the expedition medical caseload, which will generally consist of common, usually minor, ailments, most frequently gastrointestinal (GI) illnesses, followed by minor orthopedic and trauma problems, respiratory conditions, and other minor medical and surgical problems.[3,13,57] The required clinical skills of the EMO will also be influenced by the location, environment, expedition goals, and preexisting medical conditions.

Location. Remoteness of the expedition location will determine the level of clinical autonomy required. An EMO working in an isolated environment where evacuation is likely to take days or weeks, or with poor communications, would be expected to manage complex and difficult cases that elsewhere would be evacuated. In contrast, a team equipped with good communications and reliable and rapid access to definitive care might be confident working with a much lower level of medical support.

Environment. The expedition environment also influences the medical skills that are required of the EMO. A medic operating above 3000 m (9843 feet) requires familiarity with high-altitude conditions and frequently with cold injuries. This skill set is quite different from that required when operating in a jungle environment, where the likely injuries and illnesses include those resulting from local flora and fauna. Dive, cave, and maritime expeditions each require familiarity with the environment and activity-specific medical problems.

Goals. There is a long tradition within medical and scientific expeditions for the EMO also to be part of the research team to offer specific scientific skills in addition to providing medical care. More often, the EMO may provide medical support for a building project in a developing country, where traumatic injuries are likely to form a significant part of the EMO's workload. Personal development expeditions usually include a mixture of local project work with adventurous activities. Program participants, particularly on youth expeditions, may have psychological problems, so strong personal communication and counseling skills may be advantageous for the EMO. Other expedition types may include working with media production teams or film crews. The scope, duration, and workload encountered on such expeditions vary enormously and have the potential to stress not only one's

clinical skills, but also ethical and professional boundaries (see later).

Preexisting Medical Conditions. As previously discussed, increasing numbers of people with complex medical problems are successfully taking part in expeditions. EMOs should be fully familiar and able to deal with many conditions that lie outside their normal area of practice.

The EMO will often be required to possess nursing skills not normally required in the EMO's routine practice. EMOs typically need to record regular vital signs, dress wounds, clean and change soiled patients, and reposition patients to prevent pressure ulcers while awaiting rescue or evacuation. These skills are crucial to delivery of good remote-environment medical care.

Postexpedition Phase

In this phase the EMO will be responsible for the following:

- The expedition medical report
- Postexpedition medical advice for expedition members, including referral to specialists
- Follow-up where appropriate

EXPEDITION SKILLS

Expedition medicine is frequently practiced in challenging and hostile environments. A successful EMO must be capable of functioning autonomously and confidently in such environments and must possess appropriate expedition skills to permit the EMO to work effectively, without jeopardizing the safety of the expedition members. Such skills should be commensurate with the environment where the EMO is required to practice and might include the following:

- Basic camp craft: erecting a tent or hammock efficiently, cooking on a stove, and living safely and comfortably in the expedition environment
- Survival skills appropriate to the type of expedition
- Navigation: a vital skill to enable the EMO to operate safely and independently, and essential for locating casualties and organizing evacuations
- Radio communication skills: proficiency in the use of radios and satellite telephones
- Rope work and mountaineering skills

PERSONAL SKILLS

Desirable personal qualities of the EMO include self-awareness, good communication skills, empathy and compassion, adaptability, a sense of humor, and skills to facilitate conflict resolution.

Self-Awareness

An EMO should have a realistic understanding of his or her strengths and weaknesses and how the EMO interacts with the expedition team. The close proximity of expedition living heightens even minor tensions. The EMO is required to care for any team member who becomes ill or is injured, regardless of personal feelings toward the individual.

Communication Skills

Good communication skills are crucial to effectively eliciting a patient's problems and concerns. This includes communicating information and discussing treatment options and providing psychological and emotional support.[48] These communication skills are not only useful while practicing medicine, but also when working as an arbitrator in times of team conflict. This is discussed in greater detail later.

In the event of a death or serious injury, it may fall to the EMO to deal with the media (see later).

Empathy and Compassion

Emotional support of expedition members forms an important part of the EMO's responsibility. It is not unusual for individuals to place considerable emotional significance on their participation in an expedition. It may be the holiday of a lifetime or may be undertaken as affirmation after bereavement, divorce, or illness. With such psychological weight placed on the expedition, an injury or illness in an alien and threatening environment can result in an emotional response that is far greater than for a comparable problem at home, where the individual has readily available familiar support mechanisms. Increased availability of satellite telephones can actually worsen the situation. When things go wrong, the first reaction of a person is often to want to speak to family or friends. This can heighten the person's natural feeling of homesickness and further compound the emotional response. That said, reassurance that all is well at home can be very comforting when operating in remote areas.

Adaptability

A key quality of any EMO is the ability to adapt practice to the surrounding environment or conditions. Having the expectation that things may not go as planned is the first step in making allowances for these eventualities and preparing accordingly. One practical expression of this is planning a medical kit so that drugs and equipment can be used for more than one problem. The ability to think imaginatively and dynamically in changing circumstances is a crucial attribute of any EMO.

Sense of Humor

A great asset is a good sense of humor, and this is especially true of the EMO. Self-deprecating humor aids humility, promotes courage, and can diffuse tense and difficult situations. This sense of humor must be combined with sensitivity, patience, and compassion; always having a cheerful countenance can be viewed as being flippant or dismissive.

Skills of Conflict Resolution

There will be times of increased stress or pressure. The pressure has the potential to spill into professional conflict. Much that has been written on the art of conflict resolution[28] can probably be summarized in one word—*communication.* The EMO might be in the position of arbitrator during times of expedition conflict. The key to avoiding most issues of conflict is first to examine and resolve them during the expedition planning stage rather than to refrain from discussing them. Clear dialogue should highlight and resolve any issues in the following three categories:

- Decision making and hierarchy
- Expectations
- Purpose, morals, and ethics

Examine all areas that might cause a problem, and work through the issues. It is useful to consider worst-case scenarios and examine resolution strategies.

Honesty and integrity are two key aspects. There is often the temptation to skip uncomfortable issues, with the assumption that they can be addressed in a time of need during the expedition. All expedition team members should be encouraged to discuss uncomfortable issues ahead of time.

Decision Making and Hierarchy. Expedition medics are part of the expedition leadership team. Their decisions may inevitably affect members of the team, and occasionally the entire group. Therefore, it is important that persons making such decisions do so with good judgment and authority. During the planning stages, typical questions that should be asked are the following:

- Who is in overall charge of the expedition?
- What authority does the expedition medic have over factors that may influence the expedition timetable, particularly where safety is concerned?
- If an issue arises between the medic and expedition leader that cannot be solved, who can act as a mediator?

If there is an expedition medical team, establishing clarity of roles, responsibilities, and command hierarchy within this team is vitally important. By having a clear understanding of the skills, knowledge, and background of the medical team members, the lead medical officer will be able to make more informed decisions and avoid professional disagreements. This exercise should be completed at an early stage of the expedition (preferably in the planning stages) to avoid later difficulties.

Expectations. Team members may have differing expectations of the role of the expedition medic. This depends on their individual knowledge and experience and their confidence in caring for themselves. Expedition medics also vary in how much they expect individuals to look after themselves. Initially running daily clinics, where medical issues can be addressed in a more controlled environment, will enable the medical officer to decide on appropriate levels of input.

It is unlikely that the expedition medic will practice at the same intensity as in normal hospital environment, which some individuals might find frustrating. However, periods of intense activity may be required at any stage of the expedition with little or no warning. For many clinicians, this "rapid response" may be unfamiliar unless they are specialists in prehospital or emergency care.

There may be expectations surrounding the level of involvement the medic is expected to have in nonmedical expedition activities. Medical officers who opt out of nonmedical expedition work are likely to cause resentment among other hard-working team members. There must be a balance so that medic involvement in expedition activities and ensuing tiredness does not affect the ability to provide medical care in the event of an emergency.

Medics may find themselves in the position of having to provide medical care for indigenous populations. This remains a contentious subject. There is a requirement to balance help for persons in distress against the potential to undermine local health care systems. Medical officers working on expeditions in or near poor communities will be surrounded by health care problems that in their normal practice could be improved with simple interventions. There is no easy solution, and all team members are likely to find it difficult not to intervene at varying levels. The approach to providing medical care for local populations should be part of preexpedition planning and should be appropriately resourced, because use of expedition medical supplies to treat local populations might put the health of the expedition team at risk.

Another area of expectation to consider is health care and communication equipment. Members should have a clear understanding of access to medical and communication equipment while on expedition.

Conflict Stemming From Expedition Purpose, Ethics, and Morals. All team members also must have a clear understanding of the purpose of the expedition. This is equally important for the EMO. One can easily agree to take part in an expedition based on the location and work, without necessarily taking into consideration ethical or moral issues behind the trip, as in the following examples:

- Commercial adventure/charity expeditions
- TV/film production work—often in exciting locations, but sometimes with potentially questionable ethics
- Impact of the expedition on local people
- Disaster medicine and humanitarian aid work—may be motivated by good intentions, but with the potential to be carried out inappropriately
- Environmental issues associated with the expedition

Ethical considerations permeate every part of an expedition, from the expedition purpose or goal, through delivery of care to expedition members and affiliates, to the impact on host cultures and countries. The four principles of ethical debate and behavior[6] that can be appropriately applied to the individuals and expedition as a whole[2] are as follows:

1. Autonomy—the rights of individuals to decide for themselves to accept or refuse treatment, ideally based on an informed decision-making process
2. Doing of good—beneficence—making sure individuals are working for the benefit of others, through preparation, appropriate training, and delivery of care
3. Avoidance of harm—nonmaleficence—choosing when and when not to intervene and having awareness of the consequences of one's actions (physical, verbal, or emotional) on all parties, including the expedition team members, local communities, and the host country
4. Justice, equity, and fairness

WHO IS QUALIFIED TO BE THE EXPEDITION MEDICAL OFFICER?

The first EMOs were physicians who frequently combined providing medical care with their role as climbers or as physiologic or other scientific researchers.[37,39,62,64,68,71] Skills and knowledge were generally passed on to aspiring EMOs in an informal manner. With growth of commercial expeditions, many physicians with little or no experience or understanding of expedition medicine accepted the offer of a reduced-price place on an expedition. This provided the pretense of medical cover to the group, sometimes with disastrous consequences. The EMO does not necessarily need to be a physician. Emergency medical care on expeditions has been provided safely by registered nurses or paramedics with appropriate training and experience similar to civilian and military prehospital caregivers. There is no information as to how care provided by a nonphysician EMO compares with that provided by a physician; however, UK emergency nurse practitioners have demonstrated equally competent levels of skill and knowledge compared with traditionally trained medical colleagues.[5,59] No established medical specialty encompasses all the skills and knowledge required for the safe practice of expedition medicine.

If expeditions do not have a formal EMO, the preexpedition and postexpedition and expedition phases may be performed by different people. Preexpedition medical screening and planning and provision of training and medical kits may be provided by a corporate (company) EMO, whereas care in the field is delivered by the expedition leader or guide. Nonmedical veterans of many expeditions may be more experienced than the EMO, so, along with appropriately trained expedition leaders, they can provide a high standard of emergency care to expedition members. Box 80-1 gives an example of the lifesaving care provided by an expedition leader to a Nepalese porter during an expedition to Baruntse. The role of telemedicine in providing expert medical support to expeditions without an EMO and the legal responsibility of non–medically qualified leaders providing medical care to members of their group are discussed later. One unique model of care is the Everest Base Camp Medical Clinic (Everest ER), founded in 2003 by Dr. Luanne Freer to address the problems of expeditions on Mt Everest. The temporary clinic offers medical care to all expeditions on the Nepalese side of Mt Everest during the spring climbing season.[18,22]

Paralleling the explosive growth in commercial expeditions and increased formalization of all aspects of medical training are many courses around the world offering some form of wilderness, expedition, or mountain medical training. In August 1997, the medical commissions of the International Mountaineering and Climbing Federation (UIAA), International Committee on Alpine Rescue (ICAR), and International Society for Mountain Medicine (ISMM) established minimal requirements for courses in mountain medicine. These standards, last updated in 2010, have been adopted across many countries. There are now 17 UIAA-ICAR-ISMM–approved basic diploma courses in mountain medicine available worldwide. Courses are offered in France, Germany, Italy, United Kingdom, Norway, Canada, United States, Japan, and Nepal with supplementary courses in expedition medicine and rescue available in several countries.[54] With growing concern about possible litigation from expedition clients (see Legal and Ethical Considerations, later), there should be consensus among expedition medical providers about the core knowledge and clinical competencies required to practice expedition medicine in each of its major environments. Table 80-1 provides details of the UIAA-ICAR-ISMM syllabus for the Diploma in Mountain Medicine.

Satellite expeditions medically coordinated from a single, central base camp allow utilization of broader skill sets and abilities, with the most qualified or experienced medic able to provide advice or support from a central location (Figure 80-3). The numerous variations based on this theme might include having the senior EMO based with the group deemed at highest medical risk, with outpost medical support provided from that location.

BOX 80-1 Nepali Porter with Severe HACE and HAPE

A 50-year-old Nepali porter working for a commercial expedition that did not have a medical officer was taken ill at Makalu Base Camp (5450 m [17,881 feet]) in Nepal. The following is a summary of the excellent contemporaneous notes made by the expedition leader outlining the lifesaving treatment he gave to the porter:

08:20: Porter found to be semiconscious, vomiting, and to have frothy, blood-stained fluid around his mouth.
08:30: According to expedition medical protocols, the porter was given 8 mg of dexamethasone IM. He was unable to cooperate to swallow nifedipine. Shortly afterwards, the porter fitted and lost consciousness. His breathing became labored, irregular, and noisy. He was placed in a hyperbaric bag and monitored.
08:45: Contacted Kathmandu office of expedition company and confirmed need for urgent helicopter evacuation.
09:00: Regained consciousness but became distressed and disorientated. He was removed from the hyperbaric bag but seized again and once again rapidly lost consciousness.
09:10: The porter was placed back in the hyperbaric bag at 30° and monitored.
10:30: Intermittently regained consciousness but now appears unconscious. Unresponsive to sound. Respiratory rate 20 breaths/min.
11:15: Removed from hyperbaric bag. Had vomited and been incontinent of urine. Slurred speech and unable to stand. Still unable to take nifedipine. Rapidly deteriorated and put back in hyperbaric bag after it had been cleaned and his clothes changed.
14:00: Conscious and alert. Removed from hyperbaric bag. Complaining of headache. Began to become increasingly drowsy so placed back in hyperbaric bag.
14:30: Conscious and alert. Given further 4 mg dexamethasone IM. Able to take 20 mg nifedipine orally. Remained conscious and alert.
17:00: Remains out of hyperbaric bag, sleeping but rousable. Paracetamol 1 g.
20:30: Given further 4 mg dexamethasone IM and 20 mg oral nifedipine. Headache easing.

The porter was monitored overnight by his brother making observations every hour. He continued to receive regular dexamethasone and nifedipine. The following morning, when he was evacuated by helicopter to Kathmandu, his condition was much improved, although he remained very ataxic. He was cared for at the Kathmandu offices of the expedition company, where he was also reviewed by a Western physician, and made a complete recovery.

From Paul Donovan, expedition leader with Jagged Globe.
HACE, High-altitude cerebral edema; *HAPE*, high-altitude pulmonary edema; *IM*, intramuscularly.

TABLE 80-1 UIAA-Approved Basic Syllabus for the Diploma in Mountain Medicine

Basics of	Minimal Time (hr)	Instructors	Training
Altitude	3	High altitude experienced doctor	Theory
Hypothermia	4	Experienced doctor	Theory
Avalanche	4	Experienced doctor + mountain guide or avalanche/ski patroller	Theory + practical
Frostbite	2	Experienced doctor	Theory
Submersion and immersion in water	1	Experienced doctor	Theory
Heat and solar radiation	1	Experienced doctor	Theory
Survival in the mountains/exhaustion	4	Experienced doctor	Theory + workshop
Children and mountains	1	Experienced doctor (pediatrician)	Theory
Practical traumatology	4	Experienced doctor	Workshop
Weather	1	Mountain guide or meteorologist	Theory
Rescue techniques (introduction)	1	Experienced mountain rescue doctor, team member and/or mountain guide	Theory
Rescue techniques (practical)	2	Experienced mountain rescue doctor, team member and/or mountain guide	Practical
Mountaineering techniques in summer and winter, and personal mountaineering equipment	18	Mountain guides	Practical
Information About			
Nutrition	1	Experienced doctor or nutritionist	Theory
Exercise physiology	1	Physiologist or experienced doctor	Theory
Travel medicine	1	Experienced doctor	Theory
Navigation in the mountains	4	Mountain guide	Workshop + practical
Personal first-aid kit	1	Experienced doctor	Theory
Legal aspects	0.5	Experienced lawyer or doctor with medico-legal experience	Theory
Stress management	1	Experienced doctor	Theory
Preexisting clinical conditions	3	Experienced doctor	Theory
Analgesia in the field	1	Experienced doctor	Theory
International mountaineering organizations	0.5		Theory
Additional subjects selected by the course organizer	40		Theory, workshop + practical
Total	**100 hr**		

From http://www.theuiaa.org/upload_area/files/1/DIMMreg_20101-3.pdf.
UIAA, International Mountaineering and Climbing Federation.

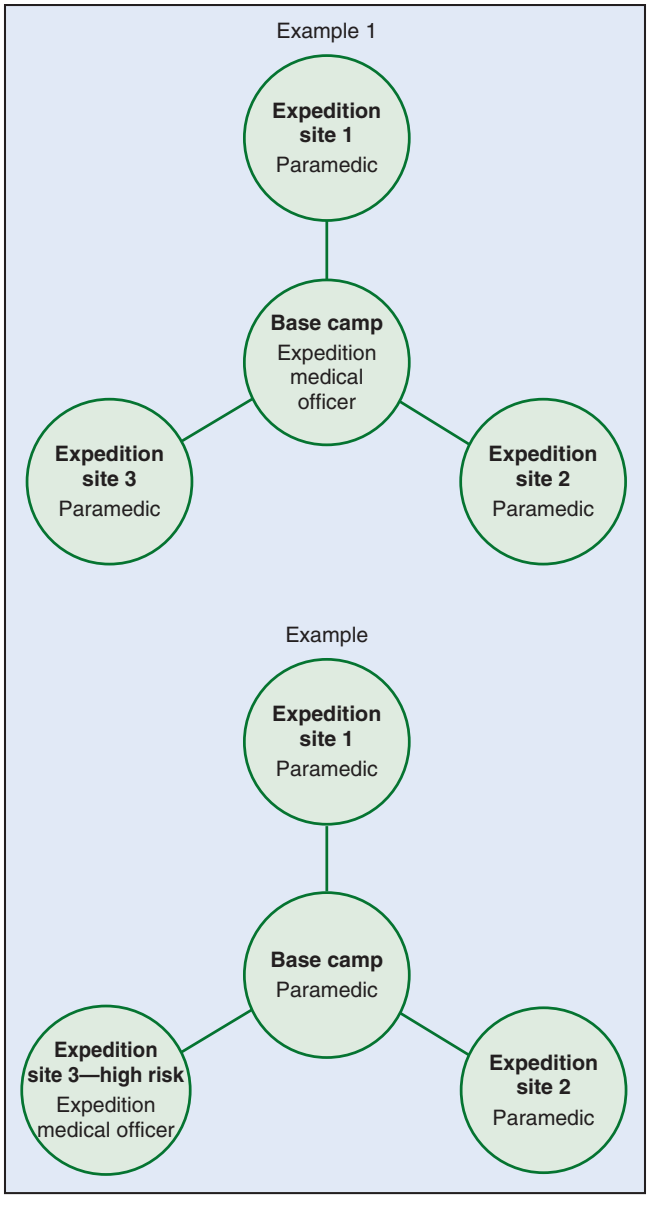

FIGURE 80-3 Allocation of medical staff according to level of risk and skills required at each expedition site. In Example 1 the expedition medical officer (EMO) with the highest level of skill and competency is based centrally with equal access to each expedition site. In Example 2 the EMO with the highest level of skill and competency has been allocated to the expedition site with the highest risk.

EXPEDITION MEDICAL PLANNING

The EMO should aim to prevent illness and injury and to treat as quickly and appropriately as possible persons who sustain injuries or become unwell. The chance of successfully achieving these aims is greatly increased by careful preexpedition planning, which should include medical screening of all expedition members and risk assessment and management. Other team members should also receive preexpedition medical training. Box 80-2 provides an expedition medical planning checklist.

MEDICAL SCREENING

Persons with special health care needs should be involved with careful preexpedition planning to aim for a safe and successful trip. Certain chronic illnesses and disabilities mean that some individuals will be unable to participate fully, but with forethought, they can still enjoy a worthwhile challenge or experience. The stresses and strains of expedition life may exacerbate underlying joint problems, inflammatory bowel disease, respiratory illnesses, angina, and other long-standing health issues. The main concerns are that if conditions worsen, definitive medical care may be very remote and evacuation times prolonged.

Before a decision can be made regarding an expedition team member's suitability for the proposed trip, it is essential to consider all risks that may lead to serious illness, or even death. For some persons, a different trip with less demanding objectives may be more suitable.

All participants should complete a detailed health questionnaire (Box 80-3). The information may prompt a request for further details from the patient, family physician, or specialist. Undeclared medical conditions may mean that the EMO is not in a position to give comprehensive medical care because of inadequate knowledge or lack of appropriate medications. It is important to determine the severity of the condition and whether the disease is stable, worsening, or improving. One useful predictor of future performance is the individual's prior ability to cope with wilderness travel in other isolated or remote areas. The individual may need to be involved in the final decision and take into consideration expedition duration and environment, presence of medical support, field communications, remoteness of location, and evacuation options.

All team members should be fully financially insured. Incomplete medical disclosure may invalidate insurance coverage.

GENERIC PREEXPEDITION ADVICE FOR PERSONS WITH PREEXISTING MEDICAL CONDITIONS

Any illness should be stable and well controlled before departure, and the individual, family physician or specialist, and EMO must

BOX 80-2 Expedition Medical Planning Checklist

- ☐ Advise and brief the team on medical issues (general and specific to expedition environment).
- ☐ Undertake medical screening of all expedition members.
- ☐ Encourage all participants to have a preexpedition dental checkup.
- ☐ Provide advice on immunizations and malaria prophylaxis.
- ☐ Organize appropriate first-aid training for all expedition members.
- ☐ Obtain, pack, and transport medical supplies and kits.
- ☐ Undertake a risk assessment, and prepare associated documents.
- ☐ Investigate local health services and medical facilities.
- ☐ Anticipate and plan evacuation of a severely ill or injured person from each part of the expedition.
- ☐ Consider the effects of weather and natural disasters such as tsunami, volcanic eruption, and earthquake.
- ☐ Prepare a communication network in case of evacuation.
- ☐ Organize medical insurance with full emergency evacuation coverage.
- ☐ Confirm that professional indemnity insurance will cover expedition medical officer role.

BOX 80-3 Health Questionnaire for Preexisting Medical Conditions

- Do you have a history of convulsions, asthma, or diabetes?
- Do you have any allergies?
- Have you ever had any heart problems?
- Have you experienced recurring back or joint problems?
- Please give details of any psychological or psychiatric illness, including eating disorders, deliberate self-harm, overdoses, depression, anxiety, or psychosis.
- Do you have any objections to any form of treatment, including blood transfusions or immunizations?
- Do you have any disabilities or ongoing medical problems?
- Do you take any medications?
- Any other medical conditions including surgical operations?

agree on a self-management plan. For example, in the case of a person with diabetes, a summary of the condition and recent test results, such as serial blood glucose levels, electrocardiogram, hemoglobin A_{1c}, and medications, are important data points for anyone who assumes care of the individual. Additional items of medical equipment may be required, so the EMO may need to acquire familiarity with uncommon medications and new equipment. During the expedition, support and advice will be readily available from the EMO. Where sufficient communications exist, it may be possible to obtain advice from an individual's physicians at home, but this should not be relied on. Potential risks and possible difficulties obtaining further medical help should be discussed openly beforehand.

Where appropriate, with conditions such as diabetes or epilepsy, other team members should have an understanding of the individual's condition and should be able to give emergency treatment if required, such as for management of hypoglycemia or convulsions. Explicit guidelines about actions to be taken with any warning signs of a worsening condition should be documented in advance. An action plan for asthmatic patients can be downloaded at http://www.asthma.org.uk/advice-asthma-action-plan.

It is important that, where appropriate, all participants are aware of and prepared to accept the risks that an individual's preexisting medical condition can bring to an expedition, such as the need for evacuation. The individual must be physically and psychologically prepared for the planned expedition. Training in a similar environment will enable an assessment to be made of how an individual will cope during the expedition.

If there have been problems during a trip, prompt reassessment should be advised on return to the home country. It is important to send a report of any significant problems to the patient's physician.

VACCINATIONS, MALARIA CHEMOPROPHYLAXIS, AND PERSONAL MEDICATION

Vaccinations

The EMO should ensure that all expedition participants have received complete proper childhood vaccinations schedule. Many communities visited by expedition teams will be vaccine naive, having never had the opportunity to receive immunizations. Ensuring childhood vaccinations reduces the chance of contracting vaccine preventable disease and, more importantly, not introducing it into local populations. Certain vaccinations recommended for travel will not be part of the childhood schedule. Expert advice should be sought as to which vaccines are appropriate for the expedition, based on location, expedition activities, and access to definitive and reasonable health care. Some countries may demand certification of vaccination, such as for yellow fever. Information about appropriate travel vaccinations can be found at http://www.cdc.gov/vaccines/schedules/index.html or www.nathnac.org.

Malaria Chemoprophylaxis

People undertaking expeditions to the tropics should obtain accurate advice regarding malaria chemoprophylaxis (see Chapter 40). One must ensure the following:

- Take the malaria chemoprophylaxis appropriate for the area to be visited.
- Take tablets as prescribed, and remember to take them for the recommended time after leaving the malaria risk area.
- Malaria chemoprophylaxis is never 100% reliable

Personal Medication

Individuals taking personal medication should ensure that:

- They have sufficient quantities for the duration of the trip, plus extra in case of emergency or delays.
- Medication can be stored appropriately.
- Medication does not contravene any international border restrictions (see www.incb.org for more accurate information about transporting medications across borders).
- Medication is not likely to interact with travel vaccinations or malaria chemoprophylaxis.

BOX 80-4 Formal Risk Assessment

- ☐ Hazard
- ☐ Risk
- ☐ Risk level
- ☐ Control measures
- ☐ Additional action
- ☐ Review mechanism

Potential Hazards

- Physical
- Biologic
- Chemical
- Human-made
- Personal safety
- Environmental impact

Personal medication should be carried in hand luggage to help prevent it from becoming lost.

Medication should be accompanied by an official letter detailing its intended use and the prescribing authority. This should be signed by the prescriber, with an official stamp, and, where possible, the needed language translations. Individuals should consider the possibility of resupplying medicine in country.

RISK MANAGEMENT

Potential risks to expedition members should be systematically identified and control measures instituted to reduce the risk.[4] This easily neglected exercise is an important part of expedition planning. The EMO should work closely with the expedition leader to formulate a formal risk assessment (Box 80-4). All team members must be fully informed before departure of the risks to which they are likely to be exposed and the means of hazard control, and they must understand that it is not possible to eliminate all risk completely (Box 80-5). With this information, they can make an informed decision about their participation in the expedition.

- A *hazard* is anything that may cause harm. Examples are fall from a height, rockfall, motor vehicle crash, and high environmental temperature.
- The *risk* is the chance that somebody could be harmed by a hazard. The chance may be very low, but there may be very serious consequences.

Risk assessments should periodically be reviewed during the expedition because hazards change. For example, while ascending Mt Kilimanjaro in Tanzania (5895 m [19,341 feet]), the hazards change from those of a tropical environment to those of a high-altitude environment.

BOX 80-5 Briefing the Expedition Team

Topics to Cover for Hazard Control and Risk Reduction

- ☐ The importance of clean water and hygienically prepared food
- ☐ Dangers of the sun—sunburn, dehydration, and heat illnesses
- ☐ The need for good personal hygiene to prevent skin and other infections
- ☐ Promoting sexual health by avoiding risky sexual activity
- ☐ Awareness of emotional problems such as isolation, homesickness, and conflict within the group
- ☐ Drug-taking behavior must be avoided, and alcohol should be used only in moderation
- ☐ Avoiding bites and stings, use of insect repellents, and dangers of walking barefoot
- ☐ Special risks for some activities, such as high-altitude mountaineering, scuba diving, kayaking, and sailing
- ☐ Appropriate preexpedition immunizations and choice of suitable antimalarials
- ☐ Preexpedition fitness, including a dental checkup
- ☐ Preparation of a suitable personal first-aid kit and first-aid training tailored to the environment and activities planned

The most serious risks while traveling are falls and other injuries; drowning; road traffic collisions; altitude illness and heatstroke; serious infections (malaria, blood borne viruses), and homicide.[4] Although the list is not exhaustive, Table 80-2 highlights the environment-specific hazards and risks that should be systematically evaluated during risk assessment.

Country-Specific Risks

Detailed information about safety and security, local laws and customs, entry requirements, and health risks for all countries can be obtained through the following websites:

- Australia: http://www.dfat.gov.au
- Canada: http://www.voyage.gc.ca
- United Kingdom: http://www.gov.uk/foreign-travel-advice
- United States: http://www.travel.state.gov
- U.S. Centers for Disease Control and Prevention: http://www.cdc.gov/travel
- World Health Organization: http://www.who.int

Before departure, or shortly after arrival on location, local medical facilities, local and regional hospitals, clinics, and pharmacies should be identified and, if possible, inspected. Embassies often provide useful information regarding good-quality medical

TABLE 80-2 Expedition Risks and Hazards: General and Specific to Environment

Setting/Cause	Hazard/Risk
Hazards Common to Most Expedition Environments	
Solar radiation	Sunburn
High or low ambient temperatures	Heat and cold injuries
Hot, dry environments	Dehydration and heat exhaustion
Poor water and food quality	Gastrointestinal illnesses
Isolation	Unfavorable psychological reactions
Overcrowding	Upper respiratory and other infections
Attitudes and behavior	Sexually transmitted infections, injuries
Wildlife Hazards	
Dogs	Infected bite wounds and rabies
Leeches	Wound infections
Snakes	Envenomation
Ticks	Typhus and other tick-borne diseases
Hippos	Animal attacks, capsizing of boats
Parasites	Infestations
Bears	Multiple injuries
Local Conditions	
Lack of shelter	Hypothermia
Dangerous roads	Road traffic collisions
Open fires and stoves	Burns and scalds
Endemic diseases	Malaria, schistosomiasis, dengue fever, encephalitis, blood borne viruses
Human factors	Assault, kidnapping, terrorism, conflict
Environment-Specific Hazards	
High Altitude	
Altitude	Altitude-related illness (acute mountain sickness [AMS], high-altitude cerebral edema [HACE], high-altitude pulmonary edema [HAPE], altitude-related cough)
Solar radiation	Sunburn and ultraviolet (UV) keratitis (snowblindness)
Cold	Hypothermia and tissue cold injury
Avalanche and rockfall	Traumatic injury
Blizzard	Becoming lost and hypothermic
Lightning	Lightning injuries
Climbing	Falls and traumatic injury
Snow holing	Carbon monoxide poisoning Asphyxiation
Desert	
Solar radiation and extreme heat	Sunburn and heat illnesses
Lack of water	Dehydration, collapse
Snakes and scorpions	Envenomation
Jungle	
Heat/high humidity	Heat exhaustion, syncope, prickly heat
River crossing	Drowning and being swept downstream
Deadfall	Injuries
Plant life	Skin reactions, anaphylaxis
Animal and insect	Snakebite, infected bites, arbovirus infections
Maritime	
Sun and wind	Sunburn/windburn and UV keratitis
Cold and heat	Thermal injuries
Saltwater	Saltwater boils
High waves	Seasickness, drowning
Ropes and pulleys	Hand trauma
High rigging	Falls and traumatic injury
Isolation	Interpersonal conflict, adverse psychological reactions

services; some insurance companies list approved hospitals or local physicians. In some parts of the world, emergency assistance may be obtained from the military. This includes search and rescue support using helicopters, inflatable rafts, and all-terrain vehicles. National parks staff and nongovernmental organizations (NGOs) may offer support in certain circumstances. In some parts of the world, there is risk from natural disasters. For further information, see http://www.preventionweb.net/english/hazards/.

EXPEDITION MEDICAL TRAINING

When operating in wilderness areas, it is common to provide medical care in remote hostile environmental conditions. The EMO will usually carry out his or her role independently with finite medical supplies, sometimes with limited communications and unreliable casualty evacuation facilities. Patient evacuation may be delayed for many reasons. When the EMO is required to look after more than one patient or casualty, resources will be stretched to the limit. It is therefore important that expedition team members be trained to give first aid and second aid. The exact nature of medical training for expeditions to wilderness areas should be tailored to suit the environment. For example, it may need to include training in tropical illnesses, malaria, cold injury, and high-altitude illness. Many of these subjects are not covered in "standard" first-aid courses. Advanced techniques that should be taught include use of select prescription medications, use of specialized rescue equipment, and reduction of simple fractures and dislocations.[12] All team members should have completed basic first-aid training. Essential topics for persons who operate in wilderness areas are the following:

- Safe approach to the injured casualty, including scene assessment
- Basic life support, including management of cardiac arrest and choking
- Understanding the causes of shock and its field treatment, especially control of bleeding
- Care of the unconscious patient, including potential causes of loss of consciousness in the expedition's environment
- Management of acute medical problems (e.g., asthma, hypoglycemia, convulsions)
- Packaging and moving patients, including stretchers and logrolling
- Patient medical reports

There is no clear consensus in the United States regarding "industry standards" for wilderness first aid.[69] In the United Kingdom, British Standard 8848 was established in April 2007 and revised in 2014. This simply states, "The venture provider shall check the first aid qualifications of the leadership team and ensure that they are commensurate with the needs of the venture."[9] Boxes 80-6 and 80-7 list common expedition complaints and recommended training courses for wilderness first aid.

EXPEDITION MEDICAL KIT PREPARATION

Choosing, assembling, and packing an expedition medical kit takes time and effort. Factors dictating the composition of medical kits are as follows:

- Number of expedition team members, including local staff
- Duration of the expedition
- Distance from medical help
- Presence of endemic diseases or environmental hazards, such as high altitude and extreme cold
- Type of activities, such as diving, rock climbing, vehicle-based travel, sailing, or caving
- Medical skills of the team
- Preexisting medical problems of the group members
- Cost, weight, and bulk

It is not possible to prepare for every possible eventuality, and there is always a balance between being underprepared and having too much in a kit.[40] For detailed recommendations regarding medical kit contents, see Appendix to this chapter.

BOX 80-6 Common Injuries and Illnesses during Wilderness Expeditions

Common Expedition Complaints
- Blisters
- Orthopedic injuries, including fractures and dislocations
- Splinters and other foreign bodies

Common Expedition Medical Conditions
- Infections, such as diarrhea, upper respiratory, and urinary
- Asthma
- Convulsions
- Fainting
- Headaches

Serious Medical Problems
- Anaphylaxis
- Chest pain
- Abdominal pain
- Cough and shortness of breath

Important Injuries
- Head and spinal injuries
- Chest injuries
- Abdominal trauma
- Pelvic injuries

Environmental Injuries
- Altitude-related illness
- Heat illnesses—heat exhaustion and heatstroke
- Cold injuries—frostbite and hypothermia
- Diving injuries
- Venomous bites and stings

Patient Handling
- Moving, lifting, and straightening of injured casualties
- Patient transportation, including improvised stretchers

Diagnostic Equipment

This should include simple diagnostic apparatus such as stethoscope, sphygmomanometer, otoscope, urine testing strips, lightweight pulse oximeter, near-patient malaria testing kits, and low-reading thermometer.

Medical Kit Packaging

Containers should be lightweight, robust, and allow easy identification of the contents. Depending on the environment, the containers should protect from impact, crush, dust, moisture, and other contamination. Medications may need to be protected from extremes of hot and cold (see Appendix: Drug Stability in the Wilderness).

In general, liquid medicines are best avoided because of weight and bulk. Tablets should be in blister packs to protect from damage during transport. Glass ampules are less robust than plastic ampules; both need to be protected from extremes of cold and heat. For insulin, snakebite serum, and other medications that must be kept cold, specialized pouches are available, such as those produced by Frio (http://www.friouk.com). Food vacuum flasks have been used to protect medication from desert heat and Arctic cold.

When preparing the medical kit, related items should be packed together. For example, dressing materials should be in one box, tablets in another. This means that many different boxes do not have to be opened to deal with one clinical problem. It

BOX 80-7 Recommendations for Comprehensive Training Courses for Wilderness Medicine

Basic First Aid
- Cardiopulmonary resuscitation (CPR) and choking management
- Control of bleeding
- Wound and burn management
- Bone and joint medicine
- Treatment of the unconscious casualty

is helpful to mark clearly the contents on the lid of each box, so that the boxes do not need to be opened to determine the contents.

Problems of Transporting Controlled Drugs

Morphine and other controlled drugs should be taken on overseas expeditions only under strict supervision. Some countries impose stringent laws,[26] including the death penalty, for possession of opiates. In the United Kingdom, a Home Office license is required to export controlled drugs, but this does not protect the individual from applicable laws in other countries.[25] If controlled drugs are dispensed, this should be recorded in a controlled drugs register.

A valuable source of information on carrying medications can be found through the International Narcotics Control Board.[42] Information is heavily weighted toward narcotics and drugs that affect the central nervous system, such as benzodiazepines, and the website contains information only for countries willing to submit data. Nevertheless, it is a valuable resource for the EMO. The EMO should pay particular attention to any medications that affect the central nervous system, any that can be abused (e.g., steroids), injectables, and large quantities of certain medications. As with personal medication, the medical kit and medication should be accompanied by an official letter, detailing the kit's intended use, the person for whom it is intended, and the prescribing authority. This should be signed by the prescriber, with an official stamp, and where possible, needed language translations.

Treating Infections

Antibiotics and antimicrobials are frequently used on expeditions to treat or prevent GI illness, wound and skin infections, respiratory infections, and important tropical illnesses such as malaria, typhus, and leptospirosis. A range of familiar antibiotics should be carried to cover common, important infections. The chosen antimicrobials should be tailored to local resistance patterns, where known, and should cater to persons who may have antibiotic allergies.

Analgesia

Many injuries and illnesses are painful, so a comprehensive range of analgesics should be available. Analgesia should be offered regularly to control pain. Ketamine may be considered by experienced practitioners for its analgesic and anesthetic properties.

Other Essential Drugs

Regardless of whether there is an asthmatic team member, all expedition medical kits should include a salbutamol inhaler and medications to treat anaphylaxis: injectable chlorphenamine, epinephrine, and prednisone or hydrocortisone. Both motion sickness and GI illness can cause incapacitating nausea and vomiting. Suitable antiemetics include ondansetron (Zofran), cyclizine (Marezine, Marzine, and Emoquil in U.S.), and prochlorperazine (Compazine, Stemzine, Buccastem, Stemetil, and Phenotil). The latter may be given intramuscularly or via the buccal route. Other injectable drugs to consider include local anesthetic agents, parenteral antibiotics, and intravenous (IV) fluids.

Creams and Ointments

Antiseptic creams, antibiotic ointment for conjunctivitis, antifungal preparations, a mild corticosteroid ointment, and antimicrobial cream or ointment for burns should be included in all kits.

Emergency Equipment

Depending on the expedition, the EMO may consider advanced airway equipment if the provider is competent in its use, and if rapid evacuation is possible in the event of using such a device, or the condition requiring such a device can be managed, unsupported, for a prolonged period. Similar consideration should be given to the appropriateness of oxygen therapy. Transporting oxygen in useful quantities presents major logistical challenges that will be beyond the scope of many expeditions.

For persons operating in areas where they may encounter severe trauma, a combat application tourniquet and QuikClot may be required for treatment of torrential hemorrhage. It is important to base the decision to carry such equipment on a realistic assessment of the likelihood of a safe and rapid evacuation of any casualty requiring such interventions. Many different emergency splints are available to manage orthopedic injuries. Improvisation is always an option.

Obtaining Medical Supplies

Purchasing medical supplies for expedition medical kits can be quite expensive. Some pharmaceutical companies may donate drugs, particularly if there is recognition of sponsorship. Hospitals and pharmacists may provide drugs at their cost. Many drugs can be purchased less expensively in destination countries, but there are important concerns regarding efficacy and counterfeit drugs.

Base Camp and Satellite Medical Kits

A comprehensive medical kit should be kept at base camp.[25] Satellite camps should have smaller kits tailored to the size of the group, medical training of team members, and likelihood of serious illness or injury. In addition, each team member should carry personal medication, with some spares (Box 80-8). For more prolonged expeditions or remote field stations, mechanisms must be in place to resupply medical kits.

Medical Kits for Special Environments

The same basic medical kit can be used in many different theaters of operation; however, modifications will be required, depending on activities and environment[60]:

- *Tropical regions:* The kit should include spare antimalarial drugs and near-patient testing kits, snakebite antivenom (controversial), and larger quantities of antibiotics for wound and skin infections. It is worth considering IV fluids for treatment of dehydration and heat illness.
- *Mountaineering expeditions:* Trips above 4000 m (13,123 feet) must include acetazolamide, dexamethasone, and nifedipine. Larger groups may consider bringing a portable hyperbaric chamber and oxygen cylinders. Chemical oxygen generators (e.g., emOx) are available in some countries.
- *Maritime and diving trips:* Seasickness medication, ear drops for otitis externa, and treatments for marine envenomation should be considered.

COMMUNICATIONS TECHNOLOGY

Expedition communication technology consisting of two-way radios (AM, high-band FM, or UHF), mobile telephones, or satellite telephones is increasingly financially accessible to even small and lightweight expeditions. Many companies now offer ready-to-use expedition communication packages complete with web hosting.

If satellite communications are part of the expedition kit, ensure that the correct documentation and visa paperwork is in place. Some countries (e.g., India) will not allow personal satellite phones into the country without appropriate documentation. Arriving without this is likely to result in a fine or even imprisonment.

Communications operate at different levels:

- *Internal communications* between expedition members to facilitate expedition logistics, information exchange, and

BOX 80-8 Team Members' Medical Kit

- ☐ Blister kit
- ☐ Adhesive plasters and dressings
- ☐ Antiseptic wipes
- ☐ Simple analgesic—acetaminophen or preferred painkiller
- ☐ Antihistamine tablets
- ☐ Hydrocortisone 1% cream—chlorphenamine tablets
- ☐ Antiemetic and oral rehydration sachets
- ☐ Personal medication, including antimalarials if appropriate
- ☐ Insect repellent and sunblock

BOX 80-9 Principles of Good Radio Procedure for Expeditions

Good radio procedure is marked by the following:
- *Clarity:* Always identify yourself and whom (you think) you are addressing. Speak slowly and clearly.
- *Accuracy:* Use the NATO phonetic alphabet to spell difficult or unusual words.
- *Brevity:* Be brief. Think about what you are going to say before transmission. If in doubt, write it down.

End each message with "Over."
Send message "Understood, over" or "Roger that, over" to acknowledge a received message.
Send message "Standing by" if you are continuing to monitor the frequency.
End message with your identity and "Out" if you have finished transmitting.
Use the mnemonic ETHANE to facilitate accurate transmission of casualty information:
- **E**xact location
- **T**ype of incident
- **H**azards
- **A**ccess
- **N**umber of casualties
- **E**mergency services on scene or required

NATO, North Atlantic Treaty Organization.

medical care. This may be over considerable distances for large expeditions with several sites. It is crucial that expedition members be familiar with radio procedures to facilitate accurate transmission of information (Box 80-9).

- *Communication with local agencies,* such as national park authorities, the military, embassies, or rescue services. It is important to ensure that one knows before departure correct telephone numbers and radio frequencies used by these agencies.
- *Communication with the expedition home country* for contact with the expedition head office, sponsors, or the media, and for expedition members to remain in touch with their families.
- *Telemedicine* is facilitation of health care delivery by exchange of health care information across distances. This can range from simple telephone advice to transmission of complex diagnostic images or data for remote analysis.[72] Telemedicine clearly has significant potential to deliver diagnostic services and expert advice into remote areas. The French Institut de Formation et de Recherche en Medecine de Montagne (Ifremmont), based in Chamonix, offers a subscription service for expedition trip leaders, guides, and EMOs that can help in expedition medical preparation. It provides 24-hour telephone access to expert medical advice in French or English in the event of a medical problem.

Box 80-10 outlines the story of a British climber who sustained frostbitten toes on Mt Aconcagua and avoided amputation through consultation with the UK Frostbite Advice Service. This service has existed since 2005 and helped approximately 150 climbers with a combination of remote service advice, often using digital imaging, and rapid follow-up consultation on return to the United Kingdom. Contact details for both Ifremmont and the UK Frostbite Advice Service are given in the Resources section at the end of this chapter.

When using communications of any type to discuss confidential patient details, remember that there is always the possibility that someone unintended may be listening.

LEGAL AND ETHICAL CONSIDERATIONS OF EXPEDITION MEDICINE

Most people who venture into wilderness areas are willing to help sick or injured travelers in their own party or strangers whom they may encounter. In some countries, such as France, laws exist that make it an offense to not provide assistance to somebody in peril. These are sometimes referred to as Good Samaritan laws. In other parts of the world, offering assistance remains only an ethical and not a legal obligation.

BOX 80-10 Telemedicine Saves Climber's Frostbitten Toes

A 48-year-old male and one companion set out on an attempt to cross Antarctica.

The team utilized kites to harness wind power and propel themselves across the ice while on skis. They averaged 47.5 km (28.5 miles) per day for 81 days and covered a total of 3854 km (2312 miles) in that time. Temperatures ranged between –30° and –45° C (–22° to –49° F). With wind chill and at higher elevations, temperatures likely were as low as –60° C (–76° F). The expedition spent much of the time between 2896 m (9500 ft.) and 3658 m (12,000 ft.).

On day 22 of the expedition, the man injured his right big toe. His toenail broke, and the distal toe subsequently became swollen and developed a friction blister. The fluid underwent repeated freezing and thawing, which contributed to cold injury. Initial care involved ibuprofen, 800 mg twice daily, and dressing the toe with both antibiotic ointment (fucidin and polysporin) and medical tape each morning and evening. On day 38, the patient sought medical advice via satellite phone from the physician based at the Union Glacier Camp (Figure 80-4). An additional opinion was requested from a UK expert in frostbite injuries; Internet communication was established, and he confirmed the diagnosis of frostbite.

On completion of the expedition, the great toe improved. After several weeks of recovery, the toe sloughed necrotic tissue, and no bone involvement was suspected. Additional consultation at the Intermountain Burn Center confirmed that both toes would likely recover without surgical debridement or amputation. The toes eventually healed as predicted.

Contributed by Professor Chris Imray.

DUTY OF CARE

Each person has a duty of care not to injure others; however, this duty is different in certain circumstances. Leaders or members of a group have a clear duty of care to the other members of their group. Moral and ethical duties may exist to rescue another person, but these must be distinguished from legal duties. Common law does not impose a legal duty on an individual to rescue another person; however, a legal duty may be imposed on certain people in certain circumstances. A physician is under a legal duty to render emergency care to his or her own patient,

FIGURE 80-4 Initial photograph of patient's frostbite on day 38 (December 12, 2011) of the expedition. *(From Russell KW, Imray CH, McIntosh SE, et al: Kite skier's toe: an unusual case of frostbite. Wilderness Environ Med 24(2):136-140, 2013.)*

although professional bodies such as the UK General Medical Council expect physicians to provide emergency assistance even when off duty: "In an emergency, wherever it may arise, you must offer anyone at risk the assistance you could reasonably be expected to provide."[24] Whether a physician is treating a patient, advising a patient, or advising an expedition company, a clear duty of care exists in law. All who provide medical care or advice, whether physicians, nurses, paramedics, or laypersons, must do so reasonably and carefully.

A parent is under a legal duty to rescue his or her child. Police and fire service personnel are under a legal duty to rescue people in distress. Once a person undertakes the rescue, there is a legal duty to do everything possible to complete the rescue without causing personal injury. The law does not expect any rescuer to lose his or her life, even when circumstances mean that there is a legal duty to rescue. In a court of law, assessment of whether an individual has met the duty of care expected of that individual would is judged according to the principles discussed next.

Level of Control and Age/Experience of the Ill or Injured Person

Supervision of any wilderness activity must be appropriate to the age and experience of the participants. This is particularly important when working with children or youths, who cannot be expected to have the same degree of knowledge in wilderness situations as would an older, more experienced adult. For commercial groups with inexperienced adults, suitable guidance should be given by persons who are familiar with the environment and management of common problems. Appropriate staff-to-participant ratios should be determined to ensure adequate supervision.

Comparison with Peers

The courts will compare the provided standard of care with that expected from a person with similar experience and training acting in the same or similar circumstances. In effect from April 2007, British Standard 8848 describes recommended safety standards for expeditions and other adventure travel. This standard was revised in 2014.[69]

Likelihood of an Incident Occurring

In law, if an accident has happened before in similar circumstances, it could do so again, and precautions should be put in place to prevent recurrence.

Maintenance of Equipment and Cost of Precautions

It is essential that medical, safety, and rescue equipment be appropriate for the wilderness area to be visited. Procedures must be in place to guarantee that equipment is fit for purpose and correctly stored and packaged to prevent damage when being transported into the theater of operation. Adequate funds must be invested in providing adequate medical kits and supplies, but a court might understand that cost of excessive precautions might preclude the activity in the first place.

Emergency Situations

In the case of an emergency, the court will take into account the specific circumstances, such as the need to act with speed in a hazardous situation, in determining whether a practitioner has acted with reasonable care. Courts recognize that medicine is practiced in remote areas and that medical resources are limited.

Standard of Care

In UK law, the case of *Bolam v Friern Hospital Management Committee* (1957) produced the following definition of what is reasonable: "The test is the standard of the ordinary skilled man exercising and professing to have that special skill. A man need not possess the highest expert skill at the risk of being found negligent. It is sufficient if he exercises the skill of an ordinary man exercising that particular art." This definition is supported and clarified by the case of *Bolitho v City and Hackney Health Authority* (1993), where the House of Lords ruled that any decision must have a logical basis.[8]

Courts have indicated that they are not prepared to allow inexperience as a defense in actions of professional negligence. If a physician is unable to exercise reasonable care in carrying out a particular task, the physician should not undertake that task. If a practitioner professes to be an expedition physician (and as such, having a "specialist" skill), the provider's actions are judged against what might reasonably be expected of a competent expedition physician, even if this is the first time the practitioner has ever taken on such a role.

Confidentiality

All persons who are ill or injured must be confident that sensitive medical information will be kept confidential. For example, such information will not be made known to the rest of the expedition team or other individuals who are not directly involved in medical treatment or nursing care. However, in the United Kingdom, the General Medical Council has made it clear that physicians also have a duty to the public at large. Rare circumstances can arise where confidentiality needs to be broken so that the health and safety of other expedition members are not jeopardized. The expedition leader may need to be informed that an individual is concealing an illness or refusing treatment. Box 80-11 gives an example of a situation where a patient's withholding information about his past medical history engendered significant consequences for himself and the expedition.

Consent

Before starting treatment, the recipient must give consent. This means explaining what treatment is planned and ensuring that the patient is aware of the rescuer's level of training and experience. There must also be agreement to continue treatment. Consent may be implied from the circumstances. Voluntary submission to treatment usually indicates consent. In the expedition or wilderness setting, verbal consent must often be sufficient. In situations where treatment carries considerable risk, or is controversial, informed consent should be obtained, documented, and ideally witnessed by an observer.

The concept of consent is governed by the law of battery. Without consent, treatment is assault. The law usually presumes

BOX 80-11 Urinary Retention at Concordia

A 68-year-old man was taking part in a commercial trek to K2 Base Camp at Concordia in Pakistan and over the Ghondokoro La (5585 m [18,323 feet]). As part of preparation for the trip, he had been required to complete a comprehensive medical questionnaire that was screened by the company medical officer, a physician with long-standing experience in mountain and wilderness medicine. The trekker declared no significant health problems.

Having arrived at Concordia, the group leader was woken at around midnight by one of the trekkers to say that his tent mate, the 68-year-old man, was unable to pass urine and was in considerable discomfort. He was well hydrated and had suffered no trauma. He again denied any significant past medical history. A satellite telephone call was made to the company's medical officer, but the connection was poor and a detailed discussion of the case was not possible.

Simple measures, including diazepam administration and sitting the man in a large bowl of warm water, produced no result. The man was now in considerable pain. An inquiry was made of all the other groups camping at Concordia that night, but none had a urinary catheter. Eventually, an intravenous administration set was found, from which was improvised a urinary catheter. The man was successfully catheterized by the group leader, who had previously trained as a radiographer. This produced 1.5 L of heavily blood-stained urine.

After a considerable wait due to bad weather, the man was evacuated by helicopter to the District Headquarters Hospital at Skardu, where it became apparent that he had a history of prostatism and had been previously taking finasteride. Because of his failure to declare his history of prostatic problems, the man's insurance was void and he was required to finance his evacuation and treatment in Pakistan.

consent in an emergency situation when immediate action is necessary for protection of the patient's life. The law presumes that most reasonable persons under the same or similar circumstances would want their lives saved, if at all possible. Competent patients have the right to refuse treatment, even if, in the rescuer's opinion, this will not be in their best interest.

Competence and Capacity

A competent person has the right to refuse treatment if the person understands the consequences of such a refusal; however, a competent adult may lack the capacity to consent as a result of a comatose state. Intoxicated adults, however, have been deemed by some courts to have the capacity to consent. Severe intoxication that substantially impairs understanding is a "gray zone."

The only person who can give consent to treatment for someone age 16 or older is that person himself. Consent to treatment for a child younger than 16 years is given by a parent or guardian, although the child should be given information relevant to his or her age and understanding, and the child's consent also should be sought. Children under 16 years can consent to medical treatment themselves if, in the opinion of the physician, they are capable of understanding the nature and consequences of that treatment. When taking children under age 16 on an expedition, it is wise to gain written permission from the parent or guardian that medical care can be given if it is thought to be in the child's best interest.

Negligence

To prove negligence and sue for damages, the plaintiff must establish a usual standard of care, then prove a breach of that standard of care and that as a result of that breach, there is demonstrable injury. It must also be proved that the breach of duty was the logical and legal cause of the claimed injury (causation).

Contributory negligence is a factor that reduces liability. For example, a novice expedition member may forget to pack essential survival items, despite being informed that these items were required. Any settlement for negligence related to not having the items might then be reduced.

How Much Should Laypersons be Taught About Medicine?

In the United Kingdom, the law does not prohibit any person from practicing medicine or dentistry; however, it is an offense for any person to pretend to be or imply that he or she is a physician. Thus, the essence of what treatment should be provided by laypeople is largely a matter of patient consent and understanding.

Persons who participate in hazardous activities may, in many circumstances, be held to consent to the risks and rigors dictated by such a circumstance. In other words, if you become injured or ill, you have accepted that medical care may be of a less satisfactory nature than in a modern emergency department. It is very important that group members are involved in the risk assessment process and are aware of the level of medical care that can be provided.

Laypeople should be taught sufficiently to enable any expedition to be safe insofar as that can be achieved. There exists a duty of care to exercise skills consistent with training, experience, and procedures. The duty of care will obviously vary. Care rendered by a completely untrained "Good Samaritan" providing urgent assistance in extreme or remote circumstances can easily be distinguished from the setting of a simple bony fracture by a trained first-aider acting at the direction of medical personnel providing advice by telephone or radio. The duty of care is defined in each individual circumstance.[17]

Legal Position of a Physician Advising Care to be Administered by a Layperson

Persons accepting responsibility to provide medical, nursing, or paramedical help must be judged according to the state of their knowledge and experience and the extent to which they follow directions or advice given to them by more highly or appropriately qualified personnel removed from the accident scene. The higher the degree of training provided and greater the detail of medical support in place, the greater is the expectation of the patient to be properly treated and rigor with which the duty of care is interpreted by lawyers.

Liability on Commercial Expeditions

Medical indemnity is discussed in detail later (see Professional Indemnity Insurance). Most medical indemnity organizations provide Good Samaritan coverage for physicians acting in any part of the world. The British Medical Defence Union (MDU) defines a Good Samaritan act as "The provision of clinical services related to a clinical emergency, accident or disaster when you are not present in your professional capacity but as a bystander," and states that "MDU members who have a current Professional Indemnity Policy are covered for claims arising from Good Samaritan acts anywhere in the world."[51] However, in an expedition setting, this would apply only where a team member just *happens* to be a physician. It would certainly not cover a physician receiving any form of inducement (e.g., a discount in the trip fee or sponsorship in kind) that implies the physician has an official medical role on the expedition.

Expedition companies have a responsibility in common law to ensure that any EMO they choose to employ is suitably experienced. In the event of a claim for negligence, the claim would normally be made against the expedition company. A liability disclaimer signed by a patient before receiving treatment is unlikely to carry much weight before a court. However, a "letter of understanding" detailing the risks and the individual's acceptance of these risks would make it clear to a judge that the participant was fully aware of the expedition environment and medical care available.

Expeditions Departing Without an EMO

Many smaller expeditions do not have the resources to be able to take an EMO into the field; however, the team still needs medical advice and suitable medical pack. In these cases, an EMO may:

- Provide advice on travel medicine, such as required vaccinations or recommended antimalarial chemoprophylaxis.
- Supply private prescriptions for an expedition. It should be kept in mind that drugs may be used for treatment of trip members previously unknown to the EMO. In these situations, the EMO (who retains a duty of care) should provide clear written guidelines, which should include indications, contraindications, doses, and side effects. It would also be prudent for the EMO to seek written assurance from the person to whom prescriptions are supplied that the medication prescribed will be used only for immediate treatment of expedition members in wilderness areas and not as a substitute for seeking professional medical advice when such is readily available.
- Delegate responsibility for initiating treatment to a trip leader.

Medical Records

Brief, accurate, and contemporaneous medical records should be made for all clinical encounters. In serious illness or injury, this is essential so that detailed clinical information can be given to those who deliver definitive care to the patient. This principle applies to both medical and nonmedical expedition staff providing medical care; Box 80-1 is an example of excellent record keeping by a nonmedical expedition leader. Whenever a patient is evacuated or referred to a formal medical facility, the person should be accompanied by clear notes outlining the history and treatment. If there are later concerns about the standards of care given in a wilderness setting, comprehensive clinical notes will help to defend actions if legal activities occur. Examples of suitable medical records for use in the field can be found at http://medex.org.uk/diploma/resources.php.

PROFESSIONAL INDEMNITY INSURANCE

Professional indemnity insurance is an increasingly contentious issue and with considerable international variation. In the United

Kingdom, professional indemnity insurance is provided by four national organizations: the Medical and Dental Defence Union of Scotland, the MDU, the Medical Protection Society, and the Royal College of Nursing. Each organization generally provides discretionary indemnity to its members for a period of volunteer or charity work, such as accompanying an expedition or trek, or being based in a mountain or wilderness clinic. Importantly, "This is dependent on the doctor confirming he or she is suitably trained and equipped to undertake that work."[51] There are a number of countries where indemnity insurance is not available, including Australia, the United States, and Canada and their dependent territories. Work for which the physician receives financial remuneration will be considered for indemnity coverage, but is likely to be charged on a pro rata basis of up to $6500 per year (as of April 2010). In the United States, medical professional liability insurance is provided by private insurance companies at considerable cost. Any American EMO needs to discuss indemnity with his or her insurance company on an individual basis.

Canadian physicians obtain indemnity insurance through the Canadian Medical Protective Association (CMPA). Fees vary from province to province. The CMPA will indemnify its members only for treating Canadian citizens in the province where they work. The CMPA does not provide indemnity insurance for overseas expedition work, so this must therefore be obtained privately. Private medical indemnity insurance can be very difficult to obtain and prohibitively expensive.

In Australia, the situation is more complex, particularly since the financial collapse in 2002 of one of the major providers of medical indemnity insurance. A variety of medical defense organizations provide cover, depending on whether the physician is self-employed or works in public hospitals. It would appear that the majority of organizations might consider providing indemnity cover for their members carrying out volunteer work in a similar manner, and with similar conditions, to the British organizations discussed earlier.

Many EMOs practice expedition medicine with inadequate indemnity insurance. We are unaware of any indemnity claim that has been brought against an EMO, but regrettably, in the current litigation climate and with the changing attitude and demographics of expedition members, it seems only a matter of time before such legal proceedings occur. It is crucial that anybody considering undertaking expedition medical work is competent to undertake the work and has a full discussion with his or her medical defense organization. With the risk for litigation and number of commercial expeditions offering medical professionals the chance to practice expedition medicine, it seems wise for anybody considering EMO activities to obtain a suitable and robust qualification, such as the Diploma in Mountain Medicine.

Nurses and paramedics acting as EMOs should inform their respective professional indemnity carriers about the potential extended scope of practice. The scope of professional indemnity insurance provided varies among national professional bodies. In the United Kingdom, nurses are assumed to work within a skill set commensurate with their level of knowledge and training and in the event of a claim would be held accountable for straying from a suitable level of competency.[66]

Some organizations requiring a medic will dictate the level of professional indemnity (PI) and personal liability (PL) coverage required. For example, the British Broadcasting Corporation (BBC) requires medics to demonstrate that they have £5 million PI and PL coverage. Currently, the RCN will provide coverage up to £2 million, necessitating the need for a separate policy.

ETHICAL CONSIDERATIONS OF INTERACTING WITH LOCAL POPULATIONS

A frequent problem confronting an expedition is the extent to which medical treatment should be provided for a local population. When an expedition arrives in a new village, particularly if it is known that there is an EMO on the expedition, a queue of local people often forms to seek consultation and treatment. There are no absolute ethical guidelines for this situation. Each expedition must decide the policy it will adopt. The factors discussed next should be taken into consideration.

Preexpedition Planning

A decision should be made at the planning stage of the expedition as to the degree the expedition will offer medical care to local people. This decision is influenced by two major factors:

- Expedition resources and budget
- Preexisting medical facilities in the area being visited

The location of local health care facilities should be researched before the expedition. It is crucial that when local health care facilities exist, however basic, the expedition does not undermine them. Local clinics continue to provide care long after an expedition has departed and are not helped in their task if an expedition falsely raises the expectations of local communities. If an expedition intends to provide treatment for local people, as in a region that lacks local health care facilities, it is important that this is anticipated and budgeted, and that extra resources are allocated.

During the Expedition

During the expedition walk-in, it is important to visit local health care facilities and to meet the staff. Such visits can provide encouragement for the local staff and inspiration for the visiting EMO, because the work carried out in such posts, often with minimal resources, is frequently impressive. It offers the opportunity to discuss with local staff the best ways in which the expedition should interact with the community. It is also useful to discuss the existence of any indigenous healers in the area and to be guided by the local health staff as to the best way in which to interact with them (Box 80-12). The visit should also be used to determine the best ways to evacuate sick expedition members if direct air evacuation is not available.

BOX 80-12 Interacting with Local Healers

The left hand of a young Sherpa boy who presented to the Community Action Nepal–International Porter Protection Group Rescue Post at Machermo in the Gokyo Valley of Nepal with a gangrenous accessory digit (Figure 80-5). His mother had been advised by a local shaman to tie a piece of the child's hair around the accessory digit. The boy was referred to the Hillary Trust Hospital at Khunde, where he underwent amputation of the digit under ketamine anesthesia without complications.

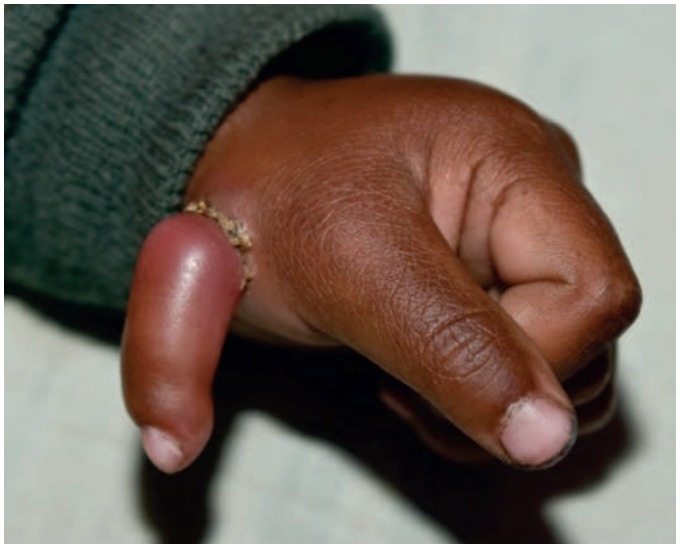

FIGURE 80-5 The left hand of a young Sherpa boy with a gangrenous accessory digit.

If local people are treated, only acute problems should be addressed. Any patient requiring ongoing treatment or follow-up should be referred to the local health care facility with a formal letter of referral. On the walk-out, it is courteous and helpful to leave any unused drugs and items of equipment that might be useful with the local health care facilities. It is essential that those receiving the donated medical items are aware of the proper use of drugs and equipment, because trade names (and sometimes generic names) differ in various countries.

Treating Local Staff

Although the extent to which expeditions should treat members of local populations is open to debate, the manner in which local staff working for the expedition should be treated is not. They should receive the same medical care as do other members of the expedition. George Finch,[21] a member of the 1922 Mt Everest expedition, wrote at the time:

> There is only one form of transportation for this cumbersome, and at times dangerous, work: the native mountain people. The natives of the Himalayas, like all mountain people, are very tough and healthy as can be; they are resolute and brave, yet always of friendly and cheerful disposition, and are excellent porters if they are treated right. But they have to be cared for properly, that is, they must be clothed appropriately and supplied with ample provisions to keep them in peak performance.

Unfortunately, this self-evident sentiment is not the experience of many local staff, who are regularly required to work without adequate clothing or shelter and too frequently abandoned and left to fend for themselves when they fall ill. This abuse of local staff, and in particular portering staff, is one of the most shameful features of modern expeditions.[49,50] Box 80-13 tells the typical story of a sick porter abandoned by his expedition. Box 80-14 gives a Nepalese porter's perspective of his work.

The International Porter Protection Group offers the following guidelines for the care of local staff[65]:

1. Clothing appropriate to season and altitude must be provided to porters for protection from cold, rain and snow. This may mean: windproof jacket and trousers, fleece jacket, long johns, suitable footwear (boots in snow), socks, hat, gloves and sunglasses.
2. Above the tree line porters should have a dedicated shelter, either a room in a lodge or a tent (the trekkers' mess tent is no good as it is not available till late evening), a sleeping mat and a decent blanket or sleeping bag. They should be provided with food and warm drinks, or cooking equipment and fuel.
3. Porters should be provided with life insurance and the same standard of medical care as you would expect for yourself.
4. Porters should not be paid off because of illness/injury without the leader or the trekkers assessing their condition carefully. The person in charge of the porters (sirdar) must let their trek leader or the trekkers know if a sick porter is about to be paid off. Failure to do this has resulted in many deaths. Sick/injured porters should never be sent down alone, but with someone who speaks their language and understands their problem, along with a letter describing their complaint. Sufficient funds should be provided to cover cost of rescue and treatment.
5. No porter should be asked to carry a load that is too heavy for their physical abilities (maximum: 20 kg (44.1 lb.) on Kilimanjaro, 25 kg (55.1 lb.) in Peru and Pakistan, 30 kg (66.1 lb.) in Nepal). Weight limits may need to be adjusted for altitude, trail and weather conditions; experience is needed to make this decision. Child porters should not be employed.

BOX 80-13 Another Nepalese Porter with HAPE and HACE

A 22-year-old Nepalese porter from the foothills of Nepal was portering for a commercial Swiss trek. Shortly after arrival at Gokyo (4750 m [15,584 feet]), which he had previously visited without problems, he began to feel unwell. As the evening progressed, he developed a headache and went to bed. He awoke in the night with severe dyspnea and orthopnea. By morning his condition had worsened. It is unlikely that the Swiss leader was aware that one of his porters was sick or that the group's sirdar had paid him off at 250 Nepalese rupees (just over $3) per day and left him to descend alone.

The porter was found collapsed at the side of the trail, about an hour's walk from Gokyo, semiconscious and vomiting, by Dutch and British trekkers. The British group's Sherpa guide carried the porter 5 km (3.1 miles) to the Community Action Nepal–International Porter Protection Group Rescue Post at Machermo (4400 m [14,436 feet]), where he was diagnosed as having severe HAPE and HACE. This proved refractory to treatment with oxygen, nifedipine, dexamethasone, tadalafil, and inhaled β_2-agonists, and it was feared that the porter would die. Thanks to the generosity of trekkers staying in the village, who between them donated the $4500 cost of the rescue flight, the porter was flown by helicopter the following day to Khunde Hospital (3800 m [12,467 feet]), where he made a full recovery and was able to leave the hospital unaided 24 hours later.

HACE, High-altitude cerebral edema; *HAPE*, high-altitude pulmonary edema.

BOX 80-14 Porter Poetry

Porter
by Laxman Tamang

I am a porter, a small man.
I carry luggage for the rich
and the foreigners.
I eat worse food than they do,
Wear tattered clothes,
Get a meagre salary,
Walk faster than them.
What can I do?
Such is my fate.
I pass my days this way.
I forget my agonies this way.

From *On a donkey's back—Poetry of the Nepalese mountain porters*, Vineland, NJ, 2008, Yileen Press.

BIOMEDICAL RESEARCH

There is a long-standing tradition of physiologic and medical research on expeditions, particularly at high altitude, where such work has made major contributions to understanding cardiorespiratory physiology at sea level as well as at altitude.[70] It is crucial that any research on human participants during an expedition meet the same ethical criteria as if it were carried out at home, namely:

- The project must have received ethics approval at the home institution and, wherever possible, from a comparable institution in the country where the research is to be carried out. This is particularly important if the research involves local populations.
- Informed consent must be obtained from all participants, who have the right to withdraw from the research at any point.
- The participants' rights to confidentiality must be respected and every step taken to ensure that data are collected and stored securely.

DEALING WITH THE MEDIA

Because of the inherent nature of expeditions, serious accidents, injury, and deaths can occur. On such occasions, it may fall to the EMO to talk to the media. This can be a very stressful experience. The manner in which such incidents are reported can have a significant effect on the public's and the legal profession's long-term interpretation of events. Box 80-15 gives guidelines on the best ways in which to interact with journalists and reporters.

BOX 80-15 The Media-Savvy Mountain Medic

Journalists want a good story, but this may conflict with your medical responsibilities and ethics. Your job is to lower the temperature, not to add fuel.

- **Never speculate, embroider, or blame**—your insurers won't like it and the true cause of an accident or a death may be unexpected. Stick to the medical facts.
- **Never name victims**—this is a job for embassies and the police. Even if next-of-kin know, they need time to tell other family members and close friends. They should not learn of a serious accident or death via a TV or radio bulletin.
- **Never say "no comment"**—you'll sound guilty. Just give a few simple facts to help a journalist. But if you say too little, unscrupulous hacks will make it up anyway. Scrupulous reporters will just speculate.
- **Always offer appropriate sympathy**—it's only human in the case of death or serious injury but it's often forgotten. Try not to over-state the case—death is a "tragedy" but calling off an expedition because the entire team has diarrhea is merely "unfortunate" or "careless."
- **Always keep promises to journalists**—it's wise to keep them on your side. Broadcasters, in particular, work to very tight deadlines, so failing to deliver information on time may well attract negative coverage or speculation.
- **Always tell the truth**—even if you can't tell the full story. A "quick bleed" is often a good policy if there's been a mistake, but insurers don't like it so don't say too much.

You should always try to prevent a crisis turning into a media disaster and feeding frenzy. And remember, inquests and other court cases can turn on public perception rather than legal argument.

RESOURCES

Institut de Formation et de Recherche en Medecine de Montagne (Ifremmont), Remote Mountain Medicine Consultation Service, Chamonix, France
http://www.ifremmont.com/en/contacts
Telephone: +33-826-14-8000
E-mail: contact@ifremmont.com

UK Frostbite Advice Service
For e-mail or telephone advice on frostbite from anywhere in the world, contact:
http://www.christopherimray.co.uk/highaltitudemedicine/frostbite.htm
or
http://www.thebmc.co.uk/how-to-get-expert-frostbite-advice

Dr. David Hillebrandt
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Dr. Paul Richards
Telephone: +44-1268-568240
E-mail: paul@medex.org.uk

International Porter Protection Group
http://www.ippg.net

APPENDIX Recommended Medical Kit

Quantities are for a group of 10 persons on a 6-week high-altitude mountaineering expedition. The list may be useful as a checklist when preparing kits for other types of expeditions.

ANTIMICROBIALS

Ceftriaxone powder for injection	4 g	5 ampules
Chloramphenicol 1% ointment	4 g	3 tubes
Clarithromycin	250 mg	40 tablets
Ciprofloxacin	500 mg	50 tablets
Amoxicillin/clavulanic acid	250/125 mg	84 tablets
Doxycycline	100 mg	80 tablets
Mebendazole	100 mg	20 tablets
Metronidazole	400 mg	100 tablets
Metronidazole suppositories	1 g	10 suppositories
Quinine sulfate	200 mg	50 tablets
Rabies vaccine	1 mL	5 vials

PAINKILLERS, LOCAL ANESTHETICS/SEDATIVES

Aspirin	325 mg	32 tablets
Bupivacaine 0.25% for injection	10 mL	5 vials
Acetaminophen/codeine	30/300 mg	80 tablets
Diclofenac	50 mg	100 tablets
Ibuprofen	400 mg	80 tablets
Ketamine solution for injection	10 mg/mL	2 vials
Ketorolac solution for injection	30 mg/mL	5 vials
Lidocaine 1% for injection	5 mL	10 ampules
Lidocaine 2% gel	30 mL	2 tubes
Lorazepam solution for injection	2 mg/mL	5 vials
Midazolam solution for injection	5 mg/5 mL	5 vials
Acetaminophen	500 mg	100 tablets
Tetracaine 0.5% eye drops	15 mL	6 bottles
Eszopiclone	7.5 mg	20 tablets

GASTROINTESTINAL

Bisacodyl	5 mg	20 tablets
Antacid tablets		100 tablets
Oral rehydration solution sachets		100 sachets
Loperamide	2 mg	50 capsules
Prochlorperazine	5 mg	56 tablets
Prochlorperazine solution for injection	12.5 mg/mL	5 vials
Prochlorperazine suppositories	25 mg	10 suppositories

CARDIOVASCULAR

Bisoprolol	2.5 mg	20 tablets
Atropine solution for injection	600 mcg/1 mL	5 vials
Enoxaparin for injection	80 mg/0.8 mL	10 prefilled syringes
Nitroglycerin sublingual spray	400 mcg/spray	1 bottle

RESPIRATORY/ALLERGY

Epinephrine 1:1000 solution for injection	1 mL	10 ampules
Beclometasone for inhalation	200 mcg	2 canisters
Chlorphenamine	4 mg	60 tablets
Chlorphenamine solution for injection (UK)	10 mg/mL	5 vials
Diphenhydramine solution for injection (U.S.)	25-50 mg	5 vials
Hydrocortisone powder for injection	100 mg/2 mL	5 vials
Prednisone	5 mg	100 tablets
Albuterol for inhalation	90 mcg	2 canisters

ALTITUDE

Acetazolamide	250 mg	250 tablets
Dexamethasone	2 mg	40 tablets
Nifedipine	20 mg	20 capsules
Portable altitude chamber and/or oxygen cylinders		1

OTHER MEDICATION

Multivitamins with minerals		500 tablets
Dimenhydrinate	50 mg	40 tablets

CREAMS AND OINTMENTS

Acyclovir cream 5%	2 g	6 tubes
Hemorrhoidal cream		1 tube
Mupirocin cream	15 g	6 tubes
Betamethasone sodium phosphate 0.1%; neomycin sulfate 0.5%	10 mL	4 bottles
Clotrimazole 1% cream	20 g	6 tubes
Aqueous cream	50 g	1 tube
Fluconazole	150 mg	4 tablets
Hydrocortisone 1% cream	15 g	6 tubes
Sunblock SPF 25+		4 tubes

DRESSINGS

Adhesive plasters		50 assorted
Alcohol swabs	100	2 boxes
Cotton wool		4 packets
Crepe bandages	7.5 cm	4 units
Medium wound dressing		2 units
Eye dressing		4 units
Fluorescein eye test strips/minims		10 strips/minims
Gauze swabs	5 × 5 cm	100 swabs
Nonadherent dressing	10 cm^2	5 dressings
Nonadherent dressing	5 × 5 cm^2	5 dressings
Hypoallergenic tape	2.5 cm	2 rolls
Adhesive strips, assorted		4 packets
Triangular bandages		8 bandages
Petrolatum gauze	10 cm^2	10 rolls
Zinc oxide roll plaster		2 rolls

INJECTION EQUIPMENT AND INTRAVENOUS (IV) FLUIDS

2-mL, 5-mL, 10-mL syringes		20 of each
25-, 23-, and 21-gauge hypodermic needles		20 of each
IV cannulas, 14 gauge, 18 gauge		10 of each
Giving sets		5 units
Normal saline	1 L	6 bottles
Hartmann's solution	500 mL	8 bottles
Dextrose 5%	500 mL	4 bottles

AIRWAY CARE

Oropharyngeal airways (sizes 2, 3, 4)	2 of each
No. 6 nasopharyngeal airway	2 units
Bag-valve-mask device	1 unit
Minitracheostomy set	1 unit
Endotracheal tubes, 7 mm, 9 mm	2 of each
Laryngeal mask airway sizes 3, 4	2 of each
I-gel supraglottic airway sizes 3, 4	1 of each
Catheter mounts for above	2 units
Laryngoscope	1 unit
Oxygen tubing	1 unit
Oxygen cylinder	1 unit
Handheld suction unit	1 unit

MAJOR TRAUMA

Nonsterile examination gloves	100 pair
Tuff cut scissors	1 unit
Chest drain 32 Fr	2 units
Heimlich valve	2 units
Kendrick Traction Device	1 unit
SAM Splint	2 units
Adjustable cervical collar (Stifneck Select)	2 units
Urinary catheter 14 Fr	2 units
Catheter bag and tubing	2 units
Bladder syringe, 50 mL	2 units
Nasogastric tube 12 Fr	2 units
Disposable scalpels	2 units
Gloves sterile (medium)	10 pair
Sutures:	
2/0 silk straight	4 units
4/0 nonabsorbable suture	5 units
5/0 nonabsorbable suture	5 units
Staples and remover	1 unit
Needle holder	1 unit
Toothed forceps	1 unit
Dressing scissors (straight/straight 5-inch)	1 unit
Spencer Wells forceps	2 units
Tissue/super glue (e.g., LiquiBand)	5 units
Dental first-aid kit	1 unit
Low-reading thermometer	1 unit
Thermometer (digital)	1 unit

EXAMINATION

Pen flashlight	3 units
Stethoscope	1 unit
Aneroid sphygmomanometer	1 unit
Ophthalmoscope/auriscope	1 unit

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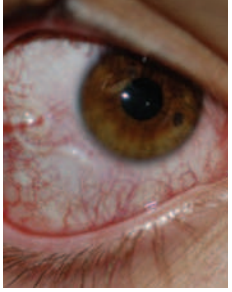

CHAPTER 81

Non–North American Travel and Exotic Diseases

KATHERINE R. DOBBS AND ARLENE E. DENT

Travelers to tropical and subtropical areas of the world, where hygiene conditions are poor and ecologic conditions are permissive, may encounter infectious agents that are no longer endemic or have never existed in temperate regions of the world. Although economic development and industrialization of developing countries of the tropics have resulted in a decreased health burden of many tropical infectious diseases, it is important to realize that there is still a risk for exposure for the traveler who is unaware of appropriate measures to prevent or treat such conditions. The most important consideration in the management of this problem, which is increasing as international travel expands, is appropriate preventive measures through counsel with a travel medicine specialist and prophylaxis using safe drugs and vaccines. This topic has been reviewed in several excellent publications.[11,52,70,81]

This chapter discusses infectious diseases that are uncommon or do not exist in North America and thus may be less familiar to most health professionals there. Other chapters give specific details relevant to malaria (Chapter 40), tick-borne diseases (Chapter 42), infectious diarrheas (Chapter 82), and travel medicine (Chapter 79). The infectious diseases discussed in this chapter should not be considered a complete listing. This is especially important to keep in mind in an era when diseases once thought to be eliminated or nonexistent in North America are emerging or reemerging at the same time as large-scale movements of human and vector populations.

MAJOR VIRAL INFECTIONS

This section describes certain viral infections that may be acquired outside North America. Emphasis is placed on viral infections that have recently been recognized as highly pathogenic and endemic in select tropical areas, such as those caused by filoviruses, and those for which effective preventive or therapeutic measures exist, such as viral hemorrhagic fever caused by the yellow fever virus, some types of viral hepatitis, and Japanese B encephalitis.

MAJOR VIRAL HEMORRHAGIC FEVERS

A diverse group of ribonucleic acid (RNA) viruses can produce the hemorrhagic fever syndrome. Fever, headache, myalgia, and malaise generally characterize the early phase of the clinical presentation of all these infections, which develops over several hours to 3 to 4 days. In the full-blown hemorrhagic fever syndrome, nonspecific clinical symptoms are followed by hemorrhagic signs, including petechiae and bleeding from the gums and gastrointestinal (GI) tract. Loss of plasma volume and a capillary leak syndrome may ensue, manifested in some individuals as increased hematocrit with hypotension and shock. Elevated blood urea nitrogen and creatinine levels indicative of renal dysfunction may develop. Death is caused by a combination of intractable hypotension, bleeding, electrolyte imbalances, and renal failure. There are many viral causes of this syndrome (e.g., Rift Valley fever), but not all of these are discussed here. In general, the management principles are the same and consist primarily of supportive therapy.

YELLOW FEVER

European physicians did not recognize the clinical syndrome now known as yellow fever (YF) until the late 1490s. Initially described by Columbus in the West Indies, large-scale epidemics were later observed throughout the Americas and tropical Africa in the 1700s and 1800s. After epidemic YF in Texas, Louisiana, and Tennessee caused 20,000 deaths in the 1880s, the Yellow Fever Commission was organized to study the problem. Identification of the mosquito vector, *Aedes aegypti,* and definitive studies conducted by the U.S. military under the leadership of Walter Reed were followed by massive campaigns to eradicate mosquito breeding sites. This led to virtual elimination of urban YF from the Americas. The last case of YF acquired in the continental United States was reported in 1911. Because it is difficult if not impossible to eliminate jungle reservoirs, cases continue to be reported annually from South America and tropical Africa.[68]

Virology and Pathophysiology

Yellow fever is a single-stranded RNA flavivirus. Strain differences are of little clinical relevance, although they may be of use in epidemiologic studies. The pathophysiologic mechanisms operating in viral hemorrhagic fevers are not well defined. In general, viral replication occurs at the site of inoculation. After the virus spreads to lymph nodes and monocyte-rich organs, further reproduction results in massive viremia.

The liver is the principal target organ. Pathology studies show coagulative necrosis of hepatocytes and appearance of various markers of cell involvement (e.g., Councilman and Torres bodies). The degree of physiologic derangement is usually much more severe than expected for the extent of hepatic damage seen on pathology examination. Perivascular edema and occasional focal bleeding occur in the kidneys, heart, and brain, but these changes are less severe than expected for the degree of clinical disease.

Ecology and Epidemiology

In the Americas, primates in the forest canopy serve as hosts for the YF virus. Mosquitoes of the genus *Haemagogus* transmit infection. Because this vector does not travel far from the forest, jungle YF occurs when humans enter jungle areas or the forest border zones. Urban YF involves a different vector, *Aedes,* that is highly anthropophilic, lives in and around human habitations, and prefers domestic water storage containers for breeding. In Africa, *Aedes* species serve as the main vectors.[67,91]

Currently, both the Americas and Africa have a constant low level of jungle YF because of inability to control either the monkey reservoir or the mosquito vector. Estimates from the 1990s placed the burden of disease at about 200,000 cases per year, resulting in approximately 30,000 deaths, primarily in sub-Saharan Africa.[77] Some suggest that these rates are underestimated by at least 10-fold. After mass YF vaccine campaigns in Africa beginning in 2006, current estimates of YF disease burden in Africa for 2013 were 130,000 cases and 78,000 deaths.[47]

Clinical Presentation and Diagnosis

Although YF may appear as an undifferentiated viral syndrome in patients who have only mild disease, classic disease is characterized by a triphasic pattern. The infection phase begins with sudden onset of headache, fever, and malaise, often accompanied by bradycardia and conjunctival suffusion. After about 3 to 4 days, patients often experience brief remission. Within 24 hours, the intoxication phase develops, characterized by jaundice, recrudescent fever, prostration, and in severe cases, hypotension, shock, oliguria, and obtundation. Hemorrhage usually

manifests as hematemesis; bleeding from multiple sites may occur. Signs of poor prognosis include early onset of the intoxication phase, hypotension, severe hemorrhage with disseminated intravascular coagulation (DIC), renal failure, shock, and coma. Death occurs in 20% to 50% of cases.

Diagnosis is difficult in the infection phase. With development of the classic syndrome, the differential diagnosis narrows somewhat, but still includes malaria, leptospirosis, typhoid fever, typhus, Q fever, viral hepatitis, and other viral hemorrhagic fevers. Laboratory diagnosis is confirmed by detection of virus-specific immunoglobulin M (IgM) and IgG antibodies in acute and convalescent serologic assays, available through the U.S. Centers for Disease Control and Prevention (CDC). It is important to obtain a YF vaccination history, because IgM antibodies to YF vaccine virus can persist for several years after vaccination. Serologic cross-reactions occur with other viruses, so positive results should be confirmed with a more specific test (e.g., plaque-reduction neutralization test). Early in the illness, YF virus or YF virus RNA can often be detected in the serum by virus isolation or nucleic acid amplification testing (e.g., reverse-transcriptase polymerase chain reaction [RT-PCR]). However, by the time overt symptoms are recognized, the virus or viral RNA is usually undetectable.

Management

Appropriate management of viral hemorrhagic fevers requires awareness of the geographic distribution of disease and travel history of the patient. In the first several days of infection, differentiation of a viral hemorrhagic fever from other infectious diseases is almost impossible. However, occurrence of an undifferentiated febrile syndrome in a traveler from a YF-endemic area warrants a careful physical examination, thick and thin blood smears to rule out malaria, and blood cultures for bacterial pathogens (e.g., *Salmonella typhi*). In recently returned travelers, dengue serologic tests should be considered. Progression to the intoxication phase or any sign of volume disturbance, renal failure, or hemorrhage mandates immediate admission to an intensive care unit (ICU). There is no effective antiviral therapy for YF. Intensive supportive care and management of end-organ failure are paramount. Severe disease carries a mortality rate of 50%.

Prevention

Avoidance of this potentially fatal infection is possible through use of YF vaccine. The vaccine strain 17D is a live-attenuated virus grown in chicken embryos. More than 95% of vaccinated persons achieve significant antibody 1evels within 10 days. Repeat vaccinations were previously recommended every 10 years, but in 2013 the World Health Organization (WHO) recommended that a single dose of YF vaccine confers lifelong protection against YF disease. However, countries with vulnerable populations and susceptible vector species may define their own YF vaccine entry requirements. WHO also recommended that all endemic countries introduce YF vaccine to their routine infant immunization programs.[59,96] YF vaccine is generally well tolerated, with headache or malaise occurring in less than 10% of vaccinated persons. Rare allergic side effects occur primarily in persons with hypersensitivity to eggs. Other serious adverse events, including death, have been reported, with the greater risk being associated with age greater than 60 years.[59,68] Vaccination is not recommended during the first 6 months of life or in other situations where live-virus vaccines are contraindicated. Although pregnant women have received the vaccine without adverse effect to themselves or their infants, it is not recommended for use in this group because of possible teratogenic effects. Other means of reducing the risk for YF (and any mosquito-borne infectious disease) include liberal use of mosquito repellent and netting in endemic areas. Outbreak control in endemic countries is primarily through focused vaccination campaigns.

DENGUE

Dengue has been reported since the late 1700s. Since World War II, increased attention has focused on the dengue virus, largely as a result of recognition of dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS). Dengue is the most common insect-borne viral infection worldwide. The infection has been reported in more than 100 countries, with a recent estimate of 390 million dengue infections per year, of which 96 million are symptomatic.[15,50]

Virology and Pathophysiology

The etiologic agent is a single-stranded RNA flavivirus, which may be one of four serotypes, denoted DEN-1 through DEN-4. As with YF, local viral replication is followed by dissemination to lymphocyte- and macrophage-rich areas, where most of the reproductive activity occurs. Infection with one virus serotype provides long-lasting immune protection against that type only. After infection with one serotype, a subsequent infection with a heterologous serotype may result in a more severe clinical course. Non-neutralizing antibodies produced in response to the primary infection are thought to facilitate entrance of the heterologous virus into host macrophages. Although cases of DHF and DSS may result from this "immune enhancement," severe DHF and DSS also occur with other serotypes in the absence of previous infection with a heterologous dengue virus serotype.[42,50] Pathology studies of DHF and DSS show hemorrhage, congestion, and perivascular edema of multiple organs. The liver may show areas of focal necrosis. As with YF, the extent of pathologic findings does not correspond to severity of the clinical course.

Ecology and Epidemiology

Aedes aegypti is the principal vector for dengue. In the Americas and Asia, viral transmission is maintained through a mosquito-human cycle without a major animal reservoir. Monkey carriers have been identified in Africa and Asia, but their importance in transmission is unclear. *Aedes albopictus,* an anthropophilic dengue vector from Southeast Asia, has also been recognized in the western hemisphere. Both these mosquitoes are capable of large-scale transmission to humans in endemic areas. Currently, dengue is endemic in tropical and subtropical Asia, Africa, South America, and the Caribbean basin.

Clinical Presentation

Most dengue infections appear after an incubation period of 2 to 14 days, either as an undifferentiated viral syndrome with fever and mild respiratory or GI symptoms or as dengue ("break-bone") fever (DF) with bone pain, generalized myalgia, severe headache, and retro-orbital pain. Febrile illnesses that appear more than 2 weeks after putative exposure to dengue virus are unlikely to be caused by this virus. After 1 to 3 days, a quiescent period may ensue. There may be a subsequent second episode of fever accompanied by a patchy maculopapular or morbilliform rash that spreads outward from the chest and ultimately desquamates. Lymphadenopathy and leukopenia occur during this phase of the illness. The distinct severe forms of dengue disease referred to as either DHF or DSS may occur around the usual time of recovery. These are caused by development of capillary leak syndrome with associated hemorrhagic manifestations (Figure 81-1).

In 2009, WHO changed the classification of DF/DHF/DSS to dengue and severe dengue (D/SD).[57] Warning signs (WS) have been established to help clinicians identify symptomatic patients who should be hospitalized and closely monitored (D+WS).[56] "Dengue without warning signs" (previously DF) is defined as laboratory-confirmed dengue, fever, and at least two of the following: nausea, vomiting, rash, leukopenia, arthralgia, myalgia, and a positive tourniquet test. "Dengue with warning signs" (D+WS, previously DHF) includes the previous features plus any of the following warning signs: abdominal pain or tenderness, persistent emesis, volume overload (edema), mucosal bleeding, lethargy, hepatomegaly, or hemoconcentration. "Severe dengue" (previously DSS) includes laboratory-confirmed dengue and shock, significant volume overload with respiratory distress, severe clinical bleeding, or organ failure.[57,93] Most studies have noted SD primarily in infants and young children, usually with a history or serologic evidence of previous heterologous dengue infection.

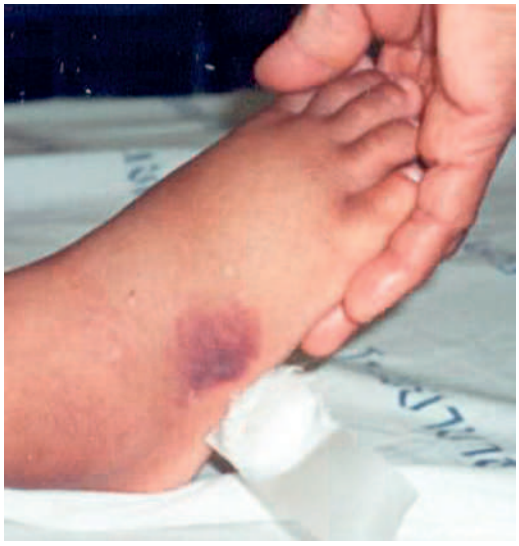

FIGURE 81-1 A Thai child with dengue hemorrhagic fever and hemorrhagic sequelae.

Prevention and Management

There is currently no vaccine to protect against dengue infection or disease, although several encouraging candidates are in development with clinical trials.[50]

Awareness of the local epidemiology of severe dengue, especially the occurrence of other cases, is important in establishing the diagnosis. The diagnosis may be confirmed by a fourfold change in antibody titer between acute and convalescent sera or by presence of antidengue IgM antibodies. In the United States, isolation of the virus from serum can be arranged through state health departments. Management is symptomatic. Hydration should be vigorously maintained. Acetaminophen may be given for fever and myalgia, but salicylates should not be used. The WHO guidelines state that patients diagnosed with dengue plus warning signs should be hospitalized for close monitoring and interventions. Infants diagnosed with dengue without warning signs should probably be admitted, whereas older patients diagnosed with dengue without warning signs may be managed as outpatients. Outpatient care requires careful monitoring of hematocrit, platelets, and electrolytes. If warning signs develop, hospitalization is appropriate for rapid and continuous assessment. Progression to severe dengue is a medical emergency and requires immediate hospitalization. There is no specific antiviral chemotherapy. Supportive measures with careful monitoring are appropriate.

LASSA FEVER

Four viral hemorrhagic fevers—Lassa, Marburg, Ebola, and Crimean-Congo—have been associated with outbreaks of fatal person-to-person spread. Although the overall number of clinical cases in travelers caused by these viruses is small, they represent potentially significant threats as emerging diseases. They have also achieved notoriety as a group as a result of media interest and their potential use as agents of bioterrorism.

Lassa fever was first recognized in 1969, when several nurses caring for febrile patients at a mission hospital in Lassa, Nigeria, became ill. Since that time, seroepidemiologic studies have established a large area of endemicity and broad spectrum of clinical manifestations of infection.

Epidemiology

The principal animal host for this virus is the rat, *Mastomys natalensis,* which prefers living in and around human dwellings. The rodents become chronically infected, secreting viral particles for long periods. Natural infection in humans occurs after rodent contamination of food and drink, inhalation of aerosolized rodent secretions, or contact with rodent material through skin abrasions. Lassa fever has been reported in several areas of sub-Saharan West Africa, with outbreaks noted in Nigeria, Sierra Leone, Guinea, and Liberia. Recent evidence indicates an expanded region of endemicity, including Mali, Burkina Faso, Côte d'Ivoire (Ivory Coast), and Ghana.[82] It affects up to 500,000 people, with 5000 deaths annually.[43] Secondary human infection (nosocomial) has been reported and may occur after contact with infected secretions.[46]

Virology and Pathophysiology

Lassa virus is a single-stranded RNA arenavirus. Proliferation and dissemination presumably occur after initial replication at the inoculation site. As with the flaviviral diseases, the extent of end-organ involvement noted at autopsy does not account for the rapid death of infected patients. Platelet dysfunction and endothelial permeability are probably induced by host factors.[79,100] DIC, believed to be a major cause of bleeding and death in patients with other viral hemorrhagic fevers, appears to play a relatively minor role in arenavirus infections. The liver is most consistently the organ in which pathologic changes are observed at autopsy.

Clinical Presentation

Most (80%) Lassa virus infections are asymptomatic. The incubation period is 3 to 21 days. Patients hospitalized with Lassa fever show a distinct clinical syndrome. Fever, malaise, and purulent pharyngitis often develop after insidious onset of headache. Retrosternal chest pain, possibly a result of pharyngitis and esophagitis, suggests the diagnosis. The combined presence of retrosternal chest pain, fever, pharyngitis, and proteinuria is the best predictor of Lassa fever. Hemorrhagic complications (hematemesis, vaginal bleeding, hematuria, lower GI bleeding, and epistaxis) were seen in fewer than 25% of patients with Lassa fever. Nonfatal disease usually begins to resolve in 8 to 10 days. The combined presence of fever, sore throat, and vomiting was associated with a poor prognosis (relative risk for death, 5.5). Terminal stages of fatal disease were accompanied by hypotension, encephalopathy, and respiratory distress caused by stridor (presumably secondary to laryngeal edema). The most common complication after recovery from Lassa fever is sensorineural hearing loss, presumably caused by host immune response reactions against elements of the inner ear.[56]

Diagnosis

Establishing an accurate diagnosis is extremely difficult during the early phase of the infection. As the classic clinical syndrome develops, differentiation from other viral hemorrhagic fevers depends on serologic confirmation. Serologic diagnosis is made by indirect fluorescent antibody (IFA) analysis of acute and convalescent sera or detection of Lassa-specific IgM antibody. Clotted whole blood may be sent to the CDC for viral culture if handled appropriately. If the diagnosis is suspected, the CDC should be contacted immediately for assistance in diagnosis, isolation, and management.

Management

Ribavirin has been used with success in patients with Lassa fever. It is most effective if started early in the course of the illness. For adults, a 2-g loading dose, followed by 1 g every 6 hours for 4 days, then 0.5 g every 8 hours for 6 days, is recommended. Additional supportive care, with maintenance of appropriate fluid and electrolytes, ventilation and blood pressure support, and treatment with broad-spectrum antibiotics for concomitant bacterial superinfections, is often necessary.

Lassa fever has been associated with outbreaks of fatal person-to-person spread. Secondary infection (nosocomial) occurs through direct contact with infected persons or their secretions.[46] The role of aerosols in person-to-person spread is unclear. Blood and body fluids should be considered infectious. In light of the potentially fatal outcome of Lassa fever and the relative ease of transmission, the CDC has published specific recommendations for management of possible or confirmed cases. If a person has (1) a compatible clinical syndrome (especially pharyngitis, vomiting, conjunctivitis, diarrhea, and hemorrhage or shock); (2) relevant travel history, including time spent in an endemic area; and (3) prior contact within 3 weeks of presentation with a

person or animal from an endemic area suspected of having a viral hemorrhagic fever, the person should be isolated and local, state, and federal health officials contacted. Ideally, an isolation unit with negative air pressure vented outside the hospital should be used. However, lack of a negative-pressure room alone is not a reason for transfer to another medical care facility.

Transmission of Lassa fever virus to medical staff can be reduced by routine blood and body fluid precautions as well as strict barrier nursing. Barrier nursing includes wearing gloves, gown, mask, shoe covers, and, if there is risk for splashing fluids, goggles whenever entering the patient's room. Decontamination of solid articles and rooms may be accomplished with 0.5% sodium hypochlorite solution. Recommendations for management of patients with viral hemorrhagic fever have been published.[18,23]

No vaccine is available for Lassa virus. Prevention is through avoidance of contact with rodents, especially in geographic areas where outbreaks occur.

EBOLA AND MARBURG VIRUSES

Ebola and Marburg viruses are closely related, large RNA viruses known as filoviruses. They cause severe viral hemorrhagic fever syndromes with some of the highest case fatality rates (~90%) of any known infectious disease. Both are endemic in focal areas of central and southern Africa.

Ebola virus seropositivity has been noted in Sudan, Democratic Republic of the Congo, the Central African Republic, Côte d'Ivoire, and Kenya. In 2014, the largest Ebola epidemic in Western Africa was reported. The first cases of Ebola were identified in Liberia in March 2014 near the Guinean border. During the epidemic, inadequate health infrastructure, lack of training and supplies, poor transportation and communication, and public fear contributed to continued transmission. As of March 2016, a total of 28,610 Ebola cases with 11,308 deaths had been reported in Sierra Leone, Liberia, and Guinea.[99a] The majority of cases and deaths occurred between August and December 2014. Contact cases were also detected in Italy, Mali, Nigeria, Senegal, Spain, United Kingdom, and United States.[10,37,58,99a]

Marburg disease is found in South Africa, Zimbabwe, and Kenya. In 2005, there was an outbreak that caused over 300 deaths in Angola.[24] Since then, sporadic cases have been observed, especially in Uganda.[31]

Although there is no definitive evidence indicating the animal reservoir that maintains these filoviruses in nature, current evidence strongly suggests that bats are involved.[66] Person-to-person transmission has been well documented, primarily through contaminated needles and contact with the secretions of infected individuals.[12,87]

Pathophysiology and Clinical Presentation

Ebola and Marburg viruses are presumed to act through similar pathophysiologic mechanisms that involve initial infection of monocytes, macrophages, and dendritic cells, which are then distributed through the circulation to many organs and cell types. The viruses suppress both innate and adaptive host immune responses, leading to overwhelming infection and wide release of proinflammatory cytokines and chemokines, causing fever, vascular instability, hypotension, and shock, followed by multiorgan failure and death.[12,31,37]

Patients present after an incubation period of 4 to 10 days with fever, headache, and myalgias. Diarrhea and abdominal pain are common. In many patients, rash, conjunctivitis, sore throat, and chest pain appear early in the disease. As in other hemorrhagic fevers, hemorrhage, hypotension, shock, and electrolyte abnormalities mark fatal courses. The high mortality reported in various outbreaks and transmission to health care workers caring for patients emphasizes the importance of intensive supportive care and precautions that limit contact with body secretions of infected individuals.

Diagnosis and Treatment

If these diseases are suspected, strict isolation procedures should be instituted and the local health authorities and the CDC notified immediately. Diagnosis may be made on a serologic basis or by polymerase chain reaction (PCR). There appears to be no serologic cross-reactivity between the two viruses.

While there are no licensed vaccines against Ebola or treatments with proven efficacy in humans (as of October 2015), the 2014 Ebola epidemic triggered rapid scale-up in research and development efforts. Three vaccine candidates have shown encouraging preclinical results and are undergoing Phase 2 and 3 clinical trials, and several other candidates are in Phase 1 trials. Blood or plasma from convalescent patients may be beneficial. Humanized monoclonal antibodies (ZMapp, Mapp Biopharmaceutical, San Diego) targeted at Ebola proteins is currently being studied in human safety and efficacy trials. Other medications in expedited clinical trials include antivirals and small interfering RNAs.[12,17,49,99b,101]

CRIMEAN-CONGO HEMORRHAGIC FEVER

Virology and Epidemiology

The etiologic agent of Crimean-Congo hemorrhagic fever (CCHF) is a bunyavirus. Ixodid ticks serve as both reservoirs and vectors of the virus. Infection in humans results from tick bites or direct contact with infected secretions from crushed ticks, animals, or humans. Most cases occur in individuals with occupations or living conditions that bring them in contact with domestic goats, sheep, or cattle on which ticks feed.[65] The disease has been observed in southeastern Europe, south-central Asia, the Middle East, and much of Africa.[13] Nosocomial transmission through contact with infected body fluids has been well documented.[65]

Pathophysiology and Clinical Presentation

Pathophysiologic mechanisms of CCHF are presumably similar to those of other hemorrhagic fevers.[30] One in five infections results in clinical disease, with case fatality rate ranging from 30% to 50%. The incubation period is approximately 1 week, with initial symptoms of fever, severe headache, myalgias, vomiting, and diarrhea. Various forms of hemorrhage, including petechiae, large ecchymoses, melena, and hematemesis, are more pronounced in CCHF than in other hemorrhagic viral diseases. Severe cases progress rapidly to DIC, shock, and death.

Diagnosis

The diagnosis of CCHF virus infection can be confirmed with acute and convalescent serologic evaluation for a fourfold rise in IgG antibody titers. The virus can be detected by PCR or cultured from whole blood if it is drawn during the first week of symptoms and kept on dry ice (or at −70°C [−94°F]) during shipment to the CDC.[92]

Management

Initial management of CCHF is similar to that for Lassa, Marburg, and Ebola virus infections, with strict patient isolation and notification of health authorities. The primary treatment is supportive therapy, with attention to fluid balance and electrolytes, oxygenation, and hemodynamic support. Although not confirmed in clinical trials, ribavirin has good activity in vitro against CCHF virus. The CDC recommends that patients believed to have CCHF receive intravenous (IV) ribavirin in the doses suggested for treatment of Lassa fever.[40] Persons in contact with CCHF patients should receive prophylactic ribavirin as suggested for Lassa fever contacts. To date, almost all therapy has used the oral form of ribavirin.

HEMORRHAGIC FEVER WITH RENAL SYNDROME AND HANTAVIRUS CARDIOPULMONARY SYNDROME

Hantaviruses, when transmitted from rodent reservoirs, cause two significant human diseases: hemorrhagic fever with renal syndrome (HFRS) in Asia and Europe and hantavirus cardiopulmonary syndrome (HCPS) in the Americas. HFRS first came to the attention of Western medical science during the Korean conflict, when febrile illness accompanied by bleeding and renal failure developed in 3000 United Nations troops and was ultimately found to be caused by the *Hantavirus* species Hantaan virus.[51] Mortality ranged from 5% to 10%. A similar, less severe syndrome

(nephropathia epidemica) had been recognized in Scandinavia since the 1930s. HCPS was first recognized in a cluster of deaths in the southwestern United States in 1993, but was brought to public attention in 2012 with an outbreak of 10 cases of HCPS, three of which were fatal, in Yosemite National Park.[27] A nonspecific febrile illness is followed by shock and alveolar pulmonary edema caused by the Hantavirus Sin Nombre virus.

Epidemiology

Hantaviruses cause chronic, nondebilitating infections of various rodent species. Human infection is initiated by contact with rodent secretions or inhalation of aerosolized rodent material. The disease occurs most commonly in rural areas, although occasional urban outbreaks occur, presumably with the common house rat as vector. Cases have been described most often from Asia, including China, Korea, Japan, and the Soviet Union, but the disease also occurs in Eastern Europe.[64] The Sin Nombre virus appears to cause chronic infection of the deer mouse, *Peromyscus maniculatus,* which is the main reservoir of the virus in the United States. Since the initial outbreak, additional cases have been described across the United States and South America. The risk for infection is likely related to rodent exposure, but transmission is infrequent.

Virology and Pathophysiology

Members of the genus *Hantavirus* (family Bunyaviridae) are enveloped single-stranded RNA viruses that form one of the largest viral families, with more than 300 species. The most common virus associated with HFRS in Asia is the Hantaan virus. The most common European Hantavirus is Puumala virus, which causes a mild form of HFRS termed *nephropathia epidemica*. Severe HFRS cases in Europe have been caused by the Hantavirus Dobrava-Belgrade virus. Sin Nombre virus is one cause of HCPS in the United States. Hantaviruses enter host endothelial cells and spread rapidly.[83]

Clinical Presentation

Hantaviruses cause a vascular leak syndrome. As with most viral hemorrhagic fevers, infection may be asymptomatic or accompanied by mild nonspecific illness. In the classic severe form, an initial febrile phase is associated with petechiae, proteinuria, and abdominal pain. After 3 to 5 days, a hypotensive phase occurs, with decreased platelet count and more severe hemorrhagic phenomena. An oliguric phase follows with concomitant electrolyte abnormalities. A diuretic phase usually commences 10 days after the onset of illness. Death occurs from hemorrhage, hypotension, and pulmonary edema, presumably secondary to fluid overload and renal failure. With modern management, the case fatality rate of classic HFRS is about 5%. The more benign nephropathia epidemica syndrome has a case fatality rate of less than 1%. In this disease, hypotension, shock, and hemorrhagic manifestations are rare. With HCPS, there is usually a prodromal illness with fever and mild respiratory or GI symptoms, followed by shock and pulmonary edema. The tempo of the disease at this stage may be rapid and may require respiratory and circulatory support in an ICU. HCPS has a case fatality rate of 50%.[54]

Diagnosis

The diagnosis of HFRS, nephropathia epidemica, and HCPS is confirmed by IFA or enzyme-linked immunosorbent assay (ELISA) for antibodies in acute and convalescent sera. IgM antibody determination may also be helpful. Virus isolation is difficult, but PCR and immunohistochemical staining may be useful when applied to affected tissues.

Management

Care of patients with HFRS is supportive. With HFRS, renal dysfunction occurs early, and patients require institution of dialysis soon after diagnosis to prevent fluid overload and correct electrolyte disturbances. Patients' secretions should be handled with care, and enteric precautions (but not strict isolation) are prudent. It is not clear whether person-to-person transmission of the virus through direct inoculation occurs. For the Hantaviruses, viremia recedes and antibody levels rise as the clinical phase appears. Accordingly, nosocomial transmission or hematogenous transmission with *Hantavirus* infections has not been frequently documented, although presumed nosocomial transmission has been reported. No vaccine is available.

JAPANESE B ENCEPHALITIS

Japanese B encephalitis (JE) is only one of several arthropod-borne viruses that may cause encephalitis in different areas of the world. Others include Murray Valley encephalitis in Australia; tick-borne encephalitis in Europe, for which a vaccine exists; and La Crosse, West Nile, and St. Louis encephalitis in the United States. JE has been recognized in Japan since the 19th century. It is the only arboviral encephalitis for which an effective inactivated vaccine has been developed. Vaccine use in Japan and elsewhere since the 1960s has resulted in a significant decrease in the disease rate; however, the inactivated mouse brain–derived JE vaccine (JE-VAX) is no longer being produced because it was associated with adverse reactions, usually with the third dose. An inactivated Vero cell–derived JE vaccine (Ixiaro) has been licensed for use in adult travelers and just recently in children as young as 2 months.[29] This vaccine is recommended if traveling to an endemic region for longer than 30 days.

Epidemiology

In Asia, JE is the most common cause of encephalitis. Of the estimated 35,000 to 50,000 cases annually, 20% to 30% of infected individuals die, and of those who recover, 30% to 50% have neurologic sequelae.[29] Transmission correlates with monsoon rains in the tropics and with the summer and fall seasons in temperate regions. Rice field–breeding and other culicine mosquitoes serve as vectors. In addition to humans, birds and pigs can be infected. Pigs play an important role as amplifying hosts because they develop high-grade viremia from which large numbers of mosquitoes may become infected.[62] Most infections in endemic areas occur in children, whereas all age groups of previously unexposed populations are at risk. Transmission of JE currently occurs in India, Southeast Asia, China, Korea, Indonesia, and the Western Pacific region.[22] Routine use of JE vaccine in Japan has been eliminated because of low risk in this country.

Virology and Pathophysiology

Transmitted by mosquitoes, JE is caused by a neurotropic flavivirus that is phylogenetically related to West Nile and dengue viruses. After initial replication near the mosquito bite, viremia occurs, which if prolonged may seed infection to the brain. The cytopathologic effect of the flavivirus is believed to cause nerve cell destruction and necrosis.

Clinical Presentation

Incubation period is typically 2 to 15 days. Most infections do not cause clinical illness. Many patients recall a mild, undifferentiated febrile illness, which probably coincides with the viremic phase of infection. Patients with encephalitis often report a similar prodrome. The encephalitis syndrome is not easily distinguished from other arboviral encephalitides. The patient usually complains of headache, lethargy, fever, and confusion and may display tremors or seizures. One clinical series suggested that the presence on admission of (1) unresponsiveness to pain, (2) low level of anti–Japanese B encephalitis virus IgG or IgM antibodies in serum or cerebrospinal fluid (CSF), or (3) virus in CSF culture was associated with death. Of the 16 patients with fatal disease, all died within 7 days of hospitalization.[20]

Diagnosis

Acute and convalescent sera for antibody determination (virus neutralization or hemagglutination inhibition assays) provide the only reliable method of diagnosis of JE. Paired sera should be sent for these assays through state health departments. Sensitive assays for determinations of IgG and IgM antibodies in serum and CSF have been developed but are not yet widely available. Because most patients seek treatment long after the viremic phase, blood cultures are rarely positive for the virus, and CSF cultures are often positive only in patients with a poor prognosis.

Management

There is no specific therapy for JE. The main interventions are prophylactic: vaccination and reduced arthropod exposure. Supportive care may require an ICU. Because the virus is present in body fluids, especially CSF, blood and body fluid precautions should be considered.

NAMED HEPATITIS VIRUSES

Although infectious hepatitis has been a well-known clinical entity for hundreds of years, it is only in the last few decades that identification of specific viral pathogens has been possible. The causes of hepatitis may be divided into two groups. First, the "named," or more accurately, *lettered,* viruses now include hepatitis A to G. These are associated with defined clinical syndromes and elevated liver function tests. Second, other organisms that cause hepatitis as part of a more systemic infection include Epstein-Barr virus, cytomegalovirus, toxoplasmosis, and leptospirosis.

Hepatitis A

Epidemiology. Hepatitis A virus (HAV) is transmitted by the fecal-oral route through either person-to-person contact or ingestion of contaminated food or water. Food items typically associated with outbreaks are raw or undercooked clams and shellfish. Risk factors include contact with a HAV-infected person, international travel, household or personal contact with a child who attends a child care center, food-borne outbreaks, male homosexual activity, and use of illegal drugs.[7,45] Occasional cases are associated with exposure to nonhuman primates. Transmission by blood transfusion has been reported, but this is an uncommon source of infection. Hepatitis A is endemic worldwide, but underdeveloped nations have a higher prevalence than those in North America. Most persons in these areas show serologic evidence of past infection with HAV. Hepatitis A is a common viral infection occurring in travelers, but rates are declining with increased use of hepatitis A vaccine.

Virology and Pathophysiology. HAV is a picornavirus with a single-stranded RNA genome. Although the pathophysiologic mechanism has not been delineated, most infections begin with introduction of viral particles into the proximal GI tract. Brief viremia precedes seeding of hepatocytes, where viral replication has been documented. With replication, hepatocellular necrosis is accompanied by lymphocytic infiltration. In the majority of cases, hepatic regeneration occurs after acute disease, and no significant sequelae are observed. Chronic infection does not occur with hepatitis A.

Clinical Manifestations. The incubation period for HAV ranges from 2 to 7 weeks. The infection may be asymptomatic or mild, especially in children, but also in a minority of adults. The classic syndrome includes anorexia followed by nausea, vomiting, fever, and abdominal pain. These symptoms may be accompanied by hepatosplenomegaly. Aspartate transaminase (AST) and alanine transaminase (ALT) levels rise within a few days of the onset of symptoms. In children, AST and ALT return to normal levels in 2 to 3 weeks, whereas in adults, resolution of elevated serum transaminase levels may take several months. Bilirubin level rises shortly after AST and ALT elevations. Jaundice usually follows GI symptoms by several days to a few weeks. Resolution of jaundice may take another 3 to 4 weeks. The syndrome is occasionally preceded by arthralgias and rash, but these prodromal symptoms are uncommon. Resolution of acute disease is permanent in most patients, but rare cases of relapse have been noted. Pregnant women have a higher risk for severe illness than the general adult population. Anti-HAV antibody (primarily IgG) is detectable in the blood for many years after infection. Presence of the antibody confers immunity. Accordingly, reinfection with HAV is not believed to occur.

Diagnosis. The clinical presentation of hepatitis A is usually milder than that of other types of viral hepatitis. Consequently, the symptoms are not distinctive enough to allow a firm diagnosis, which requires detection of hepatitis A antigen in the stool or serologic evaluation for HAV-specific IgM or total anti-HAV antibody. Stool hepatitis A antigen is maximal before the onset of symptoms but may be detected as long as 2 weeks after the onset of disease. A more practical test is measurement of HAV-specific IgM antibody, which is usually present by the time symptoms are recognized and generally absent 6 months later. Measurement of anti-HAV antibodies may be helpful in evaluating possible causes of past icteric episodes or for seroepidemiologic studies, but their presence does not differentiate recent from past infection.

Management. No specific therapy exists for hepatitis A. Affected persons are usually managed as outpatients and should be instructed on enteric precautions to avoid transmission to others. Although infectivity drops sharply soon after the onset of jaundice, it is prudent to maintain enteric and blood-drawing precautions for about 2 weeks after jaundice appears. Nosocomial transmission has also been documented, but most spread probably occurs before jaundice and diagnosis.

Prevention. Active immunization with hepatitis A vaccine is recommended for most travelers to at-risk areas.[4] In addition, hepatitis A vaccine is now recommended as part of routine U.S. infant/child immunization programs, for postexposure prophylaxis, and for close contacts of newly arriving international adoptees.[3,4,25]

Hepatitis B

The spread of hepatitis by parenteral means was noted in 1885. Recognition in the 1960s of specific viral particles (the Australia antigen) in the serum of hepatitis patients led to identification of the responsible agent.

Epidemiology. With widespread use of serologic markers for hepatitis B disease, it became apparent that spread occurs through exchange of blood, semen, or rarely, saliva of infected people. Although spread is possible from persons with acute disease, the primary sources of viral particles are chronic carriers. Persons are defined as "carriers" if blood samples obtained 6 months apart both contain hepatitis B surface antigen particles (HBsAg). The carrier state follows acute infection in up to 90% of infected infants and 10% of adults. Risk factors for acquisition of hepatitis B infection in the United States include IV drug use, homosexual activity, and working in health care. In the United States, most patients are adults, and the carrier rate in the general population is less than 0.5%. In many areas of the developing world, most infections occur in infancy or childhood, and chronic carriers may constitute as much as 10% to 20% of the total population; thus, travelers are more likely to be exposed to carriers than is the nontraveling population. The risk is higher in persons regularly exposed to body fluids, including medical personnel and persons with many sexual partners.[103]

Virology and Pathophysiology. Hepatitis B virus (HBV) is a DNA virus unrelated to the agent responsible for hepatitis A. Infection occurs naturally in humans and can be induced easily in some nonhuman primates. Most HBV infections are subclinical. In those resulting in clinical disease, entry of the virus into the liver is followed by viral replication and hepatocyte necrosis. HBsAg, a viral particle, appears in the bloodstream within 3 months of infection. In most cases, IgM antibody to the hepatitis B core antigen (HBcAg) appears first, followed by anti-HBsAg (surface) antibody. Antibody to a third hepatitis antigen, the e antigen (HBeAg), is present for variable periods. The course of the disease varies widely, depending on a number of factors that are not well defined. In brief, most cases are self-limited and resolve in 4 to 6 months. In these patients, anti-HBsAg or anti-HBcAg IgG antibodies can be detected for years after the episode of hepatitis. Chronic carriers do not develop anti-HBsAg antibody, but rather maintain measurable levels of HBsAg. Similarly, carriers with persistent HBeAg detectable in blood samples appear to be more infectious than carriers without circulating HBeAg. The intricate network of antibody-antigen relationships in hepatitis B is believed to play a role not only in development of acute and chronic hepatitis, but also in the many extrahepatic syndromes associated with hepatitis B. Immune complex formation has been suggested as etiologic in hepatitis B–associated arthritis, rash, arteritis, and renal disease.[21]

Clinical Presentation. The incubation period for hepatitis B ranges from 7 to 22 weeks; however, the patient may be

antigenemic for a large portion of that time. Manifestations of HBV infection are similar to those of hepatitis A and include fever, anorexia, nausea, vomiting, and abdominal pain. In addition, a prodrome of rash, arthralgia or arthritis, and fever is seen in up to 20% of hepatitis B patients, compared with its rarity in hepatitis A. Glomerulonephritis is occasionally seen. Jaundice usually appears a short time after the onset of GI symptoms. In the self-limited form of disease, recovery is complete by 6 months. Some HBV infections follow a fulminant course; case fatality rates are 2% or less in most series. In addition to complete resolution or death, three other sequelae are possible with acute hepatitis B. First, a person may become an asymptomatic chronic carrier and remain HBsAg positive but have no detectable active hepatitis. Second, a person may have *chronic persistent hepatitis,* a term used to describe persistent, but not progressive, hepatic inflammation (usually monitored by serum transaminase levels), often with HBsAg in the serum. Third, persons with chronic active hepatitis may be HBsAg positive and have progressive hepatitis, which may result in cirrhosis and death directly related to liver disease. Any of these three conditions results in the presence of HBV particles in the blood.[61]

Diagnosis. A variety of antigen and antibody tests have been developed for diagnosis and monitoring of HBV disease. The most practical and widely available test for diagnosis of acute disease is the assay for HBsAg. Antigen is usually present before the onset of symptoms and persists during symptomatic disease. Occasionally, HBsAg may be undetectable in patients with clinical disease caused by hepatitis B. In these cases, antibody to HBcAg is often present. Later, antibody to HBsAg will appear, but this is often long after the episode of clinical hepatitis.

Management. Management is similar to that of hepatitis A. Prolonged viremia makes blood and body fluid precautions necessary until the absence of HBsAg antigen and presence of antibody to HBsAg are established. For patients with chronic infection, therapy with interferon-α and an antiviral (lamivudine, tenofovir, entecavir, adefovir, or telbivudine, depending on individual clinical characteristics) is recommended.[63] Even in individuals with good prognostic indicators, the response rate in terms of long-term clearance of virus and seroconversion only approaches 30%.

Prevention. Universal immunization of U.S. infants beginning at birth and catch-up immunization of children and adolescents are the current recommendations. Vaccination for at-risk adults is also advised. Travelers to highly endemic areas who stay for 6 or more months or have close contact with inhabitants should be vaccinated. Available vaccines are discussed in Chapter 79.

Delta Hepatitis (Hepatitis D)

Hepatitis with the delta agent was first suspected in 1977, when cases of severe hepatitis B disease and exacerbations of hepatitis were being evaluated.

Epidemiology. Delta virus infection is found only in patients concomitantly or previously infected with hepatitis B. Transmission follows a pattern similar to HBV infection. In the United States, affected populations are IV drug abusers and multiply transfused hemophiliac patients. Serologic evidence of delta virus disease has been documented in the Mediterranean basin, West Africa, and parts of South America.[94]

Virology and Pathophysiology. The delta agent has been termed a *defective virus* because it requires HBV activity for its own replication.[76] The agent is a single-stranded RNA enclosed in a protein coat of HBsAg. The delta agent infects cells at approximately the same time as HBV (coinfection), or it may be introduced later in the course of persistent HBV infection (superinfection). In coinfected patients, the clinical picture may not differ from hepatitis B, but a higher percentage of such patients develop severe disease than do those with hepatitis B alone. Patients superinfected with the delta agent develop flare-ups of hepatitis, which may become fulminant. After the acute infection, the delta agent can cause progressive disease in previously stable hepatitis B patients. In general, infection with the delta agent worsens the prognosis of HBV disease. The diagnosis can be made by detection of antibody to the delta antigen in the serum.[76] All HBV-infected individuals should be tested for anti–hepatitis D virus (HDV) IgG antibodies at least once.

Management and Prevention. Management of acute hepatitis consists of supportive care. Only interferon-α has proven antiviral activity against HDV and is associated with clearance in approximately 20% of infected patients.[2,94] Precautions against transmission are the same as for hepatitis B. There is no specific vaccine or immunoglobulin for the delta agent. The best preventive measure is to be vaccinated for hepatitis B, because delta agent infection cannot occur in the absence of the former virus.

Hepatitis C

As serologic methods for the diagnosis of hepatitis A, hepatitis B, and delta agent were developed, it became apparent that there was a group of persons with hepatitis for which no etiologic agent had been identified. This syndrome, previously termed "non-A, non-B" (NANB) hepatitis, was thought to be caused by a heterogeneous group of etiologies. It is now clear that a majority of such cases were caused by hepatitis C.[90]

Epidemiology. Risk factors for hepatitis C include IV drug use and, before routine testing, transfusion of blood products. Nonparenteral routes of infection are less important for hepatitis C than for hepatitis B. Hepatitis C is a global problem. Approximately 80% of exposed individuals develop chronic infection, which may lead to cirrhosis in 20% of patients and hepatocellular carcinoma in up to 5% of this patient subset. Rates of infection vary from 1% to 5% in most Western countries to 20% in parts of the Middle East, such as Egypt.

Virology and Clinical Manifestations. Hepatitis C virus (HCV) is a single-stranded RNA virus of the Flaviviridae family. Acute disease is indistinguishable from HAV or HBV infections. Most infections are asymptomatic, with jaundice occurring in fewer than 20% of infected individuals. Transition to chronic hepatitis after an insidious asymptomatic infection is the usual pattern. Chronic hepatitis may be asymptomatic or associated with nonspecific symptoms, such as lethargy, nausea, and abdominal discomfort. The patterns of cirrhosis and hepatocellular carcinoma, when these occur, do not differ significantly from those of other conditions. Extrahepatic syndromes associated with HCV infection include porphyria cutanea tarda, membranous glomerulonephritis, and mixed cryoglobulinemia.

Diagnosis. Two types of tests are available for diagnosis: serologic assays and RNA detection tests. Serologic testing detects only IgG antibodies, and assays for IgM or early/acute infection are not available. False-negative results may occur early in the course of acute infection. Within 15 weeks of exposure, the majority of HCV-infected patients will seroconvert. Standard immunoassay testing is used by clinical laboratories to detect antibodies to HCV. In addition, several rapid tests for HCV antibodies have been developed for point-of-care testing, including an over-the-counter testing kit that has been approved by the U.S. Food and Drug Administration (FDA). These rapid tests have sensitivities and specificities equivalent to standard immunoassays and can be performed on various patient specimens, including finger-stick blood, serum, plasma, and saliva.[60] Viral RNA can be detected in blood 1 to 2 weeks after exposure and before IgG detection. Assays for detection of HCV RNA are used to detect infection in infants born to HCV-infected mothers, for monitoring patients receiving antiviral therapy, and to identify seropositive patients who have persistent HCV infection. RNA tests can give false-positive and false-negative results. Viral RNA can also be shed intermittently, making a single negative assay inconclusive.

Management and Prevention. Prevention of hepatitis C largely depends on risk reduction, especially with respect to IV drug use. Pooled immunoglobulin has been used after exposure, but this should be procured from donors screened for hepatitis C; however, it is not generally recommended. Unlike hepatitis B, protective antibody responses have not been demonstrated. Treatment of acute hepatitis C is supportive. People with chronic HCV infection are at risk for developing cirrhosis and primary hepatocellular carcinoma. Treatment of chronic infection is rapidly improving with development of direct-acting oral agents. Oral antiviral regimens offer the potential of a cure to more

patients than had been seen with previous interferon-α–based regimens, with significantly improved tolerability and safety profiles. The Infectious Diseases Society of America and American Association for the Study of Liver Diseases provide frequently updated recommendations on the management of chronic hepatitis C infection at http://www.hcvguidelines.org.[1]

The goal of HCV therapy is sustained virologic response, a marker for cure of the infection, defined by continued absence of detectable HCV RNA at least 12 weeks after completion of therapy. Treatment is recommended for all HCV-infected persons, except those with limited life expectancy (<12 months). The highest priority for immediate treatment is for patients with advanced fibrosis, compensated cirrhosis, severe extrahepatic disease, and liver transplant recipients. Regimen selection is based on the HCV genotype, with specific considerations for patients with cirrhosis, HIV coinfection, post–liver transplant infection, and severe renal impairment. In general, treatment-naive patients without cirrhosis are treated for 12 weeks, whereas those with cirrhosis are treated with longer courses (typically 24 weeks). Regimens based on oral direct-acting antiviral agents are highly efficacious, with cure rates greater than 90% in treatment-naive patients infected with HCV genotypes 1, 2, 3, and 4. Limited data are available regarding patients infected with the less common HCV genotypes 5 and 6.

Hepatitis E

Hepatitis E is an RNA virus provisionally placed in the Caliciviridae family. It is the second most common cause of viral hepatitis transmitted via the enteric route. The epidemiologic characteristics are similar to hepatitis A. However, hepatitis E has animals (pigs and deer) as its reservoir.[88] This group of infections is especially important in the Indian subcontinent, Middle East, and Africa. The incubation period is 2 to 6 weeks. The disease is usually self-limited but may be associated with severe illness in pregnant women. Diagnosis in travelers from endemic areas can be made on the basis of IgM antibody to hepatitis E in serum or testing of stool for viral antigen. PCR for hepatitis E may be available in some centers. In the United States, testing for hepatitis E is best undertaken in returned travelers with clinical hepatitis, although a more severe illness may occur in persons with underlying liver disease. Prophylaxis is appropriate advice for travelers and involves counseling on precautions regarding ingestion of food and water in endemic areas. In 2011, China licensed the first vaccine to prevent hepatitis E infection; it is not yet available globally.[102]

Hepatitis F and Hepatitis G

Hepatitis F is a putative hepatitis virus of uncertain significance, first described in France. Hepatitis G is a member of the Flaviviridae family with limited homology to hepatitis C. Its significance as a cause of hepatitis is also unclear.

MAJOR BACTERIAL INFECTIONS

This section reviews several bacterial diseases of relevance to the overseas traveler, including typhoid fever, meningococcal disease, pertussis, diphtheria, and tetanus. Other chapters deal with bacterial causes of gastroenteritis and diarrhea (Chapter 82), tick-borne diseases (Chapter 42), and zoonoses (Chapter 34).

TYPHOID AND PARATYPHOID FEVER

Typhoid fever was recognized as a clinical entity in the 1800s and was first associated with transmission by the fecal-oral route in the 1870s. Although effective treatment with chloramphenicol became possible in 1948, the disease continues to be a major cause of morbidity and mortality in the developing world.

Epidemiology

Enteric fever (typhoid or paratyphoid) occurs worldwide, but its prevalence and attack rates are much higher in underdeveloped countries. Humans are the only host for *Salmonella enterica* serotype Typhi (*S.* Typhi), the most common cause of the enteric fever syndrome. Almost all cases are contracted through ingestion of contaminated food or water. Transmission occurs through a variety of mechanisms, most often contact with a chronic carrier of the organism, especially food handlers, and ingestion of untreated waste material or sewage. Improved sewage and tracking of chronic carriers have greatly reduced the incidence in developed countries, although several hundred cases a year are reported to the CDC. Enteric fever is estimated to cause 26 million illnesses and 200,000 deaths per year.[34] This may be underestimated because diagnosis can be difficult (especially in children) and because enteric fever is not a reportable disease in most countries. Travel to Asia and especially India is associated with the highest risk for contracting enteric fever.[39]

Bacteriology and Pathophysiology

Salmonella species are gram-negative enteric bacilli. Enteric fever is primarily caused by *S.* Typhi and *S. enterica* serotypes Paratyphi A, B, and C. Increasing incidence of disease caused by *S.* Paratyphi A has been seen in some highly endemic areas of Asia.[35] *Salmonella* species are easily grown on routine bacterial culture plates, but if multiple organisms are present, media with selective growth inhibitors may be needed for optimal sensitivity. After ingestion of food or water containing the pathogen, organisms are subjected to the acid stomach environment, which results in significant bacterial killing. If the organisms pass through the small intestine, several processes may occur. The bacteria may simply pass through, causing few clinical symptoms. If the bacteria multiply and invade the mucosa, a gastroenteritis-like syndrome will result. Typhoid fever requires penetration of the intestinal mucosa and intestinal lymphatics, where intracellular replication of *S.* Typhi occurs. Soon thereafter, bacteria seed the bloodstream and are transported to reticuloendothelial cells throughout the body, where further intracellular replication can take place. After the acute episode of infection is over, *Salmonella* species may remain and asymptomatically reproduce in scarred or chronically inflamed tissues. Persons may shed organisms from such foci for years and serve as a source of outbreaks while they themselves are asymptomatic. The most common site for such colonization is the chronically diseased gallbladder.

Clinical Presentation

After exposure to the pathogen, 10 to 14 days usually pass before the onset of clinical illness. Some patients may experience gastroenteritis early in the course of disease, and abdominal pain or diarrhea may be present when the classic typhoid fever picture develops. Fever is usually the first sign of disease. Fever increases slowly over several days and may remain constant for 2 to 3 weeks, after which defervescence begins. With antibiotic therapy, fever resolves more rapidly, often within 3 to 4 days. Relative bradycardia may accompany fever. Most patients also report headache, malaise, and anorexia. Rose spots (2- to 4-mm maculopapular blanching lesions) are classically described on the trunk, although they are not seen in the majority of patients. Hepatomegaly and splenomegaly have been reported in a large number of patients.[16] Laboratory investigations early in the course may show a high white blood cell (WBC) count, anemia, and mild elevations of serum hepatic enzyme levels, including AST, lactate dehydrogenase, and alkaline phosphatase. Later in the disease course, leukopenia (WBCs <3500/mm^3) develops. Uncomplicated and untreated typhoid fever resolves in 3 to 4 weeks. Several complications may herald or contribute to death. Intestinal perforation, presumably secondary to necrosis of lymphoid areas of the bowel wall, may lead to peritonitis and death. Significant GI hemorrhage may occur but rarely is fatal. Secondary pneumonia is common. A subgroup of patients has more severe disease, which may include myocardial involvement, mental status changes, hyperpyrexia, and multisystem failure. Data on case fatality rates are limited; the global mortality rate is estimated to be 1%.[34]

Diagnosis

Culture of a bacterial species associated with the syndrome (most likely *S.* Typhi) from a normally sterile fluid is the gold standard; however, it is expensive and requires expertise that many developing countries cannot afford. Multiple studies have evaluated

usefulness of various diagnostic tests. In general, bone marrow culture is the most sensitive method, detecting up to 90% of cases; blood cultures are less sensitive. Both methods are most useful in the first week of disease. Stool cultures and string test cultures may be positive later in the disease course but provide only circumstantial evidence of the causative agent. Other serodiagnostic methods in development have not yet proved useful.[8]

Management

Chloramphenicol had been the mainstay of treatment for typhoid fever since the late 1940s. Ampicillin and trimethoprim-sulfamethoxazole (TMP-SMX) were the traditional alternatives. Multidrug resistance to traditional first-line agents is now widespread, so ciprofloxacin is the current first-line antibiotic. Unfortunately, increasing resistance to quinolones has been observed, especially from the Indian subcontinent. In cases of quinolone resistance, either laboratory or clinical, ceftriaxone or other third-generation cephalosporins are indicated.[9] Azithromycin is another useful alternative for treatment of uncomplicated enteric fever.[38] Other treatment modalities include fluid support and adequate nutrition. Corticosteroids have been used empirically for many years. A single randomized double-blind study showed that administration of high-dose dexamethasone (3 mg/kg for the first dose, followed by 1 mg/kg every 6 hours for eight more doses) with chloramphenicol resulted in significantly lower mortality in patients with severe typhoid fever than in those treated with chloramphenicol alone.[55] Severe typhoid fever was defined in this study by the presence of obtundation, delirium, stupor, coma, or shock. High-dose corticosteroids are not recommended for patients with less severe disease and should be used cautiously in those with severe disease.[33]

Prevention

Even when vaccines are given before travel, it is important to observe routine hygiene, preparation, and handling precautions for ingestion of food and water to prevent enteric fever and acquisition of other pathogens by the fecal-oral route. Currently, two vaccines are available in the United States for prophylaxis. The live-attenuated oral vaccine containing the Ty21a strain of *S.* Typhi is given as a four-dose series, with 1 day between each dose. Immunosuppression, antibiotic use, and gastroenteritis are contraindications to the use of this vaccine. It is licensed for use in those 6 years and older, and a booster is recommended every 5 years. The parenteral vaccine contains the Vi (virulence) polysaccharide of *S.* Typhi purified from formalin-killed bacteria. It is administered as a single intramuscular (IM) injection and is therefore most useful when vaccination is required on short notice. It is licensed for persons 2 years and older, and a booster is required every 2 years. *S.* Paratyphi lacks the Vi antigen, so the Vi-based vaccine offers no cross-protection against paratyphoid fever. There is limited evidence that Ty21a vaccine may provide cross-protection against *S.* Paratyphi A and B, although there are currently no licensed vaccines against *S.* Paratyphi.[95]

MENINGOCOCCAL DISEASE

Classically, meningococcal meningitis attacks children and young adults and is often seen in epidemic form. Although the advent of effective antibiotic therapy and useful vaccines has greatly improved the ability to manage this disease, it remains a major problem in many parts of the world.

Epidemiology

Cases of meningococcal disease occur sporadically worldwide, with epidemic disease generally limited to developing nations. The five predominant strains of meningococcal infections are A, B, C, Y, and W-135. The epidemiology of meningococcal disease is highly dynamic with considerable fluctuations and frequent outbreaks and epidemics. Serogroup A (and less so serogroup C) is most frequently associated with epidemics in sub-Saharan Africa. Increasingly, serogroup W-135 has emerged in Saudi Arabia (associated with the Hajj pilgrimage) and West Africa.[97] Epidemic situations clearly pose the greater health problem to both travelers and resident populations. The "meningitis belt" in sub-Saharan Africa, a region that extends from Ethiopia in the east to Senegal in the west, experiences 100 to 800 cases per 100,000 population per year. In contrast, the United States and Europe experience approximately 1 case/100,000/yr.[53]

Particularly in sub-Saharan Africa and China, the disease demonstrates yearly incidence peaks and periodic massive outbreaks, the exact determinants of which are unknown. Transmission of the organism occurs by exchange of respiratory secretions; contact is believed to be important in the spread of disease. Asymptomatic transient nasopharyngeal carriage of the meningococcus, occurring with a baseline prevalence of 5% to 10%, may increase during epidemic periods and in close contacts of cases. The secondary attack rate among household contacts of patients with sporadic disease is 2:1000 to 4:1000, whereas that in epidemics ranges from 11:1000 to 45:1000 household contacts.

Bacteriology and Pathogenesis

Neisseria meningitidis is a gram-negative diplococcus that grows easily on several common media, including chocolate and blood agar. The organism is characterized further on the basis of serologic analysis of capsular antigens. The most common serogroups are A, B, C, Y, and W-135. In the United States, the current serogroup distribution is 23% serogroup B, 31% serogroup C, 35% serogroup Y, and the remainder serogroup W-135 and other serogroups.[53] Asymptomatic persons may carry various serotypes of *N. meningitidis* in the nasopharynx for short periods. An antibody response is often generated to these strains during asymptomatic carriage. The conditions that cause one person to become clinically ill with invasive disease while another carrier remains healthy are not well understood. The route of entrance of the organism to the bloodstream and central nervous system (CNS) is presumably through the nasopharynx or respiratory tract.

Clinical Presentation

Meningococcal disease may appear in a variety of forms, including but not limited to bacteremia with septic shock; meningitis, often accompanied by bacteremia; and pneumonia. Sustained meningococcemia may lead to severe toxemia with hypotension, fever, and DIC. In the fulminant presentation, adrenal hemorrhage may lead to Waterhouse-Friderichsen syndrome, and death may follow intractable shock. In the United States, the case fatality rate for sustained meningococcemia is generally higher than for meningococcal meningitis. There is also a clinical syndrome of chronic meningococcemia with a much more insidious onset.

Meningitis caused by *N. meningitidis* classically begins with fever, headache, and a stiff neck. It may also be accompanied by bacteremia and any of several skin manifestations, including petechiae, pustules, or maculopapular rash. In either meningitis or bacteremia, progression of petechiae to broad ecchymoses is a poor prognostic sign. As with septic meningococcemia, severe meningitis may progress with mental status deterioration, hypotension, congestive heart failure, DIC, and death. The case fatality rate of meningococcal meningitis with or without bacteremia is estimated to be about 10%.[48] In classic cases of meningitis or bacteremia with sepsis, the peripheral WBC count is elevated, with polymorphonuclear neutrophil (PMN) cell predominance. CSF is typically purulent, usually with more than 500 PMNs/mm^3. There may be a more heterogeneous cell population and fewer cells if CSF is obtained early in the course or if the patient has been treated with antibiotics. The CSF glucose level is usually low and protein high, as in other bacterial meningitides. Gram stain of CSF may show gram-negative diplococci.

Meningococcal pneumonia is a well-known but less common clinical entity described in military recruit populations involving serogroup Y organisms.

Diagnosis

The presumptive diagnosis in an epidemic can be made on the basis of clinical presentation and purulent CSF. The presence of characteristic bacterial forms on Gram stain is also suggestive. A definitive diagnosis requires culture of the organism from CSF or a normally sterile fluid (usually peripheral blood). This may be impossible in the case of a patient who was previously treated

with antibiotics before CSF culture. Several commercial kits for measuring meningococcal antigen are now available for use on CSF or blood samples; they have variable sensitivity and specificity.

Management

Treatment of meningococcal meningitis or sepsis is a medical emergency. Fortunately, the organism remains sensitive to a large number of antibiotics. In developed countries, patients are treated with pencillin G alone or a third-generation cephalosporin. Typical duration of therapy is 7 to 10 days, although 3 to 4 days of IV therapy has been effective without increased risk of relapse. During epidemics in developing countries, a single IM injection of long-acting chloramphenicol or ceftriaxone can be sufficient treatment for meningitis.[84] Antibiotic treatment before culture or hospital referral is recommended in clinically suspected cases. Supportive care should include close monitoring for hypotension and cardiac failure. Development of DIC is an ominous sign. Although focal bleeding and adrenal necrosis may lead to acute adrenal insufficiency, the role of replacement steroids in the treatment of Waterhouse-Friderichsen syndrome is unclear.

Because the infectious agent has been found in household contacts and in persons exposed to oral secretions, contacts should receive prophylaxis to eradicate the organism. Rifampin, 600 mg orally every 12 hours for four doses, is standard adult prophylaxis. Children should receive 10 mg/kg of rifampin every 12 hours for four doses if older than 1 month and 5 mg/kg every 12 hours for four doses if younger than 1 month. More recently, alternate regimens using ceftriaxone and ciprofloxacin have also been proved to be efficacious, although rifampin remains the standard.

Ceftriaxone is given intramuscularly as a single dose (125 mg for children <15 years and 250 mg for people >15 years). Ciprofloxacin is given at 20 mg/kg (maximum 500 mg) orally as a single dose.

Prevention

Several meningococcal vaccines are available and include a quadrivalent meningococcal polysaccharide vaccine (MPSV4) and quadrivalent meningococcal polysaccharide vaccines conjugated to diphtheria toxins (MCV4). These quadrivalent vaccines contain serogroups A, C, Y, and W-135. Vaccination with MCV4 is recommended for all adolescents age 11 to 18 years. In addition, meningococcal vaccination is recommended for younger and older individuals with increased risk for invasive meningococcal disease, such as those with asplenia, complement deficiencies, military recruits, college students living in dormitories, and travelers to countries where meningococcal disease is hyperendemic or epidemic.[6,32] In 2014 the FDA approved a meningococcal serogroup B vaccine for use in individuals age 10 to 25 years. The serogroup B vaccine is now recommended for routine use in infants in the United Kingdom although it is not yet recommended for routine vaccination in the United States.[73]

PERTUSSIS

Pertussis, or whooping cough, was first recognized as a major threat in the 1500s. After introduction of a vaccine in the 1940s, the incidence of pertussis dropped sharply among immunized populations; however, neither natural infection nor immunization results in lifelong immunity. Older siblings and adults with mild or unrecognized disease are important sources of pertussis. Humans are the only known reservoir.

Epidemiology

Pertussis is found throughout the world. The incidence is highest in undeveloped countries, where immunization rates are low and socioeconomic conditions predispose to many communicable diseases. Pertussis is highly infectious, with attack rates of greater than 90% in unvaccinated household contacts. Untreated individuals remain infectious for more than 6 weeks. In the United States, the most severe disease occurs in children under 5 years old and particularly in young infants. Transmission is by airborne particles from respiratory secretions of infected persons.

Bacteriology and Pathophysiology

Bordetella pertussis is a gram-negative coccobacillus. The organism produces several toxins when present in the respiratory tract. Pertussigen stimulates lymphocytosis and hemagglutination. Dermonecrotic toxin and tracheal cytotoxins damage respiratory epithelium. In addition, endotoxin is produced. During the course of the somewhat protracted disease, complications can occur that may cause death. The most serious of these are secondary pneumonia and encephalopathy. In addition, fits of coughing often result in pneumothorax, hemorrhage (facial, conjunctival, CNS), and aspiration.

Clinical Presentation

Classic pertussis develops after an incubation period of 7 to 10 days. The disease appears in three stages: catarrhal, paroxysmal, and convalescent. The catarrhal stage lasts 1 to 2 weeks and resembles an undifferentiated upper respiratory tract infection with cough and mild fever. Progression of the cough to yield the classic whoop (which results when the patient gasps for breath after a prolonged coughing episode) marks the paroxysmal stage, which again can last as long as 2 weeks. During this stage, the WBC count may show marked lymphocytosis. Finally, cough resolves during the convalescent stage. Death may occur from pertussis alone or from complications such as aspiration pneumonia. Recent case fatality rates for Americans were 0.4% for all persons and 1% for patients younger than 1 year. The disease in adults is often milder, although it may show a severe classic pattern. Some investigators believe mild or atypical disease in adults may serve as a reservoir for infection of susceptible children.

Diagnosis

Laboratory tests for the diagnosis of pertussis include culture, PCR, and serology, which must be used in conjunction with clinical and epidemiologic data. Culture is considered the gold standard because it is the only method with 100% specificity, and it is best done from nasopharyngeal (NP) specimens collected during the first 2 weeks of cough. PCR on NP specimens has excellent sensitivity and turnaround time, although the high sensitivity of PCR increases the risk for false-positives. PCR is best done on samples obtained within 4 weeks of cough onset. Pertussis serologic tests are generally more useful for diagnosis in adults and in the later stages of disease.[72]

Management

Treatment with antibiotics, unless begun in the incubation or catarrhal period, has little effect on the course of the disease. Antibiotics can reduce subsequent transmission to contacts, however, and should be instituted as soon as the diagnosis is made. Macrolides are the drugs of choice, with azithromycin, erythromycin, or clarithromycin all appropriate choices for first-line treatment and prophylaxis. For infants from birth to age 5 months, azithromycin is given at 10 mg/kg as a single oral dose for 5 days. For older infants, children, and adults, azithromycin is given at 10 mg/kg (maximum 500 mg) as a single oral dose on day 1, then 5 mg/kg (maximum 250 mg) as a single oral dose on days 2 through 5. Other useful agents include doxycycline, TMP-SMX, and chloramphenicol. In infants with severe disease, corticosteroids may provide some improvement. Perhaps more important than specific antibiotics is supportive care, including hydration, nutrition, care to maintain adequate ventilation, and supplemental oxygen. In addition, external stimuli, which seem to exacerbate symptoms, should be kept to a minimum.

Prevention

Universal immunization of children younger than 7 years, as well as boosters for adolescents (age 11 to 18 years) and adults, is recommended. In addition, it is recommended that women receive a booster with each pregnancy.[26,28] In the United States, acellular pertussis vaccines are currently used. The pertussis vaccine is combined with diphtheria and tetanus toxoids (pediatric DTaP formulation and adolescent/adult Tdap formulations). The Tdap replaces Td to boost waning pertussis immunity in the adult population, where the majority of pertussis infections are perpetuated. In cases of pertussis exposure, immunization of

unimmunized or underimmunized individuals should be initiated. In addition, chemoprophylaxis (with azithromycin, erythromycin, or clarithromycin) should be started for all household contacts and other close contacts regardless of age and immunization status. If 21 days has elapsed since exposure, chemoprophylaxis is of limited value.[89]

DIPHTHERIA

Diphtheria, once a highly feared cause of morbidity and mortality in young people, can be controlled with appropriate vaccination. However, according to some surveys, waning immunity has left many adults (18 years of age or older) with inadequate circulating levels of antitoxin against diphtheria. Newer vaccine recommendations are aimed at ameliorating waning immunity.

Epidemiology

Humans are the natural host for *Corynebacterium diphtheriae*. Person-to-person spread occurs through contact with respiratory secretions or diphtheritic skin lesions. A carrier state exists in which people who have either been immunized or previously infected can harbor the organism and asymptomatically transmit it to others. Evidence suggests that diphtheria can be transmitted through food or water, but this is not a major route of transmission.

Bacteriology and Pathogenesis

C. diphtheriae is a gram-positive, club-shaped bacillus. On Gram stain, the clustered bacteria have the characteristic "Chinese letter" configuration. The organisms grow on standard media, but to avoid overgrowth of other oral flora, selective media (Loffler's culture medium or cysteine-tellurite agar) are suggested. The presence of a lysogenic bacteriophage in some *C. diphtheriae* organisms induces production of diphtheria toxin. The toxin is produced as a single molecule with two subunits, fragments A and B. Fragment B facilitates attachment to the cell membrane of host cells, and after attachment, fragment A enters the cell. Cell death results from large-scale disruption of protein synthesis capabilities.

Clinical Presentation

The most important manifestation of diphtheria is respiratory tract infection. Illness begins after an incubation period of approximately 1 week with nonspecific symptoms of malaise, fatigue, mild sore throat, and slight fever. The classic lesion is exudative pharyngitis progressing to a greenish gray membrane that is difficult to dislodge. This membrane may spread over the posterior pharynx, tonsils, and uvula and down the respiratory tree to involve the larynx and trachea. Any one of these areas may be involved selectively, and the severity of illness is to some extent related to the area grossly involved. In severe disease, swollen tissues may result in a bull-neck appearance. Major complications include obstruction of the respiratory tract, which may result from direct parapharyngeal swelling or laryngeal involvement in young children, and sloughing of the tracheobronchial membrane in older patients. In addition to respiratory tract damage, toxin directly injures myocardial and neural tissue. Endocarditis occurs in some patients. Early signs in the first week of disease include ST-segment–T-wave depression and atrioventricular conduction abnormalities on the electrocardiogram (ECG). Congestive heart failure and cardiac enlargement may develop. Neurologic deficits usually begin with pharyngeal and cranial nerve paralysis. Cranial nerve paralysis may progress to bilateral motor paralysis, which generally resolves over 3 to 6 months. In the tropics, cutaneous diphtheria is seen frequently. The skin lesions are not consistent in appearance, and range from very superficial impetigo-like lesions to deep ulcers. In most cases of cutaneous disease, absorption of toxin is not great enough to cause the multisystem involvement seen in respiratory tract disease. The prevalence of skin lesions increases the overall likelihood of coming in contact with toxigenic *C. diphtheriae*.

Diagnosis

Reliable isolation of the organism requires a selective medium and several days of culture. Treatment should be started as soon as the patient is evaluated and is guided by clinical manifestations.

Management

Because the toxin and not the organism per se mediates life-threatening clinical manifestations of diphtheria, neutralization of absorbed toxin is crucial. A horse-derived antitoxin is available from the CDC and should be administered as soon as the diagnosis is seriously considered. A 0.1-mL test dose of intradermal antitoxin diluted to a 1:1000 concentration (with a saline control) is observed for 20 minutes. If no reaction occurs, full doses can be given intravenously. Antitoxin should be diluted to 1:20 in saline and given no faster than 1 mL/min. The dose depends on the location and severity of disease. A dose of 20,000 to 40,000 units is recommended for pharyngeal/laryngeal disease of less than 48 hours' duration, 40,000 to 60,000 units for moderate cases with nasopharyngeal disease, and 80,000 to 120,000 units for severely ill patients with diffuse neck swelling or illness of more than 3 days' duration.[5] Erythromycin or penicillin G may be given to eradicate the carrier state, although their use has no effect on the clinical course of disease. Close observation is crucial to evaluate the need for respiratory support, especially in young children. Serial ECGs and neurologic evaluation establish the onset of complications. If significant conduction abnormalities are present, continuous heart monitoring should be undertaken. Strict bed rest is recommended for all patients for 2 to 3 weeks. Immunization should be given during convalescence, because disease survival does not necessarily confer immunity.

Prevention

Close contacts of patients with respiratory diphtheria should receive diphtheria vaccine if they have not received at least three doses previously or if 5 or more years have elapsed since the last dose. In addition, unimmunized or partially immunized contacts should receive either IM benzathine penicillin (600,000 units if younger than 6 years, 1.2 million units if older than 6 years) or 7 to 10 days of erythromycin (40 mg/kg/day for children or 1 g/day for adults, in four divided doses). Antitoxin is not recommended for contacts. The most important way to prevent diphtheria in adults, however, is to ensure that all adults receive a booster dose of Tdap every 10 years.

TETANUS

Tetanus was recognized by the early Greeks and remains a cause of infant and adult mortality. The current mortality rate approaches 90% and 40% for untreated infants and adults, respectively. Tetanus toxoid immunization has drastically reduced the incidence of disease in populations with high coverage rates.

Epidemiology

The tetanus bacterium and its spores are ubiquitous. Approximately 10% of the general population carries *Clostridium tetani* in fecal flora. Person-to-person spread is not an important cause of this disease. Disease occurs when the organism is introduced into an environment suitable for its growth, specifically wound sites with an anaerobic environment. In the developing world, the vast majority of cases are in neonates as a result of umbilical stump infections.

Bacteriology and Pathophysiology

C. tetani is a gram-positive, anaerobic, spore-forming rod. The spores are hardy and can occasionally survive boiling for short periods. After proliferating in an appropriate anaerobic environment, *C. tetani* releases the toxin tetanospasmin, which in generalized disease reaches the spinal column and CNS by hematogenous spread. The toxin is taken up by inhibitory neurons, where it interferes with release of inhibitory neurotransmitters, resulting in disinhibition of motor groups. Disinhibition of sympathetic nervous system neurons occurs through a similar mechanism. The result is muscular spasm of varying severity and signs of sympathetic nervous system hyperactivity, including tachycardia, sweating, arrhythmias, and high blood pressure.

FIGURE 81-2 Patient with tetanus following a leg wound suffered during the 2010 earthquake in Haiti. Note difficulty with handling of oral secretions. *(Courtesy Paul S. Auerbach, MD.)*

Clinical Presentation

A tetanus-prone wound precedes most adult disease, which may not be evident at presentation. Localized tetanus, with spasm of a focal set of muscle groups, may occur and remain localized for weeks, then slowly resolve. This form of tetanus is much less common than is the generalized form, which often begins with trismus, or spasm of the masticator muscle group (Figure 81-2). Gradual onset of spasm of other muscle groups usually involves the trunk and extremities. Because the posterior muscles are stronger during spasms, the patient exhibits lumbar lordosis, with the neck and legs extended and arms flexed at the elbows (opisthotonos). Spasms seem to be exacerbated by external stimuli, such as sudden sound or light. The primary danger is loss of ability to breathe, especially during prolonged spasms. Respiratory failure is the main cause of death. The clinical picture in neonatal tetanus is similar but begins with restlessness and failure to nurse, with progression to tetany and sympathetic overactivity (Figure 81-3). There is no definitive laboratory test to confirm the diagnosis of tetanus, but the clinical picture is adequate in the majority of cases.

Management

Emergency medical treatment of tetanus patients should include (1) excision of the wound, (2) administration of human tetanus immunoglobulin (TIG; 3000 to 6000 units in a single dose), and (3) administration of an antibiotic effective against *C. tetani,* such as penicillin or metronidazole for 10 to 14 days.[41] Depending on the severity of disease, different levels of supportive care and sedation may be appropriate. Benzodiazepines may be given to mildly affected patients for sedation. Patients should be evaluated carefully for dysphagia. If dysphagia is present or other respiratory difficulties arise, endotracheal intubation or a tracheostomy should be performed. With prolonged spasms, hypoxia and cyanosis may occur, and mechanical ventilation with pharmacologic paralysis is appropriate. At the same time, attention must be given to fluid balance and nutrition. Enteral feeding by a nasogastric tube is the least invasive way to supply both. β-Adrenergic blockers have been suggested to relieve symptoms of autonomic overactivity, such as tachycardia and hypertension, but their prophylactic use has no proven benefit. Sources of sensory stimulation should be reduced when the spasms are uncontrolled.

Prevention

Although rare cases of tetanus have occurred in previously immunized persons, immunization is considered at least 99.9% effective. Several vaccine formulations are available in the United States. Children younger than 7 years may receive either DTaP or DT (diphtheria and tetanus toxoid only) vaccine. A third vaccine, Tdap, is manufactured for use in persons at least 7 years old and consists of tetanus toxoid and a smaller amount of diphtheria toxoid and pertussis than is present in the pediatric vaccines. A reduced amount of diphtheria toxoid is used in the adult preparation because both the amount of toxoid and increasing age are associated with more severe reactions to vaccination. Adults who are unimmunized should be given a series of three doses (0.5 mL intramuscularly) of Tdap, with the second dose 4 to 8 weeks after the first, and the third dose 6 to 12 months after the second. A booster should be given every 10 years thereafter. All travelers should know when they were last immunized and stay current with booster doses.

From the standpoint of tetanus prevention, care of wounds is crucial. The tetanus-prone wound, contaminated with dirt or feces or caused by puncture, crush, avulsion, or frostbite, should be cleaned and debrided appropriately. Persons with tetanus-prone wounds should receive 250 units of TIG intramuscularly (for all ages) if their immunization history is unknown or their immunization series is incomplete. These persons should also receive a dose of Tdap and complete an immunization series. Persons fully immunized and given an appropriate booster before a tetanus-prone wound should not receive TIG. If they have not received a booster within 5 years, however, they should receive a dose of Tdap.

MAJOR PROTOZOAN INFECTIONS OTHER THAN MALARIA

AFRICAN TRYPANOSOMIASIS

Trypanosoma brucei rhodesiense (East Africa) and *T. brucei gambiense* (West Africa) are important infectious diseases in Africa

FIGURE 81-3 Neonatal tetanus in Kenya.

and have provided remarkable insights into the importance of antigenic variation as a strategy used by parasites to avoid the immune response.[69] *T. brucei gambiense* causes African sleeping sickness, and *T. brucei rhodesiense* causes an acute disease that may end in heart failure. The parasites are transmitted to humans by tsetse flies (*Glossina* spp.) in sub-Saharan Africa. Metacyclic promastigotes are injected into the bloodstream through the saliva of the biting tsetse fly and divide into long slender forms in the bloodstream. These eventually differentiate into short stumpy forms, which are taken up in the blood meal of the tsetse. Once in the fly, the parasite differentiates into procyclic forms. It takes approximately 3 weeks for the protozoa to develop into infective metacyclics within the tsetse fly. Approximately 10,000 human cases are reported each year. In East Africa, animals such as antelope, bushbuck, and hartebeest serve as reservoirs. In West and Central Africa, humans are the only reservoir.[44,99]

Clinical Manifestations

The initial sign of infection is a nodule at the site of the tsetse fly bite. This lesion becomes erythematous and painful over 1 week and usually recedes after several days. Dissemination of the trypanosome throughout the body causes clinical symptoms, notably fever, headache, and severe malaise. On physical examination, enlarged supraclavicular and posterior cervical lymph nodes are noted. This phase of illness lasts several days and is followed by an asymptomatic period of several weeks. The acute phase may then recur. In the case of *T. brucei gambiense* infection, symptoms are less severe and evolve into a syndrome characterized by behavioral changes and chronic somnolence. *T. brucei rhodesiense* infections cause severe anemia, frequent episodes of fever, and eventual heart failure and severe CNS involvement. Both forms have high fatality rates. Without treatment, infected patients die within weeks to months after *T. brucei rhodesiense* disease, and within a few years from *T. brucei gambiense* disease.[19]

Diagnosis

Definitive diagnosis depends on identification of parasites in blood, lymphatics, or CSF. Thick blood smears and buffy coat preparations should be prepared with Giemsa stain and examined for the presence of trypanosomes. CSF should be subjected to centrifugation and the sediment examined for parasites. Associated laboratory abnormalities include anemia, monocytosis, and elevated serum and CSF IgM levels.

Management

Suramin (available from the CDC) should be used for treatment of early *T. brucei rhodesiense* infection, although the drug may cause proteinuria. A test dose of 100 mg intravenously (IV) is first given to detect possible idiosyncratic reactions. If tolerated, 1 g should be given on the initial day of treatment and 3, 7, 14, and 21 days later. If CNS involvement is diagnosed or strongly suspected (CSF lymphocytosis and elevated IgM), melarsoprol (available from the CDC) should be administered. This drug should be given at 2 to 3.6 mg/kg/d IV for 3 days. After 1 week with no drug given, additional injections of 3.6 mg/kg/d IV for 3 days are given. Repeat again after 1 week with no drug given. This arsenical compound is toxic, causing encephalopathy and exfoliative dermatitis, and should be used only in a controlled hospital setting. For early *T. brucei gambiense* infection, pentamidine (4 mg/kg body weight intramuscularly, up to 300 mg/kg given over 7 days) is the treatment of choice. Eflornithine, 100 mg/kg every 6 hours for 14 days, should be used for more advanced cases of this infection.

SOUTH AMERICAN TRYPANOSOMIASIS (CHAGAS' DISEASE)

Trypanosoma cruzi is transmitted to humans by triatomids that live in the cracks of mud-built homes in Central and Latin America. These insects are common in areas of Brazil, Venezuela, and Argentina with poor socioeconomic development. The infection has been reported as far north as the southern United States.

Clinical Manifestations

Affected individuals generally do not recall initial contact with the insects, when triatomid feces containing the protozoan organisms are deposited on broken skin or mucous membranes and then multiply within local macrophages. The macrophages rupture and elicit an inflammatory reaction that appears as a nodule with slightly painful satellite nodules or draining lymph nodes. A symptomatic phase, characterized by fever and diffuse lymph node enlargement, develops. Hepatosplenomegaly may also occur. In severe cases, acute myocarditis, pericarditis, or endocarditis is seen. After several months, the acute phase resolves, and chronic disease appears, characterized by cardiomyopathy, megaesophagus, or megacolon.[74] It is rare for the traveler to develop these signs or symptoms.

Diagnosis

Diagnosis during the acute phase may be made by demonstration of parasites in leukocytes in Giemsa-stained blood smears. Amastigotes of *T. cruzi* may also be present in biopsy specimens of lymph nodes or muscle. Elevated IgM antibody titers to *T. cruzi* (performed by the CDC) also support the diagnosis. In the chronic phases of Chagas' disease, the clinical findings of cardiomyopathy, megaesophagus, or megacolon, in concert with isolation of *T. cruzi* from blood, support the diagnosis. To detect trypanosomes in blood, uninfected triatomids are permitted to feed on the patient's forearm for 30 minutes. The insects are then kept for 30 days, and the intestinal contents of the insect inspected for *T. cruzi*. If negative, the examination may be repeated 60 days later. This test is positive in about 50% of cases. Serologic tests, including complement fixation anti–*T. cruzi* antibodies, are useful but may also be positive in long-term residents of endemic areas.

Management

Acute Chagas' disease is treated with nifurtimox, 8 to 10 mg/kg body weight orally per day in four divided doses for 120 days. The drug is available from the CDC. Chronic disease manifestations are treated with supportive or palliative therapies, including heart transplantation for severe cardiomyopathies.

LEISHMANIASIS

Humans may be infected by *Leishmania* species that cause three clinical syndromes: cutaneous, mucosal, or visceral leishmaniasis. These intracellular parasites are transmitted by phlebotomine sandflies. Various forms of the infection occur throughout Latin and Central America, Africa, the Middle East, and Asia (Figure 81-4).[75] Cutaneous lesions are caused by *Leishmania tropica, L. major* and *L. aethiopica* (Old World species), and by *L. mexicana, L. amazonensis, L. braziliensis, L. panamensis, L. guyanensis,* and *L. peruviana* (New World species).

Cutaneous disease begins as a small ulcer with raised borders. Ulcers can persist as nodules or papules. In the chronic phase, these nonhealing ulcers frequently become secondarily infected by bacteria.[98] Mucosal leishmaniasis is typically caused

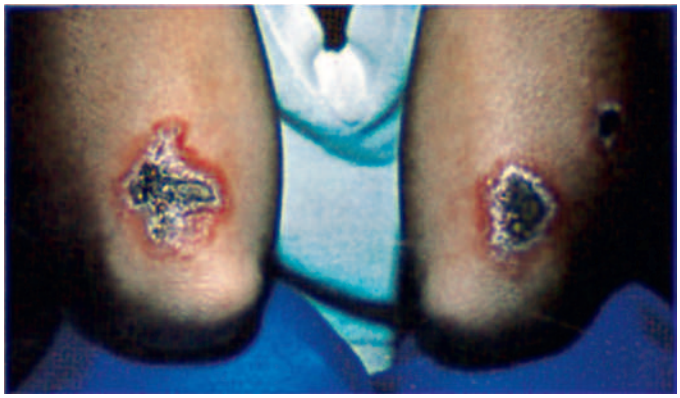

FIGURE 81-4 Old World leishmaniasis. *(Courtesy Richard Kaplan.)*

by *L. braziliensis, L panamensis*, and *L. guyanensis*. It begins as a single nodule, and months to years after the cutaneous lesion heals, progresses to the oropharyngeal or nasal mucosa, where it causes severe destruction. This disease occurs primarily in residents of the Amazon basin. Visceral leishmaniasis (kala-azar) is caused by *L. donovani, L. infantum,* and *L. chagasi*. Affected individuals generally do not recall an initial skin lesion. Several months after inoculation, fever, abdominal discomfort, and weakness develop and become progressively more severe. Nausea and vomiting are protracted, the skin becomes dry and dark, and abdominal distention with hepatosplenomegaly eventually appears.

Diagnosis is made by demonstration of the presence of the parasite in tissue biopsy or needle aspiration of affected tissue. Serologic testing is usually positive in mucosal or visceral leishmaniasis (available at the CDC). Treatment is indicated for mucosal and visceral leishmaniasis; liposomal amphotericin B is the only FDA-approved treatment. Protection from sandfly bites prevents the disease. All forms of leishmaniasis are rare in travelers and nonresidents of endemic areas.

MAJOR HELMINTHIC INFECTIONS

Worm infections are common among travelers to developing countries, especially in those who spend time in rural areas. However, unlike many viral and protozoan infections, helminths rarely cause life-threatening disease, and infested persons are often asymptomatic.

SCHISTOSOMIASIS

Three major species of schistosomes infect humans: *Schistosoma mansoni, S. haematobium,* and *S. japonicum*. *S. mansoni* infection occurs in South America and Africa. *S. haematobium* infection occurs primarily in Africa, especially Egypt and East Africa. *S. japonicum* infection is present exclusively in the Far East. Schistosomiasis is transmitted by freshwater snails. These snails release cercariae that penetrate the skin of humans. The cercariae rapidly transform into schistosomulae, which migrate to the lungs and eventually the portal (in the case of *S. mansoni* and *S. japonicum*) or vesical (in the case of *S. haematobium*) venous system to differentiate into adult worms. Fecund female worms release eggs, which may be passed in feces or urine. Miracidia released from this stage may then infect snails in water used for bathing, washing clothes, or other communal activities.

Clinical Manifestations

Signs and symptoms of infection vary among the three schistosome species. The initial presentation of acute *S. mansoni* infection may include fever, anorexia, weight loss, and abdominal pain. This unusual symptom complex, which occurs in individuals with heavy infection, has been referred to as "Katayama fever" and appears 18 to 60 days after exposure.[78] Travelers with light or moderate exposure, however, usually have no specific signs or only mild local dermatitis (swimmer's itch) associated with contact with cercariae, the infective stage of the parasite released by snails (Figure 81-5). In persons with established infections, the prevalence of clinical manifestations is low. Most individuals have no signs specifically attributable to *S. mansoni* infection. Hepatomegaly or splenomegaly, attributable to portal hypertension after granulomatous reactions to eggs deposited in the liver, occurs in 15% of patients. Eggs may also embolize to the lungs and induce granulomatous lesions and cor pulmonale. Those at greatest risk are persons who have the heaviest intensity of infection as judged by fecal egg counts. These complications may ultimately result in esophageal and GI varices, which cause acute blood loss.

Manifestations of *S. japonicum* infections are similar to those of *S. mansoni* infections, except that Katayama fever appears to be more frequent in the former case. In addition, there is a unique manifestation of *S. japonicum* infection attributable to embolization of eggs to the brain. Generalized or jacksonian seizures are the major signs of cerebral schistosomiasis. Because *S. haematobium* adult worms inhabit the venous system of the genitourinary tract, signs and symptoms of this helminth infection are primarily secondary to granulomatous reactions to eggs present in the ureters and bladder wall. Dysuria and hematuria have been reported in many individuals who reside in endemic areas.

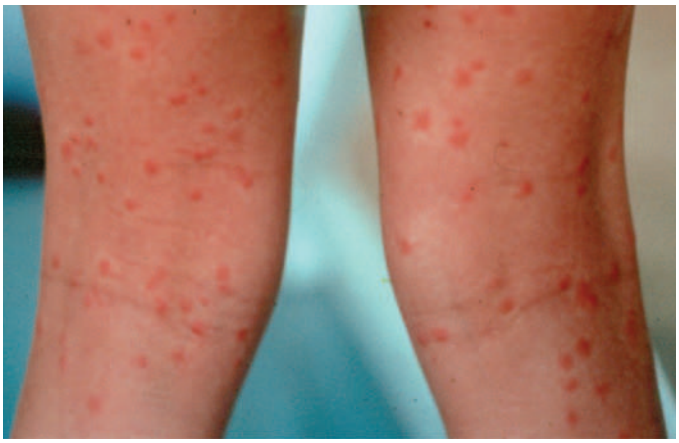

FIGURE 81-5 Mild local dermatitis associated with contact with cercariae, the infective stage of *Schistosoma* spp. released by snails. *(From Ryan ET, Wilson ME, Kain KC: Illness after international travel,* N Engl J Med *347:505, 2002.)*

Treatment and Prevention

Treatment for all *Schistosoma* species is a one-time dose of praziquantel at 40 to 60 mg/kg, depending on the species (*S. japonicum* should be treated with 60 mg/kg of praziquantel). Patients with intense reactions may benefit from a course of oral corticosteroids.

The major risk to travelers is encountered when exposure to large numbers of cercariae occurs by bathing in freshwater that contains infective snails. Cases of transverse myelitis have been reported in these circumstances. Appropriate preventive measures include counseling to avoid bathing or swimming in freshwater in endemic areas.

FILARIASES

Three major types of human filariasis exist. Infections caused by *Onchocerca volvulus* are manifest primarily as skin and eye diseases. *Brugia malayi* and *Wuchereria bancrofti* cause lymphatic filariasis. *Loa loa* infection may cause skin disease. Each of these is described separately because their ecologies and manifestations are distinct.

Onchocerciasis

Onchocerca volvulus is transmitted to humans by the bite of *Simulium* species of blackflies in Central America and West and Central Africa. Infective, or third-stage, larvae eventually develop into adult worms contained in deep subcutaneous nodules that are asymptomatic and may be palpable. Microfilariae are released from adult female worms and cause dermatitis as they migrate through the skin. The organisms have a propensity to invade the eye (especially the anterior chamber and cornea), where they cause blindness. Diagnosis is based on prolonged residence in an endemic area (e.g., Peace Corps volunteers) and parasitologic identification in skin snips or slit-lamp examination of the eye. Treatment is with ivermectin to clear microfilariae.[86] For children and adults, 150 mcg/kg of ivermectin is given as a single oral dose every 6 months.

Lymphatic Filariasis

Brugia malayi and *Wuchereria bancrofti* are transmitted by mosquitoes. Infective larvae eventually develop into lymphatic-dwelling adult worms, which release microfilariae into the bloodstream. Although chronic infection and recurrent exposure are associated with a wide variety of clinical manifestations,

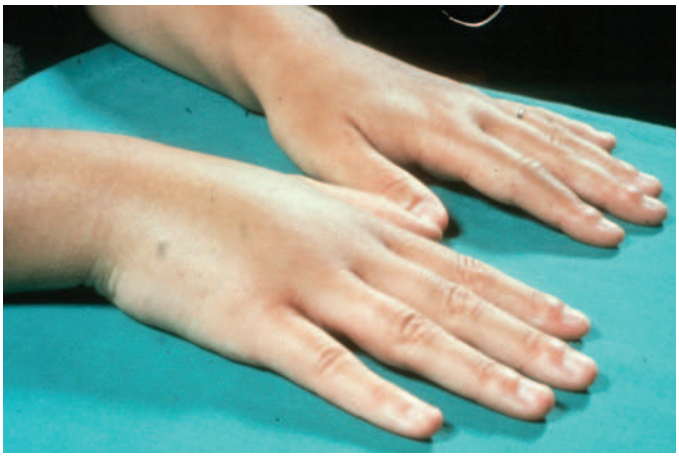

FIGURE 81-6 Calabar swellings of loiasis (loaiasis). *(From Ryan ET, Wilson ME, Kain KC: Illness after international travel,* N Engl J Med *347:505, 2002.)*

including tropical pulmonary eosinophilia, acute lymphangitis, and elephantiasis, these manifestations are rare in nonresidents of endemic areas. The only definitive diagnostic test is identification of parasites in the bloodstream. Because nonresidents and many residents who are infected may not have detectable parasitemia, other laboratory studies (eosinophilia, elevated serum IgE level) must be used as aids in diagnosis. Diethylcarbamazine (6 mg/kg/day in three doses for 12 days) is the treatment.[86]

Loiasis (Loaiasis)

Loa loa is transmitted to humans by the bites of tabanid flies that live along river edges in Central and West Africa. Microfilariae migrate in the bloodstream, whereas adult worms migrate in cutaneous tissues. The major disease manifestation is Calabar swellings, which are characterized as egg-sized or smaller raised lesions, predominantly over the extremities, that are tender and surrounded by edematous skin (Figure 81-6). They may migrate and last several days. Migration of the worm across the eye is known as loiasis, loa loa, or African eye worm (Figure 81-7). The pathogenesis may be related to migration of adult worms or release of antigens that elicit immunologic hypersensitivity reactions. Treatment is with diethylcarbamazine, 6 mg/kg/day in three doses for 21 days. Diethylcarbamazine must be administered with caution, because it can cause serious side effects, such as encephalitis and retinal hemorrhages, in patients with loiasis; the risk is increased with high microfilarial loads (>8000 microfilariae/mL).[71]

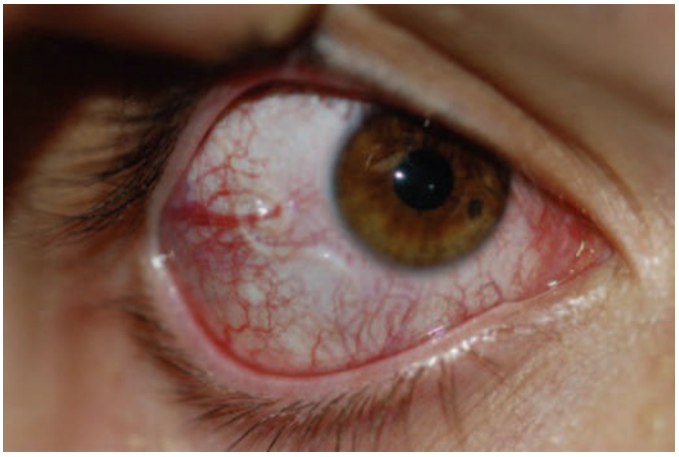

FIGURE 81-7 Loiasis. *(From Moffett S, Wills CP: Images in emergency medicine: Young man with foreign-body sensation in the right eye—loaiasis (African eye worm),* Ann Emerg Med *55:578, 2010.)*

INTESTINAL HELMINTH INFECTIONS

Ascariasis

Approximately 25% of the world's population is infected with *Ascaris lumbricoides*. Although this nematode contributes significantly to morbidity in children with poor nutrition, it generally does not cause significant health problems for the traveler. The helminth is transmitted by eggs contained in ingested pieces of soil, such as may be found on vegetables grown in countries with poor hygienic conditions. It is not limited to tropical climates and occurs in North America and Europe. Ingested eggs enter the small intestine. Larvae leave the eggshell to penetrate the mucosa and eventually enter the bloodstream and lymphatics. Between 1 and 5 days after infection, they enter the liver and, at about 14 days, the lungs. The larvae then rupture through the alveoli, ascend the trachea, and return to the intestine on being swallowed. In the small intestine, adult males and females develop into macroscopic worms (12 to 25 cm long). Eggs passed via feces continue the life cycle.

Ascaris infection is often asymptomatic, but several syndromes are associated with tissue and intestinal phases of infection. Persons who are recurrently exposed may develop pulmonary ascariasis, characterized by cough, wheezing, eosinophilia, and fleeting pulmonary infiltrates on chest radiographic examination. Children may have intestinal or biliary tract obstruction caused by infestations with large numbers of worms from repeated ingestion of *Ascaris* eggs. Intestinal symptoms are seen mainly in persons with heavy infection, an uncommon situation in the traveler.

Diagnosis of ascariasis may be made by identification of one of several parasite stages. Adult ascarids occasionally migrate from the mouth or anus. Ascaris larvae may rarely be observed in sputum or gastric washings. The most common means of diagnosis is identification of eggs in feces. Eggs are ovoid, 35 to 70 mm in diameter, and consist of an outer white shell and brownish ovum internally. The eggs are not produced until approximately 9 weeks after infection. Intestinal ascariasis is treated with albendazole or mebendazole. An alternative regimen that avoids the use of benzimidazoles (e.g., for treatment of pregnant women) is pyrantel pamoate (11 mg/kg to a maximum of 1 g).[14]

Hookworm

Ancylostoma duodenale and *Necator americanus* infections occur most often in the tropics but also in temperate climates where sanitation is poor. Hookworm is second only to *Ascaris lumbricoides* in terms of the number of people infected. Humans are infected percutaneously by third-stage larvae in the soil. The larvae enter the bloodstream, pass to the lungs, and rupture the alveolar lining, eventually to ascend the trachea and descend the esophagus to differentiate into adult worms. These adult worms contain cutting plates on the anterior end and feed on host blood obtained through their attachment sites in the upper small intestine. Each *N. americanus* infection causes an estimated 0.03 mL of blood loss per day, whereas the *A. duodenale* hookworm consumes 0.26 mL per day. Iron deficiency anemia, especially in persons with low iron intake, is the major clinical manifestation of hookworm infection.

The diagnosis may be made by identification of hookworm eggs in feces. The eggs are round, 40 to 60 mm [1.6 to 2.4 inches] in diameter, and have a "smoother" shell than do *Ascaris* eggs. Although multiple drugs are effective in treatment, albendazole is most readily available. Supplemental iron should be given to persons when necessary. Infection with hookworm is rare in the traveler from a developed country. Migrating animal hookworms, such as *Ancylostoma braziliense* and *Ancylostoma caninum,* may create serpiginous lesions in superficial tissues of humans (Figure 81-8).[14]

Strongyloidiasis

Strongyloides stercoralis infection occurs in tropical and temperate regions. The infection is initiated by contact with soil containing infective third-stage larvae. The helminth follows a route within the host similar to that described for hookworms. In

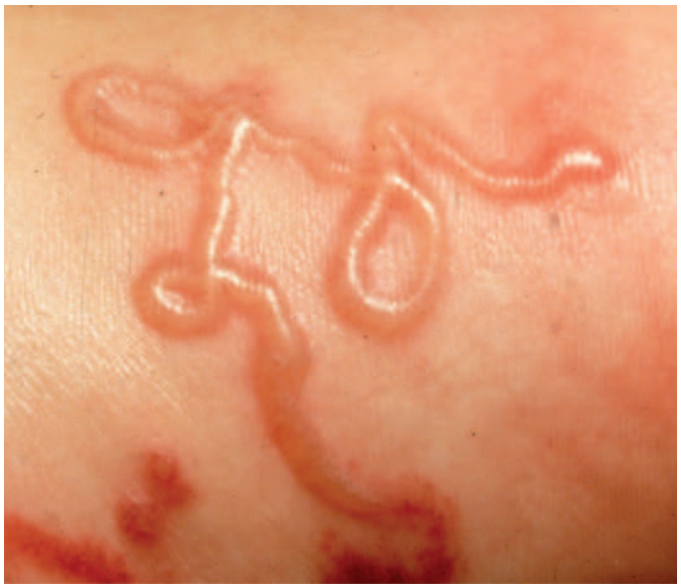

FIGURE 81-8 Migrating animal hookworms, such as *Ancylostoma braziliense* and *Ancylostoma caninum*, may create serpiginous lesions in superficial tissues of humans. *(From Ryan ET, Wilson ME, Kain KC: Illness after international travel,* N Engl J Med *347:505, 2002.)*

addition, there is an autoinfection cycle in which larvae released in the intestine may penetrate the mucosa directly and then migrate through the liver and lungs. This occurs only in immunocompromised individuals. Many persons with *S. stercoralis* infection are asymptomatic. Some persons, however, have cutaneous or intestinal manifestations. The former are urticarial lesions around the buttocks and waist that last 1 to 2 days. These are secondary to penetration of larvae present in the feces. Other symptoms include indigestion, abdominal cramps, and diarrhea. Diagnosis is made by identification of larvae in fresh stools or GI washings. Rhabditiform larvae 250 mm long and 10 to 20 mm wide are most often observed, although filariform larvae may also be present. Treatment is with ivermectin, 200 mcg/kg as a single oral dose for 1 to 2 days.[80]

ENTEROBIASIS

Enterobiasis, or pinworm infection, exists in all parts of the world. Eggs are passed from female worms in the colon. Infection is transmitted by ingestion of *Enterobius vermicularis* eggs, which develop into gravid adult female worms in the large bowel. The infection is especially common in crowded settings where sanitation is poor. The diagnosis may be made by identification of adult worms migrating along the perianal area or by eggs deposited in the same area. Eggs are detected by applying a piece of sticky cellophane tape to the area and inspecting it microscopically. Treatment is with pyrantel pamoate (11 mg/kg [maximum 1 g] as a single oral dose), mebendazole (100 mg as a single oral dose for all ages, to be repeated 2 weeks later), or albendazole (400 mg as a single oral dose for all ages, repeated 2 weeks later). Repeated treatments as a result of reinfection in crowded settings are frequently required.[85]

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Complete references used in this text are available online at expertconsult.inkling.com.

CHAPTER 82

Infectious Diarrhea from Wilderness and Foreign Travel

JAVIER A. ADACHI, HOWARD D. BACKER, AND HERBERT L. DUPONT

Acute infectious diarrhea is one of the most common and significant medical problems in any population, second only to acute upper respiratory diseases. Worldwide, diarrheal diseases caused almost 1 billion episodes of illness in 1996.[188] Rates of illness among children in developing areas of the world range from 5 to 15 episodes per child per year, with diarrhea being the most important cause of morbidity and mortality in many regions. Readily available oral rehydration solutions prevent large numbers of dehydration-associated deaths from acute diarrhea, especially in developing areas, but invasive bacterial enterocolitis (caused by *Shigella* and *Campylobacter* spp.), persistent diarrhea (defined as illness lasting 14 days or longer), malnutrition, and increased susceptibility to other infections still cause significant morbidity and mortality.[188] Specific groups of U.S. populations, including international travelers to developing regions, gay males practicing unsafe sex, non–toilet-trained toddlers in some day care centers, and mentally impaired residents of custodial institutions, can have rates of diarrhea approximating those in the developing world.

Clinical features of acute diarrheal illnesses often do not permit differentiation of a specific etiologic agent, but fortunately the majority of these infections do not require specific treatment. We formulate a clinical approach to self-therapy that is likely to minimize the complications and suffering caused by these illnesses. For this discussion, "travelers" includes business or pleasure travelers as well as wilderness and adventure travelers.

GENERAL PRINCIPLES OF ENTERIC DISEASE

EPIDEMIOLOGY

Fecal-oral contamination through ingestion of contaminated water and food (waterborne or food-borne) is the usual route of transmission of the enteric pathogens causing acute infectious diarrhea. (See Chapter 88 for further details on the relationship among enteric infections, safe drinking water, and sanitation.)

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The relative importance of food and water depends mainly on location and precautions taken. The majority of pathogens that cause traveler's diarrhea (TD) or wilderness-acquired diarrhea can be either food-borne or waterborne; however, waterborne pathogens from drinking untreated surface water or from inadvertent ingestion during recreational water activity account for most infectious diarrhea acquired in the U.S. wilderness. Prevention of infection includes proper sanitation and water disinfection.

Person-to-person transmission is seen with pathogens that have small infectious doses, such as *Shigella* spp., hepatitis A virus, *Giardia*, and noroviruses. These infections are most common in populations whose habits expose them to high levels of pathogens (e.g., infants in day care centers, homosexuals, persons with minimal access to water); prevention includes adequate handwashing and personal hygiene. Other, less common routes of fecal-oral transmission are through aerosols (some viruses), contaminated hands or surfaces, and sexual activity.

In areas of Africa, Asia, and Latin America where satisfactory sanitation is lacking, diarrhea remains the leading cause of infant morbidity and mortality. Good sanitation is related to a much lower incidence of infectious diarrhea in industrialized areas. Travelers to foreign countries and wilderness areas often leave behind their customary methods of sanitation, such as flush toilets and safe tap water, and do not have proximity to advanced medical care.

Outbreaks of infectious diarrhea in day care centers among non–toilet-trained toddlers are associated with low-inoculum organisms, including *Shigella*, *Cryptosporidium*, *Giardia,* and viral pathogens. Hospitals, especially intensive care units and pediatric wards; institutions for mentally handicapped patients; and nursing homes are also locations with a high incidence of diarrheal diseases. *Clostridium difficile* is the most important definable pathogen in these settings.[165] *Salmonella* spp., rotavirus, and enteropathogenic *Escherichia coli* may on occasion cause nosocomial outbreaks.

Antimicrobial therapy is indicated for moderate to severe TD or when a specific bacterial or parasitic pathogen is identified (see later for details). Recent use of an antimicrobial agent (or cytotoxic agent) is frequently associated with *C. difficile* infection in debilitated hospitalized patients.[77]

In the developing world, children under 5 years of age have the highest morbidity from diarrhea, and infants under 1 year of age experience the highest mortality rates.[43] The enteropathogens more common in childhood infectious diarrhea are rotavirus, enterotoxigenic *Escherichia coli* (ETEC), enteropathogenic *E. coli* (EPEC), enteroaggregative *E. coli* (EAEC), *Campylobacter* spp., and *Giardia*. Residents in industrialized countries have only one to two bouts of diarrhea per person per year, with no difference between age groups. Complications, including death, are more common in elderly persons.[125]

Organisms are shed in stool during asymptomatic and symptomatic infection and for a period after illness. Long-term fecal shedding or chronic carrier states are reported to be important only for typhoid fever; however, parasites may be persistently shed in intestinal protozoal infections, such as amebiasis, giardiasis, and cryptosporidiosis. Carriers may act as reservoirs for spreading infection, even in areas with low infection risk. A few enteric pathogens have animal reservoirs and are spread to exposed persons. These include *Salmonella* spp., *Yersinia*, *Campylobacter*, *Giardia*, *Balantidium coli*, *Sarcocystis*, and *Cryptosporidium*.

Most cases of acute diarrhea are caused by infectious microorganisms, including bacteria, viruses, and protozoa. Fungal agents have rarely been reported. Table 82-1 lists the etiologic agents often associated with travel to developing tropical areas or with wilderness travel in an industrialized region. Food-borne illness may consist of food "poisoning" or food "infection." In food poisoning, an intoxication results when toxins produced by bacteria are found in food in sufficient concentrations to produce symptoms. A rare cause of food poisoning that results in paralysis is botulism, caused when the neurotoxin of *Clostridium botulinum* is ingested. Other food-borne pathogens are viruses, including rotavirus and small, round viruses (e.g., noroviruses, astrovirus), and intestinal protozoal agents, including *Giardia*, *Entamoeba histolytica*, and *Cryptosporidium*.

TABLE 82-1 Enteropathogens Found in Tropical and Wilderness Travel

Agents	Travel to Developing Tropical Regions	Wilderness Travel or General Incidence in Industrialized Regions
Bacteria		
Enterotoxigenic *Escherichia coli*	Yes	Increasing with food imported from developing countries
Enteroinvasive *E. coli*	Rarely	Rare outbreaks
Enteroaggregative *E. coli*	Yes	Growing importance as a pediatric pathogen in diarrhea
Salmonella spp.	Yes	Yes
Shigella spp.	Yes	Yes
Campylobacter spp.	Yes	Yes
Vibrio cholerae	Limited	Not currently
Yersinia enterocolitica	Rare	Limited
Aeromonas spp.	Yes	Yes
Plesiomonas shigelloides	Yes	Rarely
Viruses		
Norovirus	Yes	Yes
Rotavirus	Yes	Decreasing due to routine vaccine use
Hepatitis A	Yes	Yes
Protozoa		
Giardia lamblia	Yes	Yes
Entamoeba histolytica	Yes	Rarely
Cryptosporidium spp.	Yes	Yes
Cystoisospora belli	Regional importance	Rarely
Cyclospora cayetanensis	Limited	Rarely
Microsporidia		
Balantidium coli	Limited	Rarely
Sarcocystis	Limited	Rarely
Blastocystis hominis	Limited	Rarely

Food intoxication, caused by ingestion of preformed toxins from *Staphylococcus aureus* or *Bacillus cereus*, typically has a short incubation period (2 to 7 hours) and causes common source outbreaks involving multiple persons.[44] Infection and diarrhea caused by a living enteropathogen must first traverse the stomach and infect the small bowel or colon, explaining a longer incubation period of 14 or more hours, and usually more than 1 day.

Immunocompromised patients, including those with advanced infection by the human immunodeficiency virus (HIV), are prone to infection by a wide variety of enteropathogens, to develop infectious diarrhea, and to experience recurrent infections. Advanced acquired immunodeficiency syndrome (AIDS) is associated with chronic diarrhea secondary to ultrastructural changes in gut morphology and malabsorption, or because of reduced immunity and coinfection with enteropathogens. The pathogens responsible in advanced AIDS include *Mycobacterium avium-intracellulare* complex, *Cryptosporidium*, *Giardia*, *Isospora*, *Cyclospora*, *Microsporidium*, cytomegalovirus, herpes simplex virus, and HIV itself (so-called AIDS enteropathy). Treatment of HIV with highly active antiretroviral therapy (HAART) and treatment of the enteric infection(s) are associated with improved symptomatology and decreased rates of infection.

PATHOPHYSIOLOGY

Three intestinal mechanisms lead to acute diarrhea. The most common pathophysiologic mechanism in acute infectious diarrhea is alteration of fluid and electrolyte movement from the

TABLE 82-2 Bacterial Enteropathogens: Virulence Properties

Pathogen	Virulence Properties
Vibrio cholerae	Heat-labile enterotoxin
Vibrio parahemolyticus	Invasiveness (?), enterotoxin, hemolytic toxin
Enterotoxigenic *Escherichia coli*	Heat-stable and heat-labile enterotoxins, colonization factor antigens
Enteroinvasive *E. coli*	*Shigella*-like invasiveness
Enteroaggregative *E. coli*	Enteroadherence, virulence characteristics associated with toxin production and local inflammation
Salmonella spp.	Cholera-like toxin, invasiveness
Shigella spp.	Shiga-like toxin, invasiveness
Campylobacter jejuni	Cholera-like toxin, invasiveness
Aeromonas spp.	Hemolysin, cytotoxin, enterotoxin
Yersinia enterocolitica	Heat-stable enterotoxin, invasiveness
Clostridium difficile	Toxins A and B, binary toxin
Clostridium perfringens	Preformed toxin
Bacillus cereus	Preformed toxins: short-acting like *S. aureus* and long-acting like *C. perfringens*
Staphylococcus aureus	Preformed toxin

serosal to the mucosal surface of the gut (secretory diarrhea). This alteration may occur as a result of cyclic nucleotide stimulation (as a second messenger) or by an inflammatory process that is associated with release of proinflammatory cytokines. The second mechanism is malabsorption or presence of nonabsorbable substances in the lumen of the bowel, including lactase deficiency and AIDS-associated malabsorption. The third mechanism of diarrhea is altered intestinal motility. Secretory mechanisms best explain acute infectious diarrhea, whereas malabsorption and altered motility are more important in chronic forms of diarrhea, such as tropical and nontropical sprue, Whipple's disease, intestinal scleroderma, irritable bowel syndrome, and inflammatory bowel disease. Table 82-2 shows the virulence factors of the most important enteric pathogens related to infectious diarrhea.

In secretory diarrhea, the unformed stools are usually of large volume and small in number (characteristically less than six bowel movements per day). Stools do not contain blood, and fever is unusual. Examples of pathogens in this group are *Vibrio cholerae*, ETEC, preformed enterotoxins, noroviruses, rotavirus, *Giardia*, and *Cryptosporidium*. Dehydration is the major complication, especially in the extremes of age. Without adequate therapy, secretory diarrhea can be followed by renal insufficiency.

Invasive pathogens involving the distal ileum and colon damage the mucosa and elicit an inflammatory response associated with secretory diarrhea and colitis. In this form of colitis, stools are typically liquid and small-volume, and may contain blood and many leukocytes. The common microorganisms in this group are *Shigella*, *Salmonella*, EIEC, Shiga toxin–producing *E. coli* (STEC) including *E. coli* O157:H7, *Yersinia enterocolitica*, *Campylobacter* spp., *Aeromonas*, *Vibrio parahaemolyticus*, and *E. histolytica*. Complications include dehydration and systemic involvement, especially in children with malnutrition.[156]

TRAVELER'S DIARRHEA

Traveler's diarrhea is the most important travel-related illness in terms of frequency and economic impact. Point of origin, destination, and host factors are the main risk determinants.[194] Although the same infections can be contracted domestically, international travel is more often associated with enteric infection and diarrhea, particularly when traveling to developing tropical regions. The 2% to 4% rate of diarrhea for people who take short-term trips to low-endemic areas (e.g., United States, Canada, Northwestern Europe, Australia, Japan) may be related to more frequent consumption of food in public restaurants, increased intake of alcohol, or stress. This rate of diarrhea increases to about 10% for travelers from these low-endemic areas to northern Mediterranean areas, China, Russia, or some Caribbean islands. The incidence increases as high as 40% to 50% for short-term travelers from low-risk countries to high-risk countries (developing tropical and subtropical regions of Latin America, Southeast Asia, and Africa). More than 100 million persons travel each year from industrialized countries to high-risk areas, resulting in more than 30 million travelers with diarrhea.[45] Multiple episodes of diarrhea may occur on the same trip. Attack rates remain high for the first 4 weeks in a country of risk,[57] then decrease, but not to the levels of local inhabitants. Immunity to ETEC infection, either asymptomatic or symptomatic, occurs after repeated or chronic exposure, which supports the feasibility of developing a vaccine.[74]

Although any food-borne or waterborne enteropathogen can cause TD, bacteria are the most common etiologic agents among persons traveling to high-risk areas. The bacterial flora of the bowel changes rapidly after arrival in a country with high rates of TD. At least 15% of travelers remain asymptomatic despite the occurrence of infection by pathogenic organisms, including ETEC and *Shigella*.[160]

DEFINITION

Traveler's diarrhea refers to an illness contracted while traveling, although in 15% of patients, symptoms first occur after returning home. Most clinical studies define TD as passage of three or more unformed stools in a 24-hour period in association with one or more enteric symptoms, such as abdominal cramps, fever, fecal urgency, tenesmus, bloody-mucoid stools, nausea, and vomiting.[49]

ETIOLOGY

Because the incidence of TD partly reflects the extent of environmental contamination with feces, the etiologic agents are pathogens causing illness in local children. Table 82-3 provides a list of etiologic agents important in TD. Twenty-five years ago, specific pathogens were found in only 20% of cases. Currently, etiologic agents can be identified in up to 80% of TD episodes.[106] In most studies, however, causative pathogens are not identified in 20% to 40% of cases. In most of these patients, antimicrobial therapy shortens illness, suggesting that this subset of diarrhea is caused by undetected bacterial pathogens.[56] Overall, the major etiologic agents and their frequency of isolation are remarkably similar worldwide.

Worldwide, ETEC is the most common cause of TD,[183] accounting for about one-third to one-half of cases. EAEC has been identified as the second most common bacterial cause of TD, causing up to 30% of cases in some areas of the world.[3] One study found that food is the source of both types of *E. coli*. Viable ETEC and EAEC were identified in hot sauces served on the table in popular restaurants in Guadalajara, Mexico.[4] *Shigella* and *Campylobacter* species cause around 20% of illness and *Salmonella* 4% to 5%, with other culprits being *Vibrio*, *Aeromonas*, *Plesiomonas*, viruses (10%), and parasites.[183] Specific pathogens may predominate at a particular time or location.

CLINICAL SYNDROMES

Table 82-4 outlines the major syndromes in patients with enteric infection. The typical clinical syndrome of TD secondary to the major infectious causes (e.g., ETEC) begins abruptly with abdominal cramping and watery diarrhea. Most cases are mild, consisting of passage of one to two unformed stools per day associated with tolerable symptoms that do not interfere with normal activities. Approximately 30% of affected persons experience moderately severe illness, with three to five unformed stools per day and distressing symptoms forcing a change in activities or itinerary. Only 1% to 3% of persons with TD occurring in Latin America or Africa experience febrile dysenteric illness,[67,134] whereas approximately 9% of travelers with diarrhea acquired in

TABLE 82-3 Major Pathogens in Traveler's Diarrhea (Travel to Developing Tropical Regions)

Agent	Frequency (%)	Distribution
Bacteria	**50-80**	
Enterotoxigenic *Escherichia coli*	5-50	Developing countries, tropical areas, infants, travelers
Enteroaggregative *E. coli*	5-30	Infants, worldwide
Salmonella spp.	1-15	Worldwide
Shigella spp.	1-15	Worldwide
Campylobacter jejuni	1-30	Worldwide, more common in Asia
Aeromonas spp.	0-10	Worldwide, especially Thailand, Australia, Canada
Plesiomonas shigelloides	0-5	Worldwide
Other	0-5	
Viruses	**0-20**	
Rotavirus	0-20	Worldwide, children 6-24 months
Norovirus	1-20	Worldwide, cruise ships
Protozoa	**1-5**	
Giardia lamblia	0-5	Worldwide, zoonosis, alpine areas
Entamoeba histolytica	0-5	Developing and tropical countries, especially Mexico, India, western and South Africa, parts of South America
Cryptosporidium parvum	0-5	Worldwide, including cooler developed countries
Unknown	**10-40**	

For details on published studies, see reference 183.

the Indian subcontinent of Asia develop this more serious form of illness.[195] Symptoms lasting more than 1 to 2 weeks suggest a protozoan etiology such as *Giardia*, *E. histolytica*, *Cryptosporidium,* or other parasite.[47] TD should be considered a self-limited nonfatal condition, but it may lead to chronic illness[47] and postinfectious irritable bowel syndrome (PI-IBS).[152,198]

An important part of initial assessment is to measure hydration, including determination of vital signs (orthostatic pulse, blood pressure), mental status, skin turgor, hydration of mucous membranes, and urine output. Dehydration is most common in pediatric and elderly populations.

Fever is a reaction to an intestinal inflammatory process. High fever suggests a pathogen invasive to the intestinal mucosa, which classically includes bacterial enteropathogens such as *Shigella*, *Salmonella*, and *Campylobacter* spp. Fever can also be produced by strains of EIEC, *V. parahaemolyticus*, *Aeromonas*, *C. difficile,* and viral pathogens.

Vomiting as the predominant symptom in a traveler usually suggests norovirus infection.[6,116] Vomiting is also seen in "food poisoning" secondary to consumption of preformed enterotoxin produced by *S. aureus* or *B. cereus.*

Dysentery is defined as passage of small-volume stools with gross blood and mucus. Common causes include *Shigella*, *C. jejuni*, *Salmonella*, *Aeromonas*, *V. parahaemolyticus*, *Y. enterocolitica*, EIEC, STEC, *E. histolytica*, and preexisting inflammatory bowel disease.

Abdominal examination in persons with TD often shows mild tenderness but should not demonstrate signs of peritoneal irritation. Rectal examination may reveal tenderness in enterocolitis, and patients may have painful external hemorrhoids as a result of excessive number of bowel movements.

Some enteric pathogens produce both diarrheal and systemic diseases. These include hemolytic-uremic syndrome related to infection with shigellosis or STEC, glomerulonephritis related to *Y. enterocolitica* (Reiter's syndrome), and sepsis seen with bacteremic salmonellosis caused by *Salmonella typhi*, *Salmonella paratyphi*, and nontyphoid strains of *Salmonella.*

TABLE 82-4 Clinical Syndromes in Enteric Disease

Syndrome	Agent
Acute watery diarrhea	Any agent, especially with toxin-mediated diseases (e.g., enterotoxigenic *Escherichia coli*, *Vibrio cholerae*)
Febrile dysentery	*Shigella*, *Campylobacter jejuni*, *Salmonella*, enteroinvasive *E. coli*, *Aeromonas* spp., *Vibrio* spp., *Yersinia enterocolitica*, *Entamoeba histolytica*, inflammatory bowel disease
Vomiting (predominant symptom)	Viral agents, particularly noroviruses, preformed toxins of *Staphylococcus aureus* or short-acting toxin of *Bacillus cereus*
Persistent diarrhea (>14 days)	Protozoa, small bowel bacterial overgrowth, inflammatory or invasive enteropathogens (*Shigella*, enteroaggregative *E. coli*)
Chronic diarrhea (>30 days)	Small bowel injury, inflammatory bowel disease, postinfectious irritable bowel syndrome, Brainerd diarrhea

PERSISTENT AND CHRONIC DIARRHEA

Diarrhea and abdominal complaints frequently persist after the traveler returns home.[141] Up to 3% of persons with TD from high-risk areas develop persistent diarrhea.[47] *Persistent* diarrhea is defined as illness lasting 14 days or longer, whereas diarrhea is considered *chronic* when it lasts 30 days or longer. The etiology of persistent or chronic diarrhea differs from acute diarrhea; important causes include protozoal parasites (*Giardia*, *Cryptosporidium*, *Cyclospora*, *E. histolytica*), bacteria (*Salmonella*, *Shigella*, *Campylobacter*, *Y. enterocolitica*), lactase deficiency induced by a small bowel pathogen (*Giardia*, rotavirus, or norovirus), and small bowel bacterial overgrowth syndrome secondary to small bowel motility inhibition (from enteric infection) or to antimicrobial use. Occasionally, other parasitic enteric infections can cause more persistent illness. These include *Strongyloides stercoralis*, *Trichuris trichiura*, and severe infection by *Necator americanus* or *Ancylostoma duodenale.* In rare cases, more protracted diarrhea may be a prominent symptom in persons with schistosomiasis, *Plasmodium falciparum* malaria, leishmaniasis, or African trypanosomiasis.

When chronic diarrhea follows a bout of TD, a pathogen is not identified, and the patient fails to respond to empirical antimicrobial therapy, activation of an underlying condition such as inflammatory bowel disease, celiac disease, or PI-IBS should be considered. Even with eradication of microbial pathogens with antimicrobial therapy, bowel habits may not return to normal for several weeks. This represents slow repair of damaged intestinal mucosa. Small bowel bacterial overgrowth has been identified in patients with persistent diarrhea after an episode of TD. In the 1980s, an idiopathic form of chronic diarrhea emerged called Brainerd diarrhea, named after the city in Minnesota where the first outbreak was identified.[155] The known vehicles of transmission of Brainerd diarrhea are raw (unpasteurized) milk[155] and untreated water, such as well water.[157] There is no diagnostic test or therapy, and the diagnosis is suspected based on the epidemiologic history (exposure to unpasteurized milk or untreated water just before onset of illness). Although the average duration of Brainerd diarrhea is 2 years, the condition invariably resolves.

The approach to evaluate persistent or chronic diarrhea in travelers should begin with diagnostic tests for conventional bacterial pathogens in stools and at least three parasitologic evaluations of freshly passed stools. Dietary modification in all cases should initially include avoidance of milk and dairy products because of the possibility of lactase deficiency. Treatment

TABLE 82-5 Indications for Laboratory Test in Diarrheal Diseases and Possible Diagnoses

Laboratory Test	Indication	Diagnosis/Agent
Fecal leukocytes or fecal lactoferrin, fecal calprotectin	Moderate to severe cases	Diffuse colonic inflammation, invasive or inflammatory bacterial enteropathogen
Stool culture	Moderate to severe diarrhea, fever, persistent diarrhea, fecal leukocytes or lactoferrin (+), male homosexual	Any bacterial enteric pathogen
Blood culture	Enteric fever, sepsis	*Salmonella*, less likely *Campylobacter* spp., *Yersinia*
Parasite examination	Persistent diarrhea, travel to specific areas, day care centers, male homosexuals	Any protozoan parasite
Parasite enzyme immunoassay	Persistent diarrhea, travel to specific areas, day care centers, male homosexuals	*Giardia*, *Entamoeba histolytica*, *Cryptosporidium*
Amebic serology	Persistent diarrhea, liver abscess	*Entamoeba histolytica*
Rotavirus antigen	Hospitalized infants (<3 years old).	Rotavirus
Clostridium difficile toxin by EIA or PCR	Antibiotic-associated diarrhea, especially occurring in hospital	*C. difficile*

EIA, Enzyme immunoassay; *PCR*, polymerase chain reaction.

should be specific, following the results of microbiologic tests. Because most of these chronic forms of diarrhea are self-limited, it is unwise to employ empirical antibiotics in these patients. If all tests are negative, some experts will prescribe a single limited empirical trial with metronidazole for possible *Giardia* infection, because three tests may still miss 10% of infections. A better choice than metronidazole for empirical treatment of parasitic infection is nitazoxanide, which offers coverage for multiple parasitic pathogens.[104]

LABORATORY TESTS AND PROCEDURES

In clinical practice, laboratory testing is reserved for ongoing illness after the patient returns home, when empirical treatment is unsuccessful, for persons with moderate to severe diarrhea, and those with persistent illness. Persons with milder forms of diarrhea usually need only clinical evaluation; etiologic assessment is unnecessary.

Several laboratory tests are useful in evaluating patients with diarrheal disease (Table 82-5). Presence of fecal leukocytes is a reliable indicator of diffuse colonic inflammation. For moderate to severe illness, this is the most rapid, useful test and ideal screening procedure. A large number of neutrophils per high-power field using dilute methylene blue or trichrome stains (which also helps with identification of parasites) can be helpful in making an etiologic diagnosis of *Shigella*, *Salmonella*, or *Campylobacter* spp. (Figure 82-1).[88] Other organisms and conditions that may lead to presence of fecal leukocytes are *C. difficile*, *Aeromonas*, *Y. enterocolitica*, *V. parahaemolyticus*, EIEC, idiopathic ulcerative colitis, and allergic colitis.

Lactoferrin is found in granules of neutrophils and can be identified in fecal samples by commercial immunoassay method (Leuko-Test, TechLab). This test does not require a freshly collected stool sample or experienced technician, and is a more sensitive marker of inflammation than microscopic examination of fecal leukocytes.[22]

Bacterial infection is specifically diagnosed by stool culture, although routine stool testing identifies few pathogens. A routine laboratory should be able to recover *Shigella*, *Salmonella*, and *Campylobacter* and, if specifically requested, *V. cholerae*, *V. parahaemolyticus*, *Aeromonas*, *Y. enterocolitica*, and *C. difficile* from a stool culture. The major indication for performing a stool culture is the presence of febrile, dysenteric disease.

Blood culture(s) should be performed in all patients hospitalized with gastrointestinal (GI) illness or those with significant fever, especially when combined with a high degree of systemic toxicity. Systemic infections by *S. typhi* and non-*typhi Salmonella*, *Shigella*, *Campylobacter fetus*, and *Y. enterocolitica* may be diagnosed by blood culture.

Patients with persistent TD should be studied for presence of parasitic infection. Immunologic techniques to detect antigens of protozoan parasites are more efficient than are stool examinations for ova and parasites, and are in common use for parasites inhabiting the duodenum (e.g., *Giardia*, *Cryptosporidium*, *E. histolytica*, Microsporidia). At times, intestinal parasites are better detected using a sample from duodenal aspiration or intestinal biopsy.[86,133]

In select cases, particularly clinical colitis and diarrhea persisting for 14 days or longer, flexible sigmoidoscopy or colonoscopy should be considered to study colonic lesions and collect samples for culture and microscopy. Lower GI tract endoscopy is particularly useful when stools contain many leukocytes per high-power field. Colonic mucosal changes may not be specific, except when pseudomembranes are sought in *C. difficile* infection. In homosexual male patients with acute diarrhea, examination of the distal colon may show evidence of proctitis (mucosal inflammation in the distal 15 cm of the colon), proctocolitis (inflammation beyond 15 cm), or enteritis. If there are no leukocytes in the stool or if colonoscopy is negative, esophagogastroduodenoscopy (EGD) should be considered, looking at duodenal mucus for *Giardia lamblia*. Tests for malabsorption and biopsy of the small bowel mucosa may be useful in making a diagnosis.

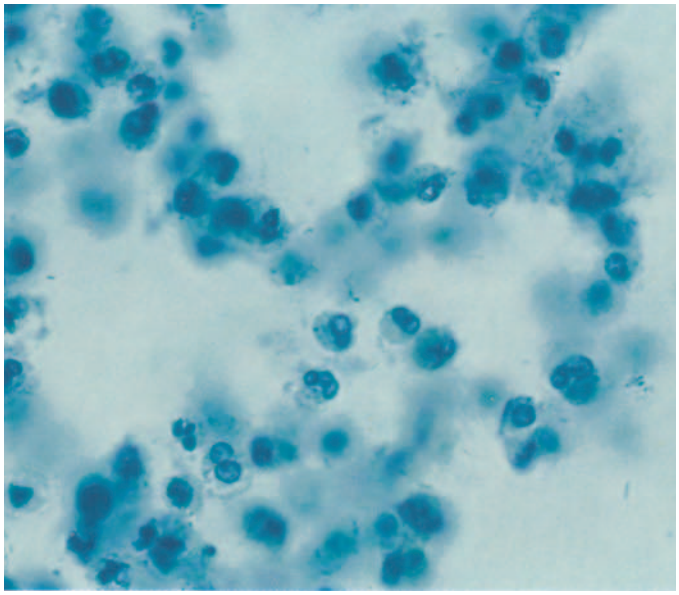

FIGURE 82-1 Methylene blue stain of a fecal smear from a patient with bacillary dysentery (×400). Numerous polymorphonuclear leukocytes are present. This indicates the presence of diffuse colonic inflammation.

Polymerase chain reaction (PCR) methods are being developed for diagnosis of various forms of diarrhea. Often, a number of pathogens are included in a multiplex approach to diagnosis.[11] PCR methods are sensitive, but in the presence of asymptomatic infection that is so common in travelers eating contaminated food, may yield a false-positive test.[46] Licensed multiplex PCR diagnostics will lead to an increased level of pathogen detection in all settings. The methodology is extremely sensitive, and we will find many false-positive results while sorting out disease etiology that will initially present clinicians with complex therapeutic decisions.

TREATMENT

Outpatient treatment with instructions for oral rehydration can be used in the vast majority of adults and children. Rehydration is particularly important in persons with cholera-like diarrhea or when diarrhea is seen in extremes of age. Significant dehydration from diarrhea in travelers is unusual.

Treatment with intravenous (IV) fluids is indicated for the following:

- Patients with hypotension
- Inability to retain oral fluids
- Systemic compromise (high fever and toxicity)
- Moderate toxicity or dehydration, and severe underlying disease
- Severe diarrhea at extremes of age

Supplemental nutrition is beneficial (essential in undernourished populations) and can be given as soon as fluid deficit losses are replaced, usually after the first 4 hours. In more severe forms of acute diarrheal disease, the intestinal tract may not be able to process complex dietary products, so patients are often told to avoid solids and eat easily digested foods. As stooling decreases and appetite improves, staple foods such as cereals, bananas, crackers, toast, lentils, potatoes, and other cooked vegetables are well tolerated and can be gradually added to the diet to facilitate enterocyte renewal, with subsequent progression to white meats, fruits, and vegetables. Dairy products and red meat are recommended only after diarrhea has resolved, usually after 2 to 3 days. Only foods and drinks that prolong diarrhea or increase intestinal motility should be avoided. Examples include foods that contain lactose, caffeine, alcohol, high fiber, and fats. Breastfeeding of infants should be continued or resumed as soon as possible. Patients with TD should avoid excessive physical activity to reduce the risk of fluid loss and dehydration.

Fluid status in the field should be assessed by physical signs related to hydration, including pulse, hydration of mucous membranes, skin turgor, and urine output. Urine color and volume are excellent measures. For travelers in the wilderness or tropics, fluid replacement must equal basic needs plus volume of diarrhea plus estimated sweat loss.

Symptomatic Therapy

Symptomatic medications are useful for treatment of milder forms of diarrhea, because they decrease symptoms and allow patients to return more quickly to normal activities. Lactobacillus preparations and yogurt are safe, but evidence is insufficient to establish their value in the therapy of TD. Adsorbent agents bind nonspecifically to water and other intraluminal material and make stools more formed. They have limited value for treatment of acute diarrhea.

The most useful drug for symptomatic therapy is the antimotility drug loperamide. In addition to slowing intestinal motility, loperamide and other antimotility drugs alter water and electrolyte transport, probably affecting both secretion and absorption. Compared with placebo, antimotility drugs reduce the number of stools passed and duration of illness by about 80%.[50,54] The usual initial dose of loperamide is 4 mg. If diarrhea continues, the drug can be given in additional doses of 2 mg after each unformed stool, not to exceed 8 mg/day. Loperamide is not given for more than 2 days. Diphenoxylate with atropine is less expensive than loperamide but has greater central opiate effects, a danger in case of accidental overdose by a child, and more side effects without antidiarrheal benefits because of the atropine, which is added only to prevent drug overdose. Tincture of opium or paregoric opium preparations are rapidly and equally effective and offer modest relief of symptoms. A major problem with this class of drugs is postdiarrhea constipation, so only the loading dose should be employed if these medications are used.

Antimotility drugs should never be used alone in patients who have dysenteric diarrhea, because inhibition of gut motility may facilitate intestinal infection by invasive bacterial enteropathogens.[58] However, this theoretical deleterious effect does not appear to be an issue when loperamide is used concurrently with an effective antimicrobial agent.[65,66,201] Antimotility drugs should not be given to children younger than 3 years.

Probiotics have been tested for treatment and prevention of infectious diarrhea. Several meta-analyses of randomized controlled trails have noted a modest effect on frequency and duration of diarrhea. Probiotics may also be of value for antibiotic-induced diarrhea and PI-IBS. Different types of probiotic bacteria are available in capsules, powder, therapeutic yogurts, and other modalities. Effective dosage is not well delineated, and the number of live microorganisms is unreliable. Probiotic preparations have not been effective in preventing TD.[209] New intestine-specific probiotics are likely to be identified as the intestinal microbiome is better characterized.

Because increased secretion of water and electrolytes is the major physiologic derangement in acute watery diarrhea, therapy aimed at this effect is appealing. Aspirin and other nonsteroidal antiinflammatory drugs (NSAIDs) inhibit secretion,[164] but their safety is a concern because of gastric mucosal toxicity. The salicylate moiety of bismuth subsalicylate reduces the number of stools passed and duration of diarrhea by about 50%, altering secretion in the intestine. Bismuth subsalicylate also has antimicrobial and antiinflammatory properties. New compounds are being developed that have antisecretory properties without motility effects.[39,53] Table 82-6 summarizes the recommended dosages of available symptomatic treatments.

Antimicrobial Therapy

Although most enteric infections do not require antibiotics, empirical antimicrobial therapy is indicated in acute TD and febrile dysenteric illness, because of the importance of *Shigella* and *Campylobacter* as etiologic agents of this syndrome. Travelers with acute diarrhea and mild symptomatology usually do not need empirical antimicrobial therapy and can be treated with oral fluids and saltine (soda) crackers. Travelers with acute diarrhea and moderate symptoms serious enough to change an itinerary and cause great inconvenience[191] should be treated with empirical antimicrobial therapy or symptomatic therapy with loperamide or bismuth subsalicylate. Finally, travelers with more severe symptoms with any degree of incapacitation or with dysentery should be treated with empirical antimicrobial therapy immediately after passage of the first unformed stool (Table 82-7).[49] Loperamide can be given with the antibacterial drug for faster clinical response.[60] Therapy for specific infections is discussed in the corresponding sections (Table 82-8).

TABLE 82-6 Nonspecific Drugs for Therapy of Traveler's Diarrhea in Adults

Agent	Therapeutic Dose
Loperamide	4 mg initially; if nonresponsive, can give 2 mg (one capsule) after each loose stool, not to exceed 8 mg (four capsules) daily; do not use in dysenteric or febrile diarrhea.
Bismuth subsalicylate	30 mL or two 262-mg tablets every 30 minutes for eight doses; may repeat on day 2
Probiotics	Dose according to package, because products and formulations vary. Daily dose may make diarrhea less severe and shorten its duration; consider for prevention of antibiotic-associated diarrhea.

TABLE 82-7 Empirical Treatment and Evaluation of Traveler's Diarrhea in Adults

Clinical Manifestations	Recommendations*
Watery diarrhea with mild symptoms (no change in itinerary)	Oral fluids and symptomatic therapy (can give antibiotics† or loperamide)
Watery diarrhea with moderate symptoms (change in itinerary but able to function)	Symptomatic treatment with loperamide and empirical antibiotic† treatment after passage of first unformed stool
Watery diarrhea with severe symptoms (incapacitating)	Antibiotic† after passage of first unformed stool
Dysentery or fever	Azithromycin, 1000 mg in single dose; loperamide is not recommended.
Persistent diarrhea (>14 days)	Parasite examination and stool culture; consider gastrointestinal evaluation.
Vomiting, minimal diarrhea	Oral fluids, and consider using bismuth subsalicylate.
Diarrhea in pregnant women	Fluids and electrolytes; if severely ill, treat with azithromycin, 500 mg once daily for 3 days.

*Treatment should be self-initiated during travel without evaluation.
†Antibiotic options include ciprofloxacin, 500 mg twice daily for 1-3 days; or other fluoroquinolone for 3 days; or azithromycin, 1000 mg in a single dose.

Fluoroquinolones, azithromycin, and rifaximin have adequate activity against bacterial enteric pathogens to be considered useful for empirical therapy of TD.[51] Ciprofloxacin is often the least expensive drug known to be effective. Problems with this drug[210] are ineffectiveness for fluoroquinolone-resistant *Campylobacter* strains,[204] depletion of gut flora,[108] predisposing to *C. difficile* infection,[147] and damage to articular cartilage.[136]

TABLE 82-8 Antimicrobial Therapy for Organism-Specific Diarrhea in Adults

Diagnosis	Recommendation
Enterotoxigenic and enteroaggregative *Escherichia coli* diarrhea	Rifaximin, 200 mg tid for 3 days *or* Ciprofloxacin, 500 mg bid for 1-3 days *or* Other fluoroquinolone for 3 days *or* Azithromycin, 1000-mg single dose
Cholera	Doxycycline, 300-mg single dose
Systemic salmonellosis (typhoid fever or bacteremic infection)	Ciprofloxacin, 500 mg bid for 5-7 days *or* Levofloxacin, 500 mg qd for 7-10 days
Salmonellosis (intestinal nontyphoid salmonellosis without systemic infection)	Antimicrobial therapy controversial if systemically ill (high fever and toxicity) or in a high-risk group: sickle cell anemia, age <3 mo or >64 yr, taking corticosteroids, undergoing dialysis, those with inflammatory bowel disease (if decision to treat, use regimen as for Systemic salmonellosis)
Shigellosis	Ciprofloxacin, 500 mg bid for 3 days *or* Levofloxacin, 500 mg bid for 3 days
Campylobacteriosis	Erythromycin, 500 mg qid for 5 days *or* Azithromycin, 500 mg qd for 3 days, or 1000 mg in single dose

bid, Twice daily; *qd,* daily; *qid,* four times daily; *tid,* three times daily.

Azithromycin is a good alternative for treatment of acute TD. It is given in a single dose of 1 g for TD.[204] Its main use is treatment of dysenteric and febrile TD. Azithromycin has the advantage of being approved for pediatric TD (5 mg/kg/day for 3 days). Rifaximin (200 mg three times daily) was approved in 2004 by the U.S. Food and Drug Administration (FDA) for treatment of TD caused by noninvasive *E. coli* in patients 12 years and older. Rifaximin is as effective as ciprofloxacin for treatment of watery diarrhea caused by noninvasive bacterial causes of TD.[61] Modification of an orally administered, poorly absorbed rifamycin molecule that concentrates in the distal small bowel and colon may increase the drug's activity against invasive bacterial pathogens.[63]

Travelers to high-risk regions should carry an antibacterial drug for treatment of bacterial diarrhea.[51] A symptomatic drug, such as loperamide, may also be included for immediate relief of symptoms. If both drugs are employed in acute TD, persons should be instructed to take loperamide only if they do not have fever and are not passing grossly bloody stools. The duration of antimicrobials needed in TD appears to be short for the absorbed drugs, which are fluoroquinolones or azithromycin. For rifaximin therapy, a full 3 days of treatment should be undertaken. An ideal approach is to have both rifaximin and azithromycin in the travel medicine kit. Rifaximin should be used with watery diarrhea (90% of illness likely to be seen), but when bloody stools are passed and fever is present, azithromycin should be taken.

PREVENTION AND PROPHYLAXIS

Food, Beverage, and Personal Hygiene

Food and water transmit the pathogens that cause infectious diarrhea and TD.[4,203,215] When diarrhea occurs, however, the exact source cannot be determined. Being careful about what is eaten is recommended and may be helpful in reducing the occurrence of illness,[118] but dietary habits usually cannot be rigidly controlled.[185] Food in developing countries is often contaminated with fecal coliforms and enteropathogens.[215] *V. cholerae* remains viable for 1 to 3 weeks in food,[70] and *Salmonella* can survive 2 to 14 days in water or in the environment at large in a desiccated state.

Risk of illness is lowest when most meals are self-prepared and eaten in a private home, intermediate when food is consumed at public restaurants, and highest when food is obtained from street vendors.[17] The following standard dietary recommendations for prevention are based more on known potential vehicles for transmission of illness than on strong evidence.

1. Avoid tap water, ice made from untreated water, and suspect bottled water. Bottled and carbonated drinks, beer, and wine are probably safe. Boiled or otherwise disinfected water is safe. Tap water in high-risk countries is difficult to implicate in TD, but has been shown to contain enteric bacteria and pathogenic viruses and parasites.[12] Bottled carbonated beverages are considered safe because of the antibacterial effects of the low acidity. Alcohol in mixed drinks does not disinfect contaminated ice cubes unless the alcohol content is at very high and potentially unsafe concentrations.[40]
2. Avoid unpasteurized dairy products. These may be the source of infection with *Salmonella*, *Campylobacter*, *Brucella*, *Listeria monocytogenes*, *Mycobacterium* spp., and others.[163]
3. Avoid raw meat and vegetables. Raw vegetables in salads may be contaminated by fertilization with human waste or by washing in contaminated water. Anything that can be peeled or have the surface removed is safe. Fruits and leafy vegetables can also be disinfected by immersion and washing in iodinated water or by exposure to boiling water for 30 seconds. Povidone-iodine 10% has been suggested as a practical disinfectant for water in the field in a wilderness setting[90] (see Chapter 88). Raw seafood, including traditional dishes such as ceviche and sashimi, has been associated with increased risk of TD. Shellfish concentrate enteric organisms from contaminated water and can carry hepatitis A, noroviruses, *Aeromonas hydrophila*, *Y. enterocolitica*, *V. cholerae*,

and *V. parahaemolyticus*. Raw fish can carry parasites such as *Anisakis simplex*, *Clonorchis sinensis*, and *Metagonimus yokogawai*. Raw meat is a source of *Salmonella* and *Campylobacter* and is the vehicle for *Trichinella*, *Taenia saginata, Taenia solium*, and *Sarcocystis*. Although adequate cooking kills all microorganisms and parasites, if food is left at room temperature and recontaminated before serving, it can transmit *Salmonella*, *Shigella*, ETEC, or EAEC. Food served on an airplane, train, boat, or bus may have been catered in the country of origin. Problems of food hygiene pertaining to these forms of public transportation may be related to employee handling of food, even in the United States.

Generally safe foods are those served steaming hot, dry items such as bread, freshly cooked food, foods that have high sugar content (e.g., syrups, jellies, jam, honey), and fruits that have been peeled.

Sanitation and hygiene are among primary means of prevention for residents in developing areas and for wilderness groups. The role for prevention for most travelers is more difficult to demonstrate. Cruise passengers using regular handwashing with soap and water can see reduction in norovirus gastroenteritis, whereas alcohol-based hand sanitizers may not be effective.[126] Regular use of alcohol hand sanitizers did not appear to offer any protection against either diarrhea or respiratory tract infection in travelers in one study,[95] undoubtedly because of the enormous dose of diarrheogenic *E. coli* needed to cause illness. Handwashing and cleaning of cookware may be useful in preventing diarrhea in wilderness backpackers where low-inoculum pathogens may be seen.[23]

Chemoprophylaxis

Chemoprophylaxis with antibiotics was shown in the 1950s and 1960s to effectively prevent TD among international travelers.[114] This was the first evidence that bacterial pathogens were the most important causes of TD. Preventive antibiotics may be recommended for trips of 2 weeks or less to high-risk regions and will require a prescription from a physician (Table 82-9).

Because of safety and efficacy, rifaximin is the optimal drug when prophylaxis is employed: the dose is one 200-mg tablet twice daily with major daily meals. Another effective dosage formulation of rifaximin is a 550-mg tablet taken once during breakfast each day of the trip.

Several non-antimicrobial agents have been studied for prevention of TD, with some found to be minimally effective. Lactobacilli have been tested on the assumption that they are safe and favorably modify intestinal flora, but they did not invariably reduce the incidence of TD and provided protective efficacy only up to 47%.[91] Of the non-antibiotic drugs, only bismuth subsalicylate (BSS), the active ingredient in Pepto-Bismol, has been shown by controlled studies to offer reasonable protection and safety.[52,64] The currently recommended dose of BSS is two tablets with each meal and two tablets at bedtime, or two tablets four times a day (2.1 g/day) while in a high-risk region for trips of 2 weeks or less. Mild side effects include constipation, tinnitus, and temporarily blackened tongue or stools. BSS should not be used by someone with aspirin allergy or in young children. The precise mechanism by which BSS prevents diarrhea is still unknown. Salicylate released during dissociation in the stomach exhibits antisecretory activity after exposure to bacterial enterotoxin on intestinal mucosa, and bismuth salts have antimicrobial activity.[83]

Immunoprophylaxis

Spurred by emergence of in vitro resistance among enteropathogens to antimicrobial agents, including the fluoroquinolones, and with the knowledge that persons develop natural protection against TD as they remain in a high-risk area, vaccines are being developed to prevent TD. Several vaccines are being or have been developed for protection against rotavirus, *Shigella, V. cholerae*, and ETEC. The vaccine most relevant to TD is ETEC, since it is the most important cause of TD and typically occurs during the first 2 weeks in a country of risk.[2] An orally administered ETEC vaccine is marketed as Dukoral in many European countries. The vaccine uses a recombinant form of the binding subunit of cholera toxin that resembles the heat-labile toxin of ETEC (LT). The vaccine was successfully employed in a study of Finnish travelers to Morocco.[158] The vaccine fails to immunize against the nonantigenic heat-stable toxin of ETEC (ST). A study of the effectiveness of Dukoral in preventing TD provided evidence that the vaccine might be expected to prevent two of seven (28%) cases of TD if routinely employed.[127] Adding whole cells containing gut attachment fimbriae of ETEC has been one approach to increase the spectrum of activity of this oral vaccine. Making sure the correct fimbrial adhesin is included in the vaccine is a challenge of this approach.[176]

BACTERIAL ENTEROPATHOGENS

ESCHERICHIA COLI

The diarrheagenic *E. coli* represent a heterogeneous group of organisms that belong to one taxonomic species, but have different virulence properties, epidemiologic characteristics, and clinical features. At least six groups have been characterized, based on genotypic or phenotypic markers.[145] Discussed here are the pathotypes of diarrheagenic *E. coli* important in TD.[216]

Enterotoxigenic *E. coli*

First identified in the 1970s, ETEC strains were shown to produce one or two enterotoxins that act on the small intestine through different cyclic nucleotide pathways showing different time responses in the gut.[145] One of these toxins is a heat-labile cholera-like toxin (LT), a high-molecular-weight protein immunologically and physiologically similar to cholera toxin. Human ETEC strains also have a low-molecular-weight, poorly antigenic toxin that is heat stable (ST).[170] One common method for diagnosis of ETEC is identification of specific DNA plasmid sequences using a hybridization technique.[145] More recently, PCR has been used to improve the level of detection.[8,15,75,205,207,216] ETEC has worldwide distribution and is the major cause of TD, accounting for 30% to 40% of cases in series from Latin America, Africa, and southern Asia (Indian subcontinent).[183] It also accounts for a large percentage of enteritis in local pediatric populations of developing countries, where contaminated food and water are the primary sources of infection. Person-to-person spread is infrequent because of the large infectious dose (10^6 to 10^{10} organisms).[55]

TABLE 82-9 Prophylactic Medications for Prevention of Traveler's Diarrhea*

Agent	Protective Efficacy	Prophylactic Dose	Comment
Bismuth subsalicylate	65%	30 mL or two 262-mg tablets before meals and at bedtime	Safe, temporary darkening of stools and tongue
Fluoroquinolones	90%	Ciprofloxacin, 500 mg once daily	Side effects and toxicity unacceptable considering expected benefit; concern with development of antibiotic resistance
Rifaximin	70%-80%	Rifaximin, 200 mg twice daily with meals	Safe, nonabsorbable, no increased resistance; should be considered the standard agent for prophylaxis during high-risk travel

*Not generally recommended for healthy travelers able to carry out preventive measures; to be used in special situations (see text) and for no longer than 2 weeks.

Enteroinvasive *E. coli*

As with *Shigella*, EIEC strains possess the property of bowel mucosa invasion, resulting in microabscesses and ulcer formation. Because of the presence of the same invasive plasmid and other antigens of *Shigella*,[121,171] EIEC must be considered in the differential diagnosis of febrile dysenteric diarrhea. EIEC strains cause a small fraction of TD cases.[212]

Enteroaggregative *E. coli*

The EAEC strains are an important cause of TD in all regions of the world.[3] These strains adhere to HEp-2 cells in a typical aggregative, "stacked brick" pattern. Several bacterial markers have been studied as possible diagnostic aids, but no single marker is present in all strains.[96,98,105] Some studies suggest that EAEC should be considered a phenotypically and genotypically heterogeneous group.[24,36,98,122,144,145] Although the pathophysiology of EAEC is not completely understood, presence of multiple virulence factors and stimulation of inflammatory cytokines/chemokines have been described.[22,84,97-99,105,107,143,218] EAEC has been associated with acute and persistent diarrhea in children living in developing countries.[32,96,148,180,218]

Diffusely Adherent *E. coli*

These strains show a diffuse, nonaggregative adherence pattern to HEp-2 cells. There is limited evidence that these strains are causes of TD[138,206] and diarrhea in children in developing countries.[79]

Laboratory culture cannot differentiate the various diarrheagenic strains of *E. coli* from normal bowel flora or from one another. Specialized assays, such as DNA probing and HEp-2 adherence technique, are specifically used for research purposes.[144] New serologic and molecular diagnostic techniques under investigation may become available in the future to differentiate these organisms.[8,12,16,75,129,146,167,190,207]

Most cases of *E. coli* diarrhea are brief and self-limited (see Antimicrobial Therapy, earlier). Treatment is with rifaximin, ciprofloxacin, or azithromycin. EIEC should be treated as for shigellosis with 3 days of therapy with a fluoroquinolone or 1 g of azithromycin in a single dose.

SALMONELLA

Salmonella infections may result in four different clinical syndromes: gastroenterocolitis, enteric (typhoid) fever, bacteremia with focal extraintestinal infection, and asymptomatic carriage.[20,179] Gastroenterocolitis and typhoid fever are the two most important forms for travelers. Although the incubation period for typhoid fever is usually 1 to 2 weeks, it is only 8 to 48 hours for intestinal infections with nontyphoid *Salmonella*.[161] Nausea, vomiting, malaise, headache, and low-grade fever may precede abdominal cramps and diarrhea. Stools are usually foul and green-brown to watery, with variable amounts of mucus, blood, and leukocytes. Cholera-like fluid loss or dysentery with grossly bloody and mucoid stools occurs less often. The acute phase lasts only a few days. Asymptomatic excretion of organisms in the stool continues for 4 to 8 weeks; chronic carriers are rare. Infants younger than 3 months experience longer illnesses (average, 8 days) with more complications. Among all ages, transient bacteremia is common, accounting for significant isolation of *Salmonella* types from blood. Fever and malaise occurring more than 1 week after resolution of diarrhea suggest a complication or another diagnosis.[110,161] In healthy adults, *Salmonella* bacteremia occurs in 5% to 8% of infections and is not distinguishable from other causes of sepsis.

Diagnosis is made by isolation of *Salmonella* from stool or blood cultured onto selective media (MacConkey or *Salmonella-Shigella* agar). Supportive treatment with fluids is sufficient therapy for most cases of uncomplicated *Salmonella* enterocolitis. Antimicrobial therapy is indicated for persons who have symptomatic *Salmonella* infection with fever, systemic toxicity, or bloody stools. Fluoroquinolones are the treatment of choice for most forms of systemic salmonellosis because they shorten duration of illness. Doses are the same as those recommended to treat shigellosis, although treatment is continued for 7 days (14 days if patient is immunosuppressed). For known intestinal salmonellosis, antibiotics are used only in the more severely ill patients or when bacteremia is suspected.

Immunity to *Salmonella* is serotype specific. Vaccines have not been successful for nontyphoid *Salmonella* because of the number of serotypes. For typhoid fever, immunoprophylaxis is available with two licensed vaccines. The first is a live-attenuated strain Ty21a that is given as one oral dose every other day for four doses.[9,78] The second is an inactivated Vi polysaccharide preparation given as a single parenteral immunization.[1] Both preparations are of approximately equal cost and effectiveness.

SHIGELLA

Shigellae are nonmotile, nonsporulating, gram-negative rods in the Enterobacteriaceae family. There are four species or groups: A (*Shigella dysenteriae*), B (*Shigella flexneri*), C (*Shigella boydii*), and D (*Shigella sonnei*); the first three contain numerous serotypes. Fecal-oral contamination is the mode of spread, most often from contaminated food in the case of TD. With an infectious dose as low as 10 to 200 organisms, person-to-person spread also occurs.[62] The essential virulence factor of *Shigella* is invasiveness associated with a large (120- to 140-megadalton) plasmid. As with most enteric pathogens, infection with *Shigella* may be asymptomatic, mild, or severe. In the classic form of shigellosis, after 1 to 3 days of small bowel disease, colonic involvement causes progression to clinical dysentery. In the dysenteric form, the volume of stools decreases and the frequency increases, with passage of up to 20 to 30 movements a day, containing gross blood and associated with fecal urgency and often tenesmus. Fever is common in dysenteric cases and found in up to one-half of cases of shigellosis. Mild abdominal tenderness is also common, but without peritoneal signs.

Laboratory tests often show mild leukocytosis with increased number of immature granulocytes. If colitis is present, microscopic examination of the stool shows countless neutrophils. Diagnosis is made by stool culture on selective media (MacConkey or *Salmonella-Shigella* agar), which is positive in most infected patients.[59] Patients with fever and dysentery should be treated with absorbed antimicrobial agents, including fluoroquinolones or azithromycin. The current dosage recommendations for fluoroquinolones are norfloxacin (400 mg twice daily), ciprofloxacin (500 mg twice daily), or levofloxacin (500 mg once daily), for a total of 3 days. Single-dose therapy is probably effective in milder forms of illness. For children, azithromycin (10 mg/kg/day for 3 days) or a 3-day course of a fluoroquinolone can safely be used, even though this class of drugs is not approved for use in children.

CAMPYLOBACTER

The organism is a small, curved, gram-negative rod, formerly classified as *Vibrio*. *Campylobacter jejuni/coli* strains are widespread in the environment, most often spread from contaminated food. The most important source for human illness is poultry, but epidemics have also been associated with ingestion of raw milk.[18,19] *C. jejuni* has been isolated from surface water and can survive up to 5 weeks in cold water, ensuring its potential for wilderness waterborne spread. Person-to-person spread occurs but is uncommon. The prevalence of *C. jejuni* as a cause of TD varies with geography and time of year. TD secondary to *C. jejuni* is more prevalent in Southeast Asia and accounts for about 3% of cases in rainy summertime and in up to 15% of cases during drier wintertime.[18,135,178] All segments of the small and large intestine may be affected in intestinal campylobacteriosis. The incubation period of *C. jejuni* enteritis is 2 to 7 days. Clinical symptoms are extremely variable and nonspecific. Patients often have a 1-day prodrome of general malaise and fever, followed by abdominal cramps and pain that herald the onset of diarrhea, with up to eight bowel movements a day. Diarrhea is initially watery, followed by passage of stools that are bile stained or bloody. *C. jejuni* infection has been associated with occurrence of Guillain-Barré syndrome.[18,100,140,169] The mechanism of development of this postinfectious complication relates to molecular

mimicry, with development of antiganglioside antibodies stimulated by infection by specific strains of *Campylobacter*.[80]

Definitive diagnosis is made by stool culture on a selective medium (e.g., Skirrow, Butzler, Campy-BAP), with isolation rates directly related to severity of disease. *C. fetus* may be grown from the blood in patients with systemic illness. Treatment is primarily supportive with oral fluids; dehydration is usually mild. Early antibiotic therapy appears to be effective in intestinal campylobacteriosis.[18] The antibiotic of choice is erythromycin or azithromycin.[82,119]

VIBRIOS

Cholera is a severe form of watery diarrhea often associated with dehydration. The disease is caused by *V. cholerae* O group 1 (O1), a motile, curved, gram-negative rod. These microorganisms have two major biotypes, classic and El Tor, which produce similar clinical illnesses, and each one contains two main serotypes, Ogawa and Inaba.[175] Non-O1 *V. cholerae* strains also produce diarrheal illness, but they show less potential for epidemic disease.[111,120] Most cases of gastroenteritis caused by noncholera vibrios have been associated with ingestion of raw seafood. Cases have been reported from travelers, particularly after visits to coastal areas of Southeast Asia and Latin America. *V. parahaemolyticus* causes 70% of cases of food-borne gastroenteritis in Japan (where large amounts of raw seafood are eaten), leads to sporadic outbreaks in the United States, and is a common cause of TD in Thailand.[21] After passing through the stomach, the organism multiplies and colonizes the small bowel. The local effects of enterotoxin account for the pathophysiology of cholera. No pathologic changes are noted in the intestinal wall. Some cholera infections are asymptomatic, and 60% to 80% of clinical cases present as mild diarrhea that never raises suspicion for cholera.[94]

After an incubation period of 2 days (range, 1 to 5 days), fluid accumulates in the gut, causing intestinal distention and diarrhea. Diarrhea may begin as passage of brown stools but soon assumes the translucent, gray, watery appearance known as "rice water" stools. In serious cases, stool volume may reach 1 L/hr, leading to severe dehydration, acidosis, shock, and death. Vomiting may occur as a result of gut distention or acidosis.[111,175]

The clinical syndrome caused by noncholera vibrios is not characteristic. Intestinal illness is associated with diarrhea, abdominal cramps, and fever, with nausea and vomiting in about 20% of cases. Diarrhea may be severe, with up to 20 to 30 watery stools per day. In outbreaks of *V. parahaemolyticus* infection, explosive diarrhea associated with abdominal cramps and nausea is often described, with vomiting in about 50% and fever in about 30% of cases. A dysentery-like syndrome with mucoid bloody diarrhea is often seen in disease outbreaks.[21] Infections are usually brief, lasting an average of 3 days, with spontaneous resolution.

Diagnosis for any of the *Vibrio* strains can be made by stool culture on suitable media (e.g., thiosulfate-citrate–bile salts–sucrose [TCBS], agar). Vibrios can survive for 1 week on a stool-saturated piece of filter paper sealed in a plastic bag, before placing it in the culture media.[111] *V. cholerae* infection can also be diagnosed using a darkfield microscopic examination of fresh stools, which may reveal the characteristic helical vibrio in motion.

Aggressive replacement of fluid and electrolytes is the cornerstone of therapy for cholera, especially in severe cases. Severe untreated cholera has 50% mortality, which may be reduced to 1% with appropriate treatment. Children are at higher risk for complications and death. In severe cholera, antibiotics shorten duration of diarrhea and excretion of organisms, and reduce fluid losses, but are not as important as fluid therapy. Oral antibiotics can be started within a few hours of initial rehydration. The drug of choice is doxycycline, 300 mg as a single dose in adults or 50 mg/kg/day in four divided doses for children. Treatment of patients infected with noncholera vibrios should also focus on fluid replacement. Little information exists on the benefit of antibiotic therapy for GI disease, but antimicrobials may be reasonable in dysentery-like cases or prolonged illness. The same antimicrobial agents used in cholera could be used against this infection.

The current parenteral cholera vaccine has no antitoxin activity and is only about 50% effective in reducing attack rates over a 3- to 6-month period for persons living in endemic areas. It is not recommended for travelers to endemic areas.[111] Outside the United States, two additional vaccines are available: an oral killed whole-cell–cholera toxin recombinant B subunit (WC-rBS) and an oral live-attenuated *V. cholerae* vaccine (CVD 103-HgR), both with 60% to 100% rate of protection against *V. cholerae* O1 for at least 6 months. They are not active against *V. cholerae* O139.[173] A bivalent (CVD103-HgR plus CVD 111) oral vaccine has been shown to be more effective than the monovalent vaccine.[10,13,87,202]

AEROMONAS SPECIES AND *PLESIOMONAS SHIGELLOIDES*

Aeromonas species and *P. shigelloides* are gram-negative, facultative anaerobic, nonsporulating rods. Their normal habitats are water and soil, and these bacteria have been implicated in a variety of human illnesses, most often gastroenteritis.[92,93,103,211] Clinical illness associated with enteric infection by *A. hydrophila* varies from acute to chronic diarrhea and from passage of watery stools to dysentery with colitis.[103,181,208] *Aeromonas* strains are susceptible to antibiotics used to treat TD. *P. shigelloides* has been associated with recent travel and ingestion of raw or inadequately cooked shellfish. *Plesiomonas* may cause dysenteric illness suggestive of an invasive organism, but its pathogenic mechanisms remain poorly defined.[93] *Plesiomonas* is susceptible to anti-TD antibiotics.

VIRAL ENTERIC PATHOGENS

Noroviruses have been shown to be important causes of approximately 10% of TD cases.[6,30,101,116] These viruses are highly infective (10 to 100 organisms per inoculum), and infection is spread by common-source vehicles with a propensity for secondary person-to-person spread (high secondary attack rate).[89] Humans are the only known carriers of noroviruses. *Norovirus* is known as the "cruise ship virus" based on its importance in that setting. Between 20% and 67% of norovirus outbreaks have been associated with food.[28,149] After a cruise ship has experienced a norovirus outbreak, this infection can continue to be a problem on future trips with the involved ship, despite extensive sanitization.[101] *Norovirus* has also been a recurrent problem among groups rafting the Colorado River. Transmission is followed by an incubation period of 24 to 48 hours, and illness begins abruptly with vomiting, abdominal cramps, and diarrhea. Stools are watery without blood or leukocytes. Other common symptoms include low-grade fever, malaise, myalgias, respiratory symptoms, and headache. Illness is almost always mild and self-limited, lasting 1 to 2 days. Complications and mortality are extremely rare and usually involve elderly and debilitated patients. Immunoassays and molecular techniques (reverse-transcriptase PCR) are available for detection of these small, round RNA viruses in stool.[6,29] Vaccine development for noroviruses is in a very early stage.[117]

INTESTINAL PROTOZOA

Protozoal infections may be pathogenic or commensal (having little or no effect) for the human host. Although acute self-limited diarrheal illness may occur, only a small proportion of cases of acute TD are caused by parasites. Symptoms are nonspecific, and diagnosis is often made on stool examination. Most protozoal infections are suspected on the basis of subacute or chronic GI symptoms, which may fluctuate over time.

Several factors have increased the prevalence of intestinal parasites in the United States and worldwide: an increase in immunocompromised patients, who frequently become infected by these organisms; improvement in diagnostic techniques; increase in group settings (day care centers and nursing homes); more frequent international travel; and in the United States, increased immigration of people from developing countries.[113,133]

All intestinal protozoa are transmitted by the fecal-oral route. Thus, infection rates are highest in areas and groups with

poor sanitation, close contact, or particular customs favoring transmission. These reemerging infections have been related to large outbreaks of communicable diseases in the United States, often secondary to water contamination.[217] In addition to spread by food, water, and person-to-person contact, mechanical vectors such as flies may also spread these organisms. Transmission of intestinal protozoa is favored by a hardy cyst, which is passed in the feces of an infected host. In addition to an infective cyst, the life cycle for most intestinal protozoa includes a trophozoite, which is responsible for reproduction and pathogenicity. Only a single host is required, except for *Sarcocystis*, which requires ingestion of raw meat from an intermediate host. Zoonotic spread to humans has been documented for *Giardia*, *Cryptosporidium*, *Entamoeba polecki*, and *Balantidium coli*.

As with enteric bacteria, symptoms from infection by intestinal protozoa depend on the level of bowel colonized. Those colonizing the small intestine, such as *Giardia* and coccidia (see *Cryptosporidium*), cause a wide spectrum of GI complaints, including malabsorption (resulting in foul stools and flatulence) and weight loss in persistent infections. Although many protozoa are capable of superficial mucosal invasion, only *E. histolytica* and *B. coli*, which colonize the colon, can ulcerate the bowel wall, cause dysentery, and spread to other tissues.[86] Most infections are asymptomatic and self-limited in immunocompetent persons, but can be persistent and severe in immunocompromised hosts. Table 82-10 summarizes treatment of intestinal protozoal infections.

Prevention of infection is focused on interruption of fecal-oral transmission and is similar to other bacterial and viral causes of TD, including personal hygiene, water disinfection, basic food precautions, and care in food preparation. Currently, no vaccines are available for enteric protozoan infections, although there are efforts to develop a vaccine for *E. histolytica*.

GIARDIA LAMBLIA

Giardia lamblia (also known as *Giardia intestinalis* or *Giardia duodenalis*) is a flagellate protozoan. Classification of *Giardia* species remains controversial, but there are at least six species and other genotypes, primarily distinguished by host. *G. duodenalis* is the species of major concern for human infection.[5]

TABLE 82-10 Antiparasitic Therapy for Giardiasis

Adult Treatment	Pediatric Treatment and Other Drugs
Tinidazole, 2000 mg single dose	Tinidazole, 50 mg/kg single dose
or	
Nitazoxanide, 500 mg bid for 3 days	Children age 1-4 yr: nitazoxanide, 100 mg bid for 3 days;
or	Children age 4-11 yr: nitazoxanide, 200 mg bid for 3 days
Metronidazole, 250 mg tid for 5-7 days or 2 g/day in a single dose for 3 days (high dose has more side effects),	Metronidazole, 15 mg/kg/day divided tid for 5-7 days
or	
Albendazole, 400 mg single dose or qd for 5-7 days (single dose less effective),	Albendazole, 10 to 15 mg/kg qd for 5-7 days
or	
Diloxanide (Furamide), adults and children age 12 yr and older: 500 mg tid for 5-10 days	Children up to age 12 yr: diloxanide, 20 mg/kg/day in three divided doses for 5-10 days

Data from references 25, 26, 33, 69, 72, 76, 85, 130, 142, 150, 153, 159, 162, 172, 182, 187, 189, and 213.
bid, Twice daily; *qd,* daily; *tid,* three times daily.

Giardia is the most common protozoal intestinal parasite isolated worldwide, including in the United States. Prevalence ranges from 3% to 7% in the United States to 30% or more in developing areas with poor sanitation. All age groups are affected. In the United States, a seasonal peak in cases coincides with the summer recreational water season and likely reflects increased outdoor activities and exposures, such as camping and use of communal swimming venues (e.g., lakes, rivers, swimming pools, water parks).[217]

Persons at increased risk for infection reflect the fecal-oral transmission through food, water, and person-to-person contact with a low infectious dose, including (1) travelers to disease-endemic areas; (2) children in child care settings; (3) close contacts of infected persons (family or household contacts); (4) persons who ingest contaminated drinking water, recreational water (lakes, rivers, and pools), or untreated surface water (backpacking or camping); (5) persons who have contact with infected animals; and (6) men who have sex with men.

Giardia accounts for a small percentage of TD. Because of the relatively long incubation period and persistent symptoms, *Giardia* is more likely to be found as the cause of diarrhea that occurs or persists after returning home from travel to a developing region.

Epidemiologic studies suggest acquired resistance, with lower rates of infection and illness among residents of endemically infected areas compared with visitors, and among adults compared with children; however, reinfection occurs.

Natural Reservoirs

Giardiasis usually represents a zoonosis and has been detected in almost all classes of vertebrates, including domestic animals and wildlife, including beavers, cattle, dogs, cats, rodents, and sheep. Although *G. intestinalis* infects both humans and animals with cross-infectivity, molecular epidemiology suggests that the role of zoonotic transmission to humans and importance of animal contamination of food and water may be less than previously thought.[217]

Transmission and Infectious Dose

Giardia infection is transmitted by the fecal-oral route and results from ingestion of *Giardia* cysts through consumption of fecally contaminated food or water or through person-to-person (or, to a lesser extent, animal-to-person) transmission. The cysts are infectious immediately on being excreted in feces. Infected persons have been reported to shed 10^8 to 10^9 cysts in the stool per day and to excrete cysts for months. The infective dose of *Giardia* for humans is low; 10 to 25 cysts caused infection in 8 of 25 individuals; more than 25 cysts caused infection in 100%. Infectivity apparently depends on both host and parasite factors.[153] Person-to-person spread may be the most common means of transmission for humans. Areas and populations with poor hygiene and close physical contact have higher rates of infection, and infection of other household members is common. Venereal transmission occurs through direct fecal-oral contamination.

Water is a major vehicle of infection in community outbreaks, usually in small water systems that use untreated or inadequately treated surface water, and may play a significant role in U.S. wilderness travelers who develop intestinal illness.[112,217] Cysts retain viability in cold water for as long as 2 to 3 months. Giardiasis has been called "backpacker's diarrhea" because of the common association with alpine mountain waters.

Pathophysiology and Clinical Presentation

The pathophysiologic mechanisms of diarrhea and malabsorption in giardiasis are poorly understood, and more than one mechanism, including altered gut motility and hypersecretion of fluids, is probably involved. Most small bowel biopsies in human patients demonstrate minimal or no changes. Enterotoxins have not been found.[153,162]

Most infections are asymptomatic, but carriers can excrete high numbers of cysts in stools. The attack rate for symptomatic infection in the natural setting varies from 5% to 70%. Correlation between inoculum size and infection rates has been noted, but not with numbers of cysts passed or severity of symptoms.

The incubation period averages 1 to 2 weeks, with a mean of 9 days. A few people experience abrupt onset of explosive watery diarrhea accompanied by abdominal cramps, foul flatus, vomiting, low-grade fever, and malaise. This typically lasts 3 to 4 days before transition into the more common subacute syndrome. In most patients, onset is more insidious and symptoms are persistent or recurrent. Stools become mushy, greasy, and malodorous. Watery diarrhea may alternate with soft stools and even constipation. Upper GI tract symptoms, typically exacerbated postprandially, accompany stool changes, but they may be present in the absence of soft stool. These include midabdominal and upper abdominal cramping, substernal burning, acid indigestion, sulfurous belching, nausea, distention, early satiety, and foul flatus. Constitutional symptoms of anorexia, fatigue, and weight loss are common. Unusual presentations include allergic manifestations such as urticaria, erythema multiforme, and bronchospasm. Some *Giardia* infections are associated with chronic illness. Adults may have a long-standing malabsorption syndrome and marked weight loss, and children may have failure-to-thrive syndrome.[68,86]

Immunologic responses are effective in the majority of infections, because spontaneous clinical recovery is common with or without the disappearance of organisms. Average duration of symptoms in all ages ranges from 3 to 10 weeks. Both cellular and humoral responses to *Giardia* have been demonstrated.

Diagnosis

Direct stool examination may be used when newer immunologic tests are not available. Cyst passage is extremely variable and not related to clinical symptoms, so multiple stool collections (i.e., three stool specimens collected every other day) increase test sensitivity. One stool sample will allow detection of 60% to 80% of infections, two stool samples will allow detection of 80% to 90%, and three stool samples will allow detection of more than 90%. Trophozoites may be found in fresh, watery stools (Figure 82-2) but disintegrate rapidly. Stools should be preserved in a fixative, such as polyvinyl alcohol, or a formalin preparation if not immediately examined. In the office, fresh stool can be mixed with an iodine solution (e.g., Gram's iodine) or methylene blue and examined for cysts on a wet mount. Many antibiotics, enemas, laxatives, and barium studies mask or eliminate parasites from stools, so examinations should be delayed for 5 to 10 days after these interventions. Trichrome stain is better than the formalin-ether concentration technique for identification of protozoal cysts and trophozoites. Another noninvasive office test is duodenal mucus sampling using a string test (Enterotest), which has reported sensitivity of 10% to 80%. Duodenal biopsy is a sensitive test, but rarely necessary.[133] Direct fluorescent antibody (DFA) testing is an extremely sensitive and specific detection method and is considered the gold standard by many laboratory workers. Immunologic tests on stool are replacing direct microscopy because they are much easier and require less experience to interpret. Immunoassays using enzyme-linked immunosorbent assay (ELISA) or enzyme immunoassay (EIA) on stool approach 100% sensitivity and specificity. Other molecular techniques are available but not commonly used in clinical settings.

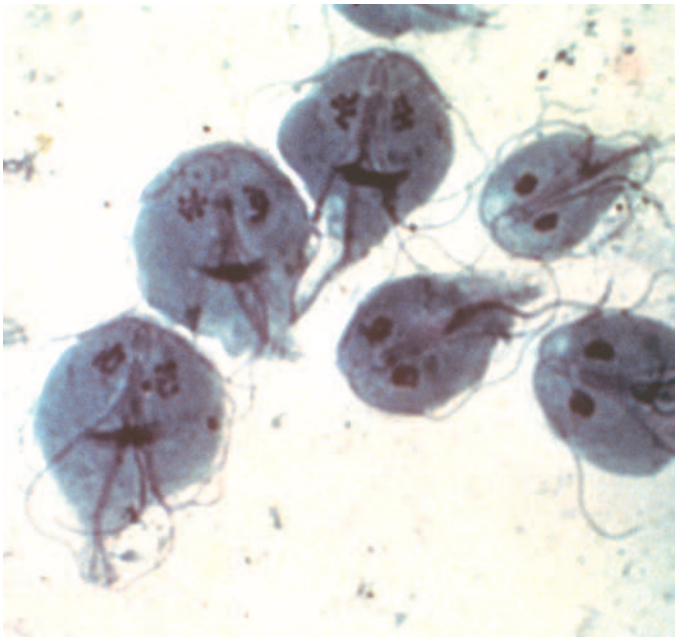

FIGURE 82-2 *Giardia* trophozoites seen in culture. The finding of cysts or trophozoites in a patient with diarrhea is sufficient to make a tentative diagnosis of giardiasis. *(Courtesy D. Lindmark.)*

Treatment

Because of the difficulty and expense of confirming the diagnosis in some patients, a therapeutic trial of drugs may be attempted when suspicion is high. In the field, it is reasonable to initiate presumptive treatment for *Giardia* for secretory diarrhea (nondysentery) lasting more than 1 week that does not respond to a trial of antibiotic therapy.

Symptomatic patients should be treated for comfort and to prevent development of chronic illness. Asymptomatic carriers in nonendemic areas should be treated when identified because they may transmit the infection or develop symptomatic illness. No drug is effective in all cases. In resistant cases, a longer course of two drugs taken concurrently has been suggested. Relapses occur up to several weeks after treatment, necessitating a second course of the same medication or an alternative drug. Malabsorption usually resolves with treatment, but persistent diarrhea may result from lactose intolerance or a syndrome resembling celiac disease, rather than from treatment failure.

The three groups of drugs currently being used are nitroimidazoles (metronidazole, tinidazole, albendazole, ornidazole, nimorazole), nitrofuran derivatives (furazolidone), and acridine compounds (mepacrine, quinacrine).[26,76] Tinidazole and nitazoxanide (Alinia) have similar or better effectiveness (average, 85% to 90%) than does metronidazole and have been approved by the FDA for this use in the United States. Tinidazole is licensed for children older than 3 years, and nitazoxanide is available in suspension for children as young as 1 year. Albendazole has comparable effectiveness with metronidazole and is often used outside the United States because of its broad activity against other parasitic worms.[189] Other alternatives include furazolidone, which results in cure rates between 80% and 96% and is also available as a pediatric suspension. Paromomycin (Humatin) is a nonabsorbable drug that is recommended for pregnant women or for use in severely symptomatic individuals. Quinacrine (Atabrine) achieves high cure rates, but it is no longer available in the United States because it produces frequent and potential severe side effects, especially in children, and safer medications are available. Mebendazole and ornidazole are two other nitroimidazoles that have been used successfully, but less data are available for these drugs. Treatment of giardiasis has been extensively reviewed.[76]

ENTAMOEBA

The genus *Entamoeba* contains many species. Six that can reside in the human intestinal lumen are *E. histolytica*, *E. dispar*, *E. moshkovskii*, *E. polecki*, *E. coli*, and *E. hartmanni*. *E. histolytica* is the only species definitely associated with clinical pathology in humans. The others are considered commensal; however, *E. polecki* and *E. moshkovskii* have been suspected of causing lower intestinal symptoms in cases involving heavy infection.[71] In addition, isoenzyme analysis has recognized 22 different zymodemes of *E. histolytica*, which may explain geographic differences in rates of invasive disease.[166]

Epidemiology and Risk

Entamoeba histolytica is found worldwide. Similar to *Giardia*, transmission is fecal-oral through person-to-person contact or contaminated food or water. Cysts remain viable outside the body for weeks to months, unlike the fragile trophozoites. Unlike *Giardia*, there is no zoonosis, and the reservoir of infection is human. Approximately 12% of the world's population is infected,

although this figure may include *E. dispar*, which is not pathogenic. Higher prevalence in tropical countries is related to increased risk of fecal-oral contamination, which depends on sanitation, cultural habits, crowding, and socioeconomic status.[192] *E. histolytica* is a leading cause of death by parasitic infection worldwide. The World Health Organization (WHO) estimates that *E. histolytica* infects 500 million people per year, causes disease in 50 million, and kills 100,000 individuals annually. Importation of infections by travelers and immigrants accounts for most cases in the United States and other temperate countries. Amebiasis accounts for less than 1% of TD cases.

Pathophysiology and Clinical Course

The pathogenicity of *E. histolytica* is still not well understood. Invasion may be a function of motility, soluble toxins, cysteine protease, or lytic enzymes.[177,192] The cecum and ascending colon are most frequently involved, followed by the rectum and sigmoid colon, with lesions of increasing severity and depth of inflammation and ulceration. Extraintestinal spread is hematogenous. Abscesses containing acellular debris develop primarily in the liver but may involve the brain and lung.

The incubation period ranges from 1 to 4 months. Although 80% to 99% of infections result in asymptomatic carriers, a spectrum of GI diseases may result, with considerable variation in severity. Most often, colonic inflammation without dysentery causes lower abdominal cramping and altered stools, sometimes containing mucus and blood.[102] Weight loss, anorexia, and nausea may be present. Symptoms usually fluctuate and persist for months. The subacute infection may evolve into a chronic, nondysenteric bowel syndrome with intermittent diarrhea, abdominal pain, weight loss, and flatulence. Dysentery may develop suddenly after an incubation period of 8 to 10 days or after a period of mild symptoms. Affected persons may have frequent passage of bloody stools, tenesmus, moderate to severe abdominal pain and tenderness, and fever.[168,192]

Amebic liver abscess is the most common and serious complication from hematogenous spread. Individuals can present with liver abscess months to years after travel or residency in an endemic area. The disease should be suspected in anyone with an appropriate exposure history (residency or travel in an endemic area) presenting with fever, right upper quadrant pain, and hepatic tenderness.

The fatality rate for amebic dysentery and its complications is about 2%. Complications of intestinal involvement develop in 2% to 20% of patients and include perforation, toxic megacolon, and ameboma, which is an annular inflammatory lesion of the ascending colon containing live trophozoites. A postdysentery syndrome can occur in patients with acute amebic dysentery and can be confused with ulcerative colitis. Asymptomatic carriers of *E. histolytica* can develop invasive disease, but more often the infection resolves spontaneously.

Humoral antibodies increase with invasive disease and persist for long periods. Although they do not protect against reinfection or bowel invasion, they may prevent recurrent liver infection. Mucosal immunity may provide some protection against recurrent intestinal infection with *E. histolytica*; once the infection is cleared, recurrence is unusual. However, asymptomatic cyst shedding and active GI illness may persist for years, indicating lack of consistent immune response in the intestinal lumen. Oral vaccines and DNA-based vaccines have been successfully tested in animal models, but human testing has not been done, and no vaccine is currently available.[192,193]

Diagnosis

Routine screening of asymptomatic persons of high-risk groups is not cost-effective, except perhaps for food handlers and persons returning from an extended stay in endemic countries. The diagnosis of invasive amebiasis is most frequently attempted by a combination of microscopy of a fecal specimen, serologic testing, and where indicated, colonoscopy and biopsy of intestinal amebic lesions or drainage of a liver abscess. Where available, detection of *E. histolytica*–specific antigen and DNA in stool and other clinical samples (ELISA[42]) may replace microscopic stool examination, which is complicated by morphologically similar, nonpathogenic species. Antigen detection using ELISA is both rapid and technically simple to perform and can be used in laboratories that do not have molecular facilities, making it appropriate for use in the developing world, where amebiasis is most prevalent.[200]

Serologic tests are not useful for identifying asymptomatic carriers but are positive in 85% to 95% of patients with dysentery and 90% to 100% of patients with liver abscess. In combination with ultrasound or other abdominal imaging, serology is helpful for diagnosis where PCR is not routinely available. Because they do not distinguish between current and prior infections, serologic tests are more useful in developed countries with low incidence of infection. The combination of serologic tests with detection of the parasite (by antigen detection or PCR) offers the best approach to diagnosis.[71] New antigen detection techniques can differentiate between *E. histolytica* and *E. dispar*. PCR techniques have been developed and show greater than 95% sensitivity and specificity.

Diagnosis of intestinal amebiasis by microscopic identification of cysts or trophozoites in stool still plays a significant role where other techniques are not available. Mucus from fresh stools or sigmoidoscopic scrapings and aspirates mixed with a drop of saline may show trophozoites if examined within 1 hour. For delayed examination, stool must be preserved in polyvinyl alcohol or other fixative and may be examined later with trichrome stain. Fecal shedding of cysts is irregular, but three stools on alternate days identify most infections. Sigmoidoscopy or colonoscopy is useful for viewing the pathologic lesions and obtaining selective samples of mucus and biopsies of mucosal ulcers, which usually contain organisms. Finding cysts does not confirm the diagnosis of symptomatic intestinal amebiasis. The key to establishing the diagnosis is finding motile trophozoites with ingested red blood cells. It is rare to identify *E. histolytica* in stool samples from patients with liver abscesses.

Culture techniques are available but not generally used in clinical laboratories because they are expensive and time-consuming.

Treatment

There are multiple benefits to treatment of *E. histolytica* infection, including reducing the infectious period, length of illness, risk of transmission to others, rates of severe illness, and preventing complications of invasive disease.[37] U.S. guidelines suggest that asymptomatic carriers should be treated because a cyst passer represents a potential health hazard to others, and reinfection in the United States is uncommon. Moreover, asymptomatic colonization with *E. histolytica*, if left untreated, can lead to invasive disease. Treatment of amebiasis is based on location of infection and degree of symptoms. Medications are divided into tissue amebicides (e.g., metronidazole, tinidazole, emetine, dehydroemetine, chloroquine), which are well-absorbed drugs that combat invasive amebiasis in the bowel and liver, and poorly absorbed drugs (e.g., iodoquinol, paromomycin, diloxanide furoate) for luminal infections. In general, treatment is effective for invasive infections but disappointing for intestinal colonization. The current drug of choice for asymptomatic carriers is iodoquinol. Side effects are mild and consist of abdominal pain, diarrhea, and rash. Diloxanide furoate (Furamide) is another drug of choice, but in the United States, it is classified as an investigational drug, available only through the Centers for Disease Control and Prevention (CDC). Paromomycin is also effective. Although metronidazole has been used in asymptomatic carriers with 90% success, most reserve this drug for invasive and symptomatic infections[14,166] (Table 82-11).

Invasive disease is treated with a tissue-active drug, followed by a luminal agent (in the same dosages as for asymptomatic infection). Tinidazole or metronidazole are the drugs of choice for oral therapy of amebic dysentery or liver abscess. Tinidazole has slightly better effectiveness and fewer side effects than does metronidazole. Other nitroimidazoles that have been tested include ornidazole, nitazoxanide, and secnidazole. Emetine and dehydroemetine are used parenterally in severe cases of amebiasis, primarily extraintestinal, followed by iodoquinol for 20 days. These two drugs have frequent systemic side effects, including development of cardiac arrhythmias requiring hospitalization for

TABLE 82-11 Therapy for Infectious Diarrhea Caused by Protozoa*

Diagnosis	Recommendation	
	Adult Dose	Pediatric Dose and Other Potential Treatment Drugs
Entamoeba histolytica Treatment for asymptomatic cyst excretion	Iodoquinol, 650 mg tid for 20 days *or* Paromomycin, 500 mg tid for 7 days	Children: iodoquinol, 10-13.3 mg/kg tid for 20 days Children: paromomycin, 25 mg/kg/day in three doses for 7 days
E. histolytica Treatment of diarrhea	Metronidazole, 750 mg tid for 5 to10 days *or* Tinidazole, 1000 mg bid for 3 days *or* Secnidazole, 2000 mg single dose Followed by: Iodoquinol, 650 mg tid for 20 days *or* Paromomycin, 500 mg tid for 7 days	Children: metronidazole, 50 mg/kg/day in three doses for 10 days Children: tinidazole, 50 mg/kg/day in three doses for 3 days Children: secnidazole, 30 mg/kg/day single dose
Cryptosporidiosis	Nitazoxanide, 500 mg bid for 3 days In severe cases or patients with AIDS, consider: Nitazoxanide, 500 mg bid for 2 weeks Paromomycin, 500-750 mg tid or qid for 2 weeks	Children: nitazoxanide Age 12-47 mo: 100 mg (5 mL) bid for 3 days Age 4-11 yr: 200 mg (10 mL) bid for 3 days Adult alternatives: Azithromycin, 1200 mg qd for 4 weeks Albendazole, 400 mg bid for 7-14 days
Cyclosporiasis	TMP/SMX, 160 mg/800 mg bid-qid for 7 days In patients with AIDS, follow with: TMP-SXZ, 160 mg/800 mg 3 times per week	Children: TMP/SMX, 5 mg/25 mg/kg/day for 7 days
Cystoisosporiasis	TMP/SMX, 160 mg/800 mg qid for 10 days, followed by: 160 mg/800 mg bid for 3 weeks Pyrimethamine, 75 mg qd, with folinic acid, 10 mg (or divided dose bid), for 2 weeks	Alternatives: Pyrimethamine, 25 mg, and sulfadoxine, 500 mg (Fansidar) *or* Ciprofloxacin, 500 mg bid for 7 days
Microsporidiosis	Albendazole, 400 mg bid for 2-4 weeks In patients with AIDS: follow with chronic suppression	
Balantidium coli (symptomatic)	Tetracycline, 500 mg qid for 10 days *or* Metronidazole, 750 mg tid for 5-10 days *or* Iodoquinol, 650 mg tid for 20 days	Children: metronidazole, 35-50 mg/kg/day in three divided doses for 5 days Children: iodoquinol, 30-40 mg/kg/day (max 2 g) in three doses for 20 days
Blastocystis hominis (symptomatic)	Nitazoxanide, 500 bid for 3 days *or* Metronidazole, 750 mg tid for 5-10 days	Children: nitazoxanide Age 12 to 47 mo: 100 mg (5 mL) bid for 3 days Age 4 to 11 yr: 200 mg (10 mL) bid for 3 days
D. fragilis	Paromomycin 25-35 mg/kg/d PO in 3 daily doses/d for 7 days *or* Metronidazol 500-750 mg PO tid for 10 days *or* Iodoquinol 650 mg PO tid doses for 20 days	Paromomycin 25-35 mg/kg/d PO in 3 daily doses/d for 7 days *or* Metronidazole 30-50 mg/kg/d PO tid for 10 days *or* Iodoquinol 30-40 mg/kg/d (max 2 g) PO in 3 daily doses for 20 days

See Table 82-10 for treatment of giardiasis.
*Effectiveness of many antiparasitic agents is not well demonstrated for each protozoan infection.
bid, Twice daily; *qd,* daily; *qid,* four times daily; *tid,* three times daily; *TMP/SMX,* trimethoprim/sulfamethoxazole.

cardiac monitoring. Because this class of drugs is related to ipecac, the drugs also cause vomiting.

Successful resolution of symptoms from *E. polecki* has been reported with metronidazole followed by diloxanide furoate, in the same dosages as for amebiasis.

CRYPTOSPORIDIUM

Cryptosporidium is a coccidian parasite related to *Toxoplasma* and *Plasmodium*. Other coccidia capable of causing human intestinal infection include Microsporidia, *Cyclospora*, and *Isospora*. In the environment, *Cryptosporidium* exists as a hearty, 5-mm-diameter oocyst containing four sporozoites. As with *Giardia*, the cysts are infectious when excreted. Humans and animals are infected by ingesting oocysts, which travel through the gut lumen to the small intestine, where they release the sporozoites.[27,31,34,35,38,85,115,137,151,172,187]

Epidemiology and Risk for Wilderness and International Travelers

The epidemiology and transmission of *Giardia* and *Cryptosporidium* spp. are similar. *C. parvum* causes a ubiquitous zoonosis with worldwide distribution. *Cryptosporidium* infects a wide variety of domestic and wild animals. *C. hominis*, the human pathogen, is important and underappreciated.[174] Molecular analysis has revealed at least 14 species of *Cryptosporidium* that are distinguished primarily, but not solely, by host and cannot be distinguished by morphology. It is a reemergent enteric pathogen in humans. Prevalence of infection in human populations varies from 0.1% to 3% in cooler, developed countries (Europe, North

America) to 0.5% to 10% in warmer countries (Africa, Asia). The infection has been described in persons who have contact with animals, such as veterinarians and farmers; infants in day care centers; travelers to endemic areas; and patients who have AIDS or who are otherwise immunocompromised. It has infected large numbers of individuals in community-wide waterborne outbreaks.[217] *Cryptosporidium* poses a risk to wilderness users because oocysts are found widely in surface water and have high degree of resistance to chlorine.[123,124] The infective dose of *Cryptosporidium* for humans is low (mean, 132 cysts in a human challenge trial), similar to that seen with *Giardia* spp.[48] Fecal-oral contamination is the mode of transmission. The different routes of transmission are waterborne, especially in large community outbreaks; person-to-person, especially in day care centers, custodial institutions, and hospitals; food-borne; sexual, with no association with specific behavior; and zoonotic.

Pathophysiology and Clinical Course

The pathophysiologic mechanisms of diarrhea and malabsorption are not completely understood. The parasites may activate cellular and humoral immune and inflammatory responses, leading to cell damage and ultimately producing malabsorption and osmotic diarrhea.

Clinical manifestations depend on the patient's immune status, but asymptomatic infection occurs in both normal and immunocompromised hosts. In immunocompetent persons, the usual incubation period of *Cryptosporidium* is from 5 to 28 days. Symptoms consist of watery diarrhea associated with cramps, nausea, flatulence, and at times, vomiting and low-grade fever. The syndrome is generally mild and self-limited, lasting 5 to 6 days in some groups (range, 2 to 26 days). In contrast, immunocompromised hosts experience more frequent and prolonged infections, with profuse chronic watery diarrhea, malabsorption, and weight loss lasting months to years. Fluid losses can be overwhelming in a fulminant cholera-like illness, with high mortality. Cyst passage in stool usually ends within 1 week of resolution of symptoms but may persist for up to 2 months after recovery. Reinfection of an immunocompetent person has been documented. Rarely, *Cryptosporidium* can infect other organ systems, including the respiratory system, liver and biliary system, and stomach, particularly in immunocompromised persons.

Diagnosis

Oocysts can be routinely found in stools in intestinal infections, even though shedding may be intermittent. Concentration techniques and staining with modified acid-fast, Giemsa, or Ziehl-Neelsen techniques facilitate identification of *Cryptosporidium* oocysts. The Enterotest is also useful to diagnose cryptosporidiosis. Newer immunologic techniques (immunofluorescence, EIA) to detect antigen in stools are faster and have adequate sensitivity and excellent specificity.

Treatment

Because this disease is usually mild and self-limited in immunocompetent hosts, supportive care in some cases may be sufficient. Treatment is indicated for severe disease in otherwise healthy people and in immunocompromised patients with illness. Nitazoxanide is the most useful drug for treating cryptosporidiosis (see Table 82-11). Paromomycin and azithromycin have also shown some effectiveness against *Cryptosporidium*. Roxithromycin, ionophores, sulfonamides, and mefloquine have also been tested against cryptosporidiosis, especially in patients with AIDS and chronic diarrheal disease, with variable but generally positive effects.

The most effective prevention in HIV patients is HAART that supports the immune system.

CYSTOISOSPORA BELLI

Cystoisospora belli is a coccidian protozoal parasite. It is an uncommon cause of diarrhea in humans, but its prevalence, as with *Cryptosporidium*, has been increasing in immunocompromised patients. Ingested oocysts release sporocysts in the small intestine that develop into trophozoites.[35,81,130,133,162,213]

Epidemiology and the Risk for Wilderness and International Travelers

Humans are the only host (although there are a few reports in dogs), and infections are transmitted by fecal-oral contamination through direct contact with food and water, so rates are typically higher in settings with high density of people, close contact, or poor hygiene. *C. belli* is endemic in areas of South America, Africa, and Asia. The prevalence is not precisely known, but ranges from 0.2% to 3% in U.S. patients with AIDS and from 8% to 20% in Haitian and African patients with AIDS. Infection rates in otherwise healthy persons with diarrhea are usually low. Most cases have been identified in tropical regions among natives, travelers, and the military.

Pathophysiology and Clinical Course

The life cycle and pathogenesis of *C. belli* are similar to those of *Cryptosporidium*. The organism invades mucosal cells of the small intestine, causing an inflammatory response in the submucosa and variable destruction of the brush border.

In immunocompetent persons, *C. belli* infection may be asymptomatic or may cause mild transient diarrhea and abdominal cramps. Other symptoms include profuse watery diarrhea, flatulence, anorexia, weight loss, low-grade fever, and malabsorption. Generally, infection is self-limited, ending in 2 to 3 weeks, but some persons have symptoms lasting months to years. Infections in immunocompromised patients tend to be more severe and follow a more protracted course. Rarely, acalculous cholecystitis or reactive arthritis has been reported. Recurrences are common.

Diagnosis

Diagnosis can be made by identification of immature oocysts in fresh stool. However, excretion may occur sporadically and in small numbers, so concentration techniques are usually required. Staining with modified Ziehl-Neelsen can also be useful. When stools are negative, the organism can be recovered from the jejunum through a biopsy or string test. Unlike the other intestinal protozoa, *C. belli* may cause eosinophilia.

Treatment

Successful treatment has been reported with trimethoprim-sulfamethoxazole (TMP-SMX) (see Table 82-11). Other options are pyrimethamine with folinic acid, metronidazole, and nitazoxanide (for patients allergic to sulfonamides). In patients with HIV infection, chronic lifetime suppression therapy is indicated with either TMP-SMX or pyrimethamine plus folinic acid daily.

CYCLOSPORA CAYETANENSIS

Cyclospora species were initially thought to be blue-green algae (cyanobacteria-like organisms). The life cycle and pathogenesis of *C. cayetanensis* are not completely understood. Oocysts need about 7 to 15 days to sporulate and become infectious, so they are not immediately infectious on passage.[7,35,81,131,154,162,184,197]

Epidemiology and the Risk for Wilderness and International Travelers

Cyclospora cayetanensis has been shown to be an important cause of acute and protracted diarrhea. Fecal-oral transmission occurs through food, water, and soil. The organism is endemic in many developing countries in all continents. There are numerous reports of *Cyclospora* infection with diarrhea in travelers to Nepal, Haiti, Peru, and Guatemala. In the United States, most of the outbreaks have been food-borne, associated with ingestion of contaminated imported raspberries. Humans are the only known reservoir; there is conflicting evidence for a zoonosis.

Pathophysiology and Clinical Course

The onset of diarrhea is usually abrupt, with symptoms lasting 7 weeks or even longer. Other symptoms include anorexia, nausea, flatulence, fatigue, abdominal cramping, and weight loss. In patients with AIDS, the duration may be longer and severity greater.

Diagnosis

Small, spherical organisms can be detected in fresh or concentrated stool. They show variable staining with acid-fast methods, but stain best with carbolfuchsin. Phase-contrast microscopy and autofluorescence are also useful in the diagnosis. A PCR method is used primarily for research.

Treatment

The treatment of choice is TMP-SMX. This treatment provides rapid clinical and parasitologic cure, with few recurrences. In patients with AIDS, chronic suppression with TMP-SMX may be required. Ciprofloxacin has been used successfully in persons with sulfa allergy (see Table 82-11).

MISCELLANEOUS PARASITIC AGENTS

Microsporidia

More than 100 genera and 1000 species of microsporidia exist in the phylum Microspora. Most species infect insects, birds, and fish. Only 12 species have been reported to infect humans, and of these, only two, *Enterocytozoon bieneusi* and *Encephalitozoon intestinalis*, have been found to cause diarrhea in humans. Microsporidia are obligate intracellular protozoa.[33,35,41,73,81,128,133,139,186,213,214]

Transmission is thought to be fecal-oral or urinary-oral and the infection zoonotic. Spores are environmentally resistant, so waterborne transmission also occurs. Prevalence of microsporidiosis in patients who have AIDS and chronic diarrhea is 7% to 50%. Diarrhea from microsporidia has been reported in travelers to the tropics. Clinical manifestations of intestinal microsporidiosis are chronic diarrhea, loss of appetite, weight loss, malabsorption, and fever. Acute self-limited diarrhea has been reported in immunocompetent hosts. Other infections include keratoconjunctivitis, hepatitis, peritonitis, myositis, central nervous system infection, urinary tract infections, sinusitis, and disseminated disease.

Diagnosis involves trichrome staining of concentrated stools or intestinal biopsy sampling. Electron microscopy is considered the gold standard. Immunologic and molecular biologic techniques are still under evaluation. The most effective drug against most species is albendazole (400 mg twice daily for 2 to 4 weeks). Other drugs that show different efficacies include atovaquone, metronidazole, furazolidone, azithromycin, itraconazole, and sulfonamides.

Sarcocystis

Few human infections with *Sarcocystis* have been reported.[35,81,182,213] Infection may be asymptomatic or associated with diarrhea, abdominal pain, nausea, and bloating. Symptoms typically improve within 48 hours of onset of illness. Diagnosis is based on identification of cysts in concentrated feces. No specific treatment has been established, but TMP-SMX and furazolidone have had variable efficacy (see Table 82-11).

Balantidium

Balantidium coli is a rare pathogen in humans.[182,213] It is the largest and only ciliated protozoa that infects humans. The life cycle involves only trophozoite and cyst stages. Many aspects of the epidemiology are unclear. Pigs appear to be the primary reservoir, although other animals have been implicated. There is no intermediate host. Transmission is fecal-oral, and water is the most common vehicle. Infection is most common in tropical and subtropical regions with poor hygiene. Clinical features resemble those of amebiasis, with a spectrum including asymptomatic infection, chronic intermittent diarrhea of variable intensity, acute dysentery with mucosal invasion, and rarely, metastatic abscesses. Diagnosis is made by observing the organism in a wet mount sample of stool. Trophozoites are seen much more often than are cysts. Recommended treatment is tetracycline or metronidazole. Nitazoxanide is an alternative (see Table 82-11).

Blastocystis

The role of *Blastocystis hominis* in diarrheal disease is still controversial.[132,196,199,213] The life cycle of *B. hominis* continues to be debated. The organism is frequently identified in stool samples by its characteristic appearance, but often is not directly correlated with symptoms, which might be caused by other, undetected pathogens. However, well-defined outbreaks of *B. hominis* have been reported. Treatment is not warranted in asymptomatic infections. When found in large numbers as the sole pathogen, *B. hominis* is suspected as the potential etiologic agent of diarrheal illness. In these cases, therapy may be attempted with nitazoxanide or metronidazole (see Table 82-11).

Dientamoeba

Dientamoeba fragilis occasionally causes diarrhea, occurring characteristically in tropical regions.[109,182,213] It may be found in stools of persons without enteric symptoms. Because cyst forms have not been identified, the mode of transmission remains unknown. Illness caused by the parasite typically resembles giardiasis. Identification can be done from stool samples, a fixative, and almost any type of stain. Treatment of *D. fragilis* is effective with iodoquinol and tetracyclines. There are also reports of successful treatment with metronidazole, paromomycin, and secnidazole[182,213] (see Table 82-11).

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