Chapter 37

DISEASES TRANSMITTED BY FOOD, WATER, AND SOIL

DAVID N. TAYLOR, MD
SHARON L. LUDWIG, MD, MPH
LEONARD N. BINN, PHD
JAMES FLECKENSTEIN, MD
JOSE L. SANCHEZ, MD, MPH
WILLIAM A. PETRI, JR., MD, PHD
JOANNA M. SCHAENMAN, PHD
CHARLES W. HOGE, MD
JOHN H. CROSS, PHD
W. PATRICK CARNEY, MPH, PHD
NAOMI E. ARONSON, MD
DUANE R. HOSPENTHAL, MD, PHD
MAY-ANN LEE, PHD
ERIC P. H. YAP, MBBS, DPHIL

D.N. Taylor, MD, Colonel, Medical Corps, US Army (Retired); Department of International Health, Johns Hopkins University Bloomberg School of Public Health, 624 North Broadway, Baltimore, MD 21205; Formerly, Research Coordinator for Prevention of Diarrheal Disease, Division of Communicable Diseases and Immunology, Walter Reed Army Institute of Research, Silver Spring, Maryland

S.L. Ludwig, MD, MPH, Commander, US Public Health Service, Operational Preventive Medicine/Epidemiology Staff Officer, US Coast Guard Commandant (G-WKH-1), 2100 Second Street SW, Washington DC 20593

L.N. Binn, PhD; Supervisory Research Microbiologist, Department of Virus Diseases, Division of Communicable Diseases and Immunology, Walter Reed Army Institute of Research, Silver Spring, MD 20910-7500

J. Fleckenstein, MD; Assistant Professor of Medicine, Departments of Medicine and Molecular Sciences, Infectious Disease Division, University of Tennessee Health Science Center and Veterans Affairs, 1030 Jefferson Avenue, Memphis, TN 38104; Formerly: Lieutenant Colonel, Medical Corps, US Army; Infectious Disease Service, Walter Reed Army Medical Center, Washington, DC 20307

J.L. Sanchez, MD, MPH, Colonel, Medical Corps, US Army; Medical Epidemiologist and Military Chief, Global Epidemiology and Threat Assessment, HIV Research Program, Walter Reed Army Institute of Research, 13 Taft Court, Rockville, MD 20850

W.A. Petri, Jr., MD, PhD; Professor of Medicine, Microbiology, and Pathology, Division of Infectious Diseases, Room 2115, MR4 Building, University of Virginia Health Sciences Center, Charlottesville VA 22908

J.M. Schaenman, PhD; Chief Resident, Department of Internal Medicine, Stanford University School of Medicine, 300 Pasteur Drive, Stanford, CA 94305

C.W. Hoge, MD, Colonel, Medical Corps, US Army; Chief, Department of Psychiatry and Behavioral Sciences, Division of Neuropsychiatry, Walter Reed Army Institute of Research, Silver Spring, MD 20910-7500; Formerly, Principal Investigator, Department of Enteric Infections, Division of Communicable Diseases and Immunology, Walter Reed Army Institute of Research

J.H. Cross, PhD; Professor of Tropical Public Health, Uniformed Services University of the Health Sciences, 4301 Jones Bridge Road, Bethesda MD 20814-4799

W.P. Carney, MPH, PhD, Captain, MSC, US Navy (Ret.); Professor, Department of Preventive Medicine and Biometrics, Uniformed Services University of the Health Sciences, 4301 Jones Bridge Road, Bethesda, MD 20814-4799

N.E. Aronson, MD, Colonel, Medical Corps, US Army; Director, Infectious Diseases Division, Room A3058, Uniformed Services University of the Health Sciences, 4301 Jones Bridge Road, Bethesda, MD 20814

D.R. Hospenthal, MD, PhD, Lieutenant Colonel, Medical Corps, US Army; Chief, Infectious Disease Service, Brooke Army Medical Center, 3851 Roger Brooke Drive, Fort Sam Houston, TX 78234-6200

M-A. Lee, PhD; Programme Head, Defence Medical and Environmental Research Institute, @DSO National Laboratories, 27 Medical Drive, Singapore 119597

E.P.H. Yap, MBBS, DPhil; Programme Head, Defence Medical and Environmental Research Institute, @DSO National Laboratories, 27 Medical Drive, Singapore 119597

DIARRHEA CAUSED BY *ESCHERICHIA COLI*

Escherichia coli is a gram-negative, facultatively anaerobic, rod-shaped bacterium that is generally a normal, nonpathogenic inhabitant of the intestine of mammals. It is a member of the large family of bacteria known as the Enterobacteriaceae, which also includes salmonellae and shigellae. *E coli* that compose the normal intestinal flora may become pathogenic when seeded outside the intestine, as a cause of sepsis, focal infections, or wound infections. *E coli* may acquire virulence factors that render them pathogenic to humans in the gut. These virulence factors are usually stabile genetic characteristics that are passed on from generation to generation resulting in a stable clone or strain.

Four general categories of *E coli* have been recognized as enteric pathogens:[1] Enterotoxigenic *E coli* (ETEC), enterohemorrhagic *E coli* (EHEC), enteroinvasive *E coli* (EIEC), and enteropathogenic *E coli* (EPEC). EPEC organisms are part of a larger group generally referred to as enteroadherent *E coli*.

Enterotoxigenic *Escherichia coli*

Introduction and Military Relevance

ETEC is one of the most common causes of diarrheal diseases among children in developing countries[2,3] and is the most common cause of traveler's diarrhea acquired in those countries.[4,5] Diarrheal disease has accompanied military campaigns for centuries,[6] but traveler's diarrhea was only described as a clinical syndrome after World War II when travel to exotic locations by air became more feasible.[7] It was not until the early 1970s that ETEC was recognized as an enteric pathogen in both humans and animals.[8] One of the first known ETEC outbreaks occurred in British troops stationed in Aden in the Persian Gulf region in the 1960s.[9] Rowe identified a single *E coli* serotype (O148:H28) as the cause of illnesses that occurred in the first few weeks of the deployment. These strains of *E coli*, as well as others (O6:H16) from US military forces serving in Vietnam, were shown to be pathogenic in volunteers and were subsequently found to produce enterotoxins.[10] Ever since, ETEC has been found to be an important cause of diarrhea during many deployments in the developing world, most notably the Middle East and Africa (Table 37-1). Diarrheal disease was a major problem during the Persian Gulf War,[11] and ETEC and *Shigella* organisms caused the majority of these illnesses (Table 37-2).

Description of the Pathogen

ETEC produces either a heat-labile toxin (LT), a heat-stable toxin (ST), or both toxins (LT/ST). The isolation rates of ETEC producing these toxins from persons with diarrhea varies from survey to sur-

TABLE 37-1

ISOLATION RATES OF ENTEROTOXIGENIC *ESCHERICHIA COLI* AMONG PERSONNEL ON MILITARY DEPLOYMENTS (1987–1993)

Exercise (Country)	Year	Number cultured	Percentage ETEC	Reference
Operation Restore Hope (Somalia)	1992-1993	113	16	1
Operation Desert Shield (Saudi Arabia)	1990	432	29	2
Operation Bright Star (Egypt)	1989	104	57	3
USS Kennedy (Alexandria, Egypt*)	1988	118	34	4
Operation Bright Star (Egypt)	1987	183	33	5

*port visit

References: (1) Sharp TW, Thornton SA, Wallace MR, et al. Diarrheal disease among military personnel during Operation Restore Hope, Somalia, 1992-1993. *Am J Trop Med Hyg*. 1995;52:188–193. (2) Hyams KC, Bourgeois AL, Merrell BR, et al. Diarrheal disease during Operation Desert Shield. *N Engl J Med*. 1991;325:1423–1428. (3) Taylor DN, Sanchez JL, Candler W, Thornton S, McQueen C, Echeverria P. Treatment of travelers' diarrhea: Ciprofloxacin plus loperamide compared with ciprofloxacin alone; a placebo-controlled, randomized trial. *Ann Intern Med*. 1991;114:731–734. (4) Scott DA, Haberberger RL, Thornton SA, Hyams KC. Norfloxacin for the prophylaxis of travelers' diarrhea in U.S. military personnel. *Am J Trop Med Hyg*. 1990;42:160–164. (5) Haberberger RL Jr, Mikhail IA, Burans JP, et al. Traveler's diarrhea during joint American–Egyptian armed forces exercises in Cairo, Egypt. *Mil Med*. 1991;156:27–30.

TABLE 37-2

BACTERIAL ENTEROPATHOGENS IDENTIFIED IN STOOL SAMPLES FROM 432 US MILITARY PERSONNEL WITH ACUTE GASTROENTERITIS DURING OPERATION DESERT SHIELD

Enteropathogen	Isolation Rate	
	Number	Percent
ETEC*		
Heat-labile toxin	15	3.5
Heat-stable toxin	44	10.2
Heat-labile and heat-stable toxin	64	14.8
Mixed ETEC infection	2	0.5
Total of ETEC	125	28.9
Shigella organisms		
S dysenteriae	4	0.9
S flexneri	12	2.8
S boydii	8	1.9
S sonnei	89	20.6
Total of *Shigella* organisms	113	26.2
EIEC†	3	0.7
Salmonella	7	1.6
Campylobacter	2	0.5

*Enterotoxigenic *E coli*
†Enteroinvasive *E coli*
Reprinted from: Hyams KC, Bourgeois AL, Merrell BR, et al. Diarrheal disease during Operation Desert Shield. *N Engl J Med*. 1991;325:1423–1425.

vey, but in most studies the isolation rates of each toxin type are approximately equal.[12] Strains producing ST or LT/ST are more pathogenic than strains producing only LT and belong to a small number of O:H serotypes; most have recognized intestinal cell adherence or colonization factors.[1] Strains producing only heat-labile toxin belong to a much larger number of O:H serotypes and often do not possess known colonization factors.[12]

Epidemiology

Transmission. Most epidemiologic studies have implicated contaminated foods as the main source of ETEC. The human reservoir is large, and fecal spread to food via hands is probably the main method of contamination.[13,14] ETEC can also be isolated from domestic animals, and contamination of meats with intestinal contents may be another important source in food. Vegetables can be contaminated with human feces used as fertilizer or with untreated sewage. During the Persian Gulf War, vegetables acquired from local markets were an important source of contamination. Decontamination of salad vegetables in chlorinated water was unsuccessful because the volume of food required was too great to allow for the proper contact time.[15]

Geographic Distribution. In tropical climates, disease caused by ETEC occurs year-round; in more temperate climates, disease is more common in the warmer summer months. In the developed world, ETEC is a rare cause of diarrhea, and almost all of the epidemiologic data that are available is from foodborne or waterborne outbreaks.[16–18]

Incidence. Diarrhea caused by ETEC is a major health problem for infants and children in the developing world and is the major cause of traveler's diarrhea in those traveling to the developing world. Studies in areas of the developing world where hygiene is poor suggest that exposure to ETEC is nearly constant. Under these circumstances, the level of immunity is the key factor in determining susceptibility to disease. Infants and newly arriving travelers have the least immunity and more frequently develop severe diarrhea when infected. After repeated exposure, illnesses become less severe or less symptomatic. Because ETEC is endemic in developing countries, outbreaks are rare except in new arrivals, such as travelers. During the build-up stages of the Persian Gulf War (August to October 1990), diarrhea affected as many as 5% of the service member strength per week (Figure 37-1).

Pathogenesis and Clinical Findings

ETEC can cause a severe watery diarrhea similar to cholera. ETEC must adhere to the small intestinal mucosa to cause disease. ETEC adherence is mediated by fimbriae on the surface of the organism. These fimbriae, called colonization factor antigens, are encoded by plasmids that usually encode heat stable toxin and often heat labile toxin.[1] The pathophysiology of diarrhea caused by ETEC is primarily determined by the production of these enterotoxins. Similar to cholera toxin, heat labile toxin is composed of one A subunit and 5 B subunits that bind to ganglioside GM1 on eucaryotic cell surfaces. The A subunit undergoes proteolytic cleavage that produces two fragments designated A1 and A2. The A1 fragment activates adenylcyclase and increases cyclic adenosine monophosphate through adenosine diphosphate ribosylation of the cell membrane, which causes fluid secretion by inhibiting sodium and chloride absorption and chloride secretion.

ETEC causes a secretory diarrhea with fluid and electrolyte loss without evidence of inflammation. The amount of diarrhea may be mild or massive, cholera-like purging. Generally, an inoculum of about 10^8 organisms is required to infect 50% of persons exposed.[10] Disease severity increases with inoculum size and may also be associated with the quantity of toxin produced by the organism. In travelers, disease occurs most commonly in the first weeks of travel. The incubation period ranges from 12 to 48 hours and shortens with higher inoculum size. Symptoms that accompany ETEC diarrhea are malaise, anorexia, abdominal cramping, nausea, vomiting in 25%, and low-grade fever in 30%. Untreated the illness lasts 1 to 5 days but can last as long as 2 weeks. Stool frequency is usually around 10 episodes per day for 1 or 2 days.[7,19] Complications are usually associated with dehydration. These include lethargy, muscle cramping, loss of consciousness, renal failure, and death. Infants and children may have a decreased absorptive capacity of the small bowel for several weeks after the illness, which can lead to malnutrition.

Diagnostic Approaches

E coli is a gram-negative rod that grows readily on routine culture media under aerobic conditions. *E coli* is identified on MacConkey agar as a lactose-fermenter. *E coli* can be isolated after several days from fecal specimens preserved in Cary-Blair transport media. There is no biochemical or serological

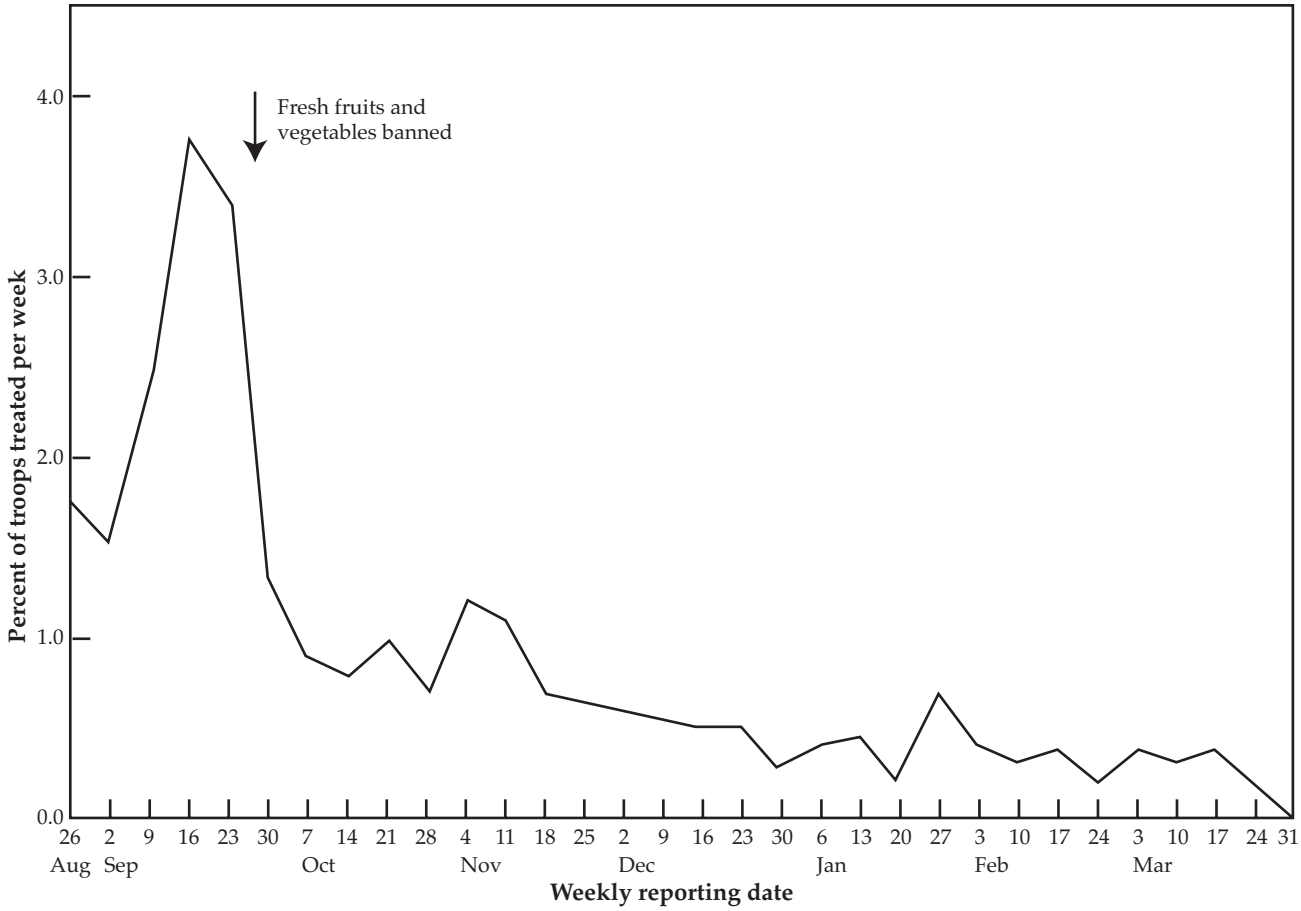

Fig. 37-1. This graph shows the weekly rates of gastroenteritis among 40,000 Marine Corps ground troops stationed in northeast Saudi Arabia in 1990 and 1991. The arrow indicates when fresh produce was removed from their diet, which was followed by a sharp decrease in the diarrheal disease incidence.
Reprinted with permission from: Hyams KC, Hanson K, Wignall FS, Escamilla J, Oldfield EC III. The impact of infectious diseases on the health of US troops deployed to the Persian Gulf during Operations Desert Shield and Desert Storm. *Clin Infect Dis*. 1995;20:1497–1504.

test that can be used to identify all ETEC serotypes, therefore methods to detect the heat-labile and heat-stable toxins must be used. The traditional methods have been Y1 or CHO cell culture assays to identify heat-labile toxin and the suckling mouse assay for heat-stable toxin.[19] These assays are difficult to maintain in most laboratories and are being replaced with DNA hybridization assays.[20] The hybridization can be detected using radioisotopes or by an enzyme-linked system. No commercial assays are available to detect ETEC.

Recommendations for Therapy and Control

In developing countries, diarrhea caused by ETEC is a disease of children younger than 5 years old. The mainstay of treatment is replenishing fluid and restoring electrolyte balance.[21] This can be accomplished with oral rehydration solution or, if that fails, with intravenous fluid. Breast feeding and the use of rice-based oral rehydration solution may provide some protection against malabsorption.[22] In addition, the use of vitamin A and zinc may prevent or shorten the illness.[23]

For travelers, other prophylactic and treatment modalities are useful. Treatment of traveler's diarrhea is aimed at decreasing the total amount of diarrhea and the number of days of illness. Many of the agents that can be used for prophylaxis can also be effectively used as treatment. Fluoroquinolones (eg, ciprofloxacin, norfloxacin) taken twice daily for 3 days are currently regarded the drugs of choice because of increased resistance among ETEC strains to trimethoprim-sulfamethoxazole (TMP/SMX) and the tetracyclines.[24]

Antimotility drugs also have a role in treatment. US military personnel in Thailand responded more rapidly to ciprofloxacin plus loperamide than to ciprofloxacin alone.[25] Loperamide acts more rapidly than antibiotics, so loperamide given in combination with ciprofloxacin provides the most rapid improvement. This regimen is generally recognized as the treatment of choice for adults.[24]

Good personal hygiene, in particular hand washing, is important in preventing all enteric infections. The warning to travelers to "cook it, boil it, peel it, or don't eat it" is good advice and reminds the individual that food left out at room temperature can easily become contaminated. To ensure that bacteria have been killed, foods should be served hot to the touch. Local water may not be adequately chlorinated and therefore should be avoided unless reboiled or chlorinated. Bottled water and boiled water are usually safe. Careful food inspection and food handling procedures are particularly important for military units working in the tropics. If food is bought from local sources, it must be assumed to be contaminated. Meats need to be prepared away from salad vegetables to prevent cross-contamination. Local produce should be decontaminated with chlorinated water.

Prophylaxis with antimicrobial agents (eg, doxycycline, TMP/SMX) is generally well tolerated but is only effective in areas where enteric pathogens are still susceptible to these antibiotics. Ciprofloxacin and norfloxacin once daily are currently the most effective prophylactic agents,[26] but because these agents are also used for treatment, they are not recommended for most travelers and all long-term residents abroad.[27] Bismuth subsalicylate in fairly large doses appears to decrease the incidence of diarrhea,[24] but this regimen is expensive, time consuming, and only partially effective.

The heterogeneity of the serotypes, adherence factors, and toxins have made vaccine development a difficult task. An oral, whole *E coli* cell plus CT B subunit vaccine is being developed.[28]

Enterohemorrhagic *Escherichia coli*

Introduction and Military Relevance

E coli serotype O157:H7, the most famous EHEC serotype, was first recognized as a pathogen in 1982 when two geographically separated outbreaks of hemorrhagic colitis associated with eating undercooked beef from a fast food restaurant occurred.[29] Since 1982, many well-described outbreaks and numerous sporadic cases have been reported, including a large outbreak of more than 600 cases again associated with undercooked hamburgers from a fast food restaurant in the northwestern United States.[30] Initial reports identified most cases from the northern United States (most frequently the Pacific Northwest) and Canada, but increasing awareness has identified cases throughout the United States. Outbreaks of EHEC have occurred in the United Kingdom, Germany, Argentina, and Japan.[31] Foodborne transmission has been associated with undercooked ground or roast beef, unpasteurized milk, improperly processed water and cider, contaminated mayonnaise, and vegetables fertilized with manure or irrigated with tainted water.[30] Service members consume as much, if not more, of these foodstuffs as their civilian neighbors and so are at risk of EHEC infection.

Description of the Pathogen

The prototype EHEC isolate is serotype O157:H7. A number of other serotypes of *E coli* causing an identical disease spectrum have been reported, including O26:H11, O111:H8, and O111:NM. EHEC is not invasive, nor does it produce enterotoxins. However, EHEC, like other enteric pathogens, must adhere to the intestinal epithelium to cause disease. The elaboration of cytotoxins distinguishes EHEC from other *E coli* pathogens.[32] The cytotoxins produced by EHEC are known as Shiga-like toxin 1 and 2 (for their similarities to Shiga toxin isolated from *Shigella dysenteriae* 1 [Shiga's bacillus]) or verotoxin 1 and 2 (for their effects on Vero tissue culture cells). EHEC strains can produce either of the Shiga-like toxins or both of them.

Epidemiology

Transmission and Geographic Distribution. Most outbreaks are foodborne, and ground beef is the most frequently implicated source. A cluster of cases in Connecticut were associated with a particular retail supermarket.[33] This study emphasizes the importance of meat-handling practices and the need for frequent decontamination. Widespread testing for *E coli* O157:H7 led to one of the largest recalls of frozen ground beef in 1997.[34] Several outbreaks have been associated with unpasteurized apple juice and sprouts.[35,36] Another outbreak was associated with swimming in a contaminated lake in Oregon.[37] *S sonnei* was also implicated in this outbreak. The findings demonstrated that transmission of these two organisms can be very similar. Although food, especially ground beef, seems to be the most important vehicle for acquisition of infection, person-to-person transmission has also been described.[38] Cattle appear to be the most important reservoir for EHEC. Three percent of dairy calves in the United States are estimated to be infected.[30]

Incidence. With the development of simple microbiologic screening tests has come the awareness that, at least in North America, *E coli* O157:H7 is a common cause of infectious bloody diarrhea. In a prospective, population-based study in Washington state,[39] *E coli* O157:H7 was identified in 25 (0.4%) of 6,485 stool specimens, and isolation of this serotype was associated with illness in all patients. In this study, and in two other studies conducted in Canada,[30] the isolation rates of *E coli* O157:H7 were similar to those for other well-recognized enteropathogens, such as shigella, salmonella, and campylobacter, and ranged from 0.4% to 1.9%. Disease caused by EHEC occurs at all ages; however, the very young and very old are more likely to have severe disease or to develop complications such as hemolytic-uremic syndrome. The incidence of nonbloody diarrhea or asymptomatic infection caused by EHEC is not known.

Pathogenesis and Clinical Findings

EHEC, most commonly *E coli* O157:H7, is an important cause of nonbloody diarrhea, hemorrhagic colitis, and hemolytic-uremic syndrome.[40–42] EHEC produces two types of Shiga-like toxins, which mediate both hemorrhagic colitis and hemolytic uremic syndrome. There is a 5- to 9-day interval between the onset of diarrhea and the onset of hemolytic uremic syndrome. Reports from outbreaks and sporadic cases indicate that bloody diarrhea is the most common symptom of illness caused by EHEC. Some patients may have mild disease with nonbloody diarrhea. The frequency with which mild disease occurs is not known, although approximately 25% of cases in outbreaks may have nonbloody diarrhea.[30] The disease is typically ushered in by severe abdominal cramping and watery diarrhea, which is soon followed by grossly bloody stools. The amount of blood in the stool may range from streaking to frank blood. Indeed, many of the initial cases of hemorrhagic colitis were confused with gastrointestinal bleeding. The duration of bloody diarrhea is generally 2 to 4 days.[40] Vomiting occurs in approximately one third to one half of persons with bloody diarrhea. Fever occurs in the minority of patients and is usually low-grade (< 39°C [102°F]). Fecal leukocytes may be present but are not a common feature. The severity of abdominal cramping and the frequent absence of fever can lead clinicians to consider other diagnoses, such as acute abdomen, inflammatory bowel disease, ischemic bowel, and intussusception. Failure to consider EHEC may lead to unnecessary diagnostic and surgical procedures.

Hemolytic-uremic syndrome, consisting of hemolytic anemia and acute renal failure, is the most serious complication of disease caused by EHEC. Most outbreaks report hemolytic-uremic syndrome in less than 10% of ill persons[43] and almost always in young children and the elderly. *E coli* O157:H7 has also caused illness in elderly patients that is recognized by clinicians as thrombotic thrombocytopenic purpura. Hemolytic-uremic syndrome or thrombotic thrombocytopenic purpura in association with EHEC in the elderly carries a high risk of mortality.[42]

Diagnostic Approaches

On routine culture media, EHEC cannot be visually differentiated from nonpathogenic *E coli* flora. However, because *E coli* O157:H7 ferments sorbitol slowly and since only 6% to 7% of all *E coli* is sorbitol-negative, the use of MacConkey or similar media containing 1% sorbitol provides a simple screening method. Sorbitol-negative colonies can be picked and agglutinated with commercially available O157 antisera for presumptive identification. Definitive identification requires serotyping and assays for toxin production.

Recommendations for Therapy and Control

Although *E coli* O157:H7 is sensitive to most antibiotics in vitro, antibiotics have not been shown to limit the duration of the illness or ameliorate the symptoms.[41] The illness is self limited, but the time to resolution can vary from a few days to several weeks. Treatment is supportive. Immune globulin preparations have been reported to be beneficial in a few cases of hemolytic-uremic syndrome,[42] and the finding that commercially available preparations contain anticytotoxin-neutralizing antibodies supports further investigation of this therapeutic modality. Oral ingestion of a synthetic receptor for Shiga-like toxin may be useful in binding unbound toxin and may prevent hemolytic-uremic syndrome.[44]

The catastrophic nature of EHEC illness in elderly patients emphasizes the importance of impeccable technique in food preparation and early recognition and intervention in outbreaks. All *E coli*, including EHEC, are frequent contaminants of ground beef and may remain viable in undercooked food. In response to an increase in cases in 1993, the Food and Drug Administration issued an advisory that all ground meat be uniformly heated to at least 71°C (160°F) for at least 8 seconds to kill all contaminating *E coli*.[45,46] Cooking procedures should be monitored to assure that the time and temperature parameters are met. Milk and cider should be pasteurized, and drinking water should be adequately disinfected.

Enteroinvasive *Escherichia coli*

Introduction and Military Relevance

Certain strains of *E coli* are capable of penetrating cells of the intestinal epithelium, producing a disease spectrum virtually identical to that caused by *Shigella* organisms. The incidence of disease caused by EIEC is not well studied, primarily because of difficulties in identification of the organism. It appears to be a relatively infrequent cause of sporadic diarrhea and has been found less often than *Shigella* organisms in studies in which both pathogens have been looked for.[43] Military personnel are at risk under field conditions similar to their risk of shigellosis. Outbreaks have occurred in military settings in Israel.[45]

Description of the Pathogen

Strains recognized as EIEC belong to a number of *E coli* serotypes, including O28ac, O29, O112ac, O124, O136, O143, O144, O147, O152, O164, and O167.[1] The EIEC serotypes are distinct from those of ETEC, EPEC, and EHEC. There exists no simple method to reliably identify EIEC. EIEC shares many microbiologic features with *Shigella* organisms. Although many EIEC serotypes do not ferment lactose and most are lysine decarboxylase–negative and nonmotile, no biochemical test is absolutely specific in identifying these organisms. There are also cross-reactions between EIEC and *Shigella* O antigens, which may result in misidentification of some lactose-negative EIEC serotypes that agglutinate in *Shigella* antisera. The lactose-positive strains cannot be visually differentiated from nonpathogenic *E coli* flora.

Epidemiology

Outbreaks of illness due to EIEC from contaminated food have been described[47,48] but are infrequent. Person-to-person transmission has been described[49] and may be important for sporadic cases, but most cases have been associated with outbreaks that have been foodborne. EIEC is a recognized enteric pathogen in pediatric populations of some developing countries[47] and has been detected in travelers with diarrhea.[50]

Pathogenesis and Clinical Findings

The pathogenetic mechanisms of EIEC are similar to those of *Shigella* organisms. As with shigellae, EIEC possesses a large virulence plasmid, which confers the capacity for epithelial cell invasion and is necessary for full pathogenicity. The large virulence plasmids of EIEC and *Shigella* organisms are functionally identical and exhibit considerable DNA homology.[51] Like *Shigella* organisms, EIEC does not produce enterotoxins. One notable difference between EIEC and *Shigella* organisms is that a much larger inoculum of the former is required to cause disease (10^8 versus about 10^2 organisms, respectively);

however, this has only been definitively shown for one EIEC strain.[10]

Although the illness caused by EIEC cannot be differentiated from shigellosis, the overall severity of illness is probably less with EIEC.[43] Diarrhea, fever, nausea, and abdominal cramping are the most common symptoms.[10,47,48] Bloody diarrhea and severe illness requiring hospitalization are uncommon, and the disease is self-limited.

Diagnostic Approaches

When conventional methods do not identify pathogens associated with invasive disease, random lactose-positive *E coli* colonies can be picked and saved for further identification by a reference laboratory. The individual colonies can then be tested for invasiveness in the definitive biological test of guinea pig keratoconjunctivitis (Sereny test). An enzyme-linked immunosorbent assay that detects the presence of outer membrane proteins associated with the virulence plasmid has been shown to be a useful screening tool and correlates closely with a positive keratoconjunctivitis test.[43] DNA probes based on the virulence plasmid[43,52] have been shown to be sensitive epidemiologic tools for rapidly screening large numbers of *E coli* samples to identify EIEC.

Recommendations for Therapy and Control

Little is known about the antibiotic-resistance patterns of EIEC or about the usefulness of antibiotic treatment for EIEC-related illness. Keeping in mind the other similarities of EIEC-related illness to shigellosis, though, significant symptomatic illness with fever and dysentery should probably be treated with antibiotics such as TMP/SMX, ampicillin, or one of the quinolones.

Enteropathogenic *Escherichia coli* and Other Types of Enteroadherent *Escherichia coli*

Introduction and Military Relevance

EPEC strains are a common cause of diarrhea, particularly among children living in developing countries and may be a cause of traveler's diarrhea as well. It is significant for the military in that it is one of the many undiagnosed causes of diarrheal disease in the developing world. The first association with *E coli* and enteric infection was made in the 1940s when certain serotypes of *E coli* were incriminated by epidemiologic methods as important causes of infantile summer diarrhea and epidemic diarrhea in nurseries.[53] The most frequently incriminated serogroups (ie, O55, O86, O111, O114, O119, O125, O126, O127, O128, O142) were termed "enteropathogenic *E coli*" or EPEC.[54]

Description of the Pathogen

EPEC organisms do not produce enterotoxins or cytotoxins and do not invade and destroy intestinal epithelial cells. EPEC is now defined as a class of *E coli* capable of causing diarrhea in humans that attaches to and effaces the microvilli of enterocytes but does not produce high levels of Shiga-like toxins.[55] The in vitro adherence pattern of EPEC on HEp-2 cells is described as localized adherence.[56] *E coli* not belonging to the EPEC serotypes can adhere in patterns described as diffuse or enteroaggregative, and the role of these pathogens in causing diarrheal disease for adults in the developing world is unclear. One such strain was isolated from a traveler to Mexico.[57,58] The best documented association was a foodborne outbreak in 1991 in Minnesota that was associated with *E coli* O39 that produced the enteroaggregative heat-stabile toxin (EAST).[46] This class of *E coli* may be one of the undocumented causes of diarrhea in the developing world.

Epidemiology

EPEC and other adherent *E coli* possess a virulence factor known as enteroadherent factor (EAF). In a case-control study of endemic diarrheal disease, EAF-positive *E coli* was isolated from 7% of 272 Thai children under 6 months of age with diarrhea and 3% of controls.[3] There was no association with diarrhea in children older than 6 months of age. The two most commonly isolated EAF-positive *E coli* were classic EPEC serotypes O119:H6 and O127:H6. Overall, of the 64 EAF-positive *E coli* samples, 35 belonged to EPEC serogroups (21 were EPEC O:H serotypes) and 29 did not belong to EPEC serogroups. It is not clear if EPEC organisms of nonclassic serotypes are as pathogenic to humans as EPEC organisms of classic serotypes. Diffuse *E coli* was not associated with diarrhea. In Brazil, localized-adherence *E coli* was isolated from 23% of infants younger than 1 year old with diarrhea and 2% of controls, a significant difference.[59]

Pathogenesis and Clinical Findings

EPEC strains appear to cause disease by tightly adhering to the intestinal mucosa of animals and humans. Biopsies of the small bowel reveal that EPEC has the ability to adhere to the intestinal epithelium in discrete microcolonies, causing a destruction of the cell below. The histopathologic lesion is caused by

EPEC's adherence to the enterocyte surface.[60] In electron microscopic studies of EPEC, Knutton and colleagues[61] have found that EPEC causes effacement at the apical enterocyte membrane and localized destruction of brush border microvilli of the intestinal epithelial cell. The enterocyte membrane forms a pedestal or platform on which the bacteria adhere. Effacement appears to be a crucial step in the pathogenesis of EPEC diarrhea and requires the 80-kilobase EAF plasmid. Strains lacking the EAF plasmid no longer adhere to epithelial cells and are less virulent.[62] EPEC strains express bundle-forming pili that form a meshwork to stabilize the bacterial colony on the epithelium.[63] The gene coding for bundle-forming pili filament is encoded on the EAF plasmid.

In outbreaks occurring in infants in nurseries and daycare centers, infections can be severe and similar to rotavirus infection. In the developing world, EPEC may be a cause of acute and chronic diarrhea.[64] In adult volunteers, EPEC causes watery diarrhea 7 to 16 hours after ingestion of a large inoculum.[62] Three to four liters of diarrheal stool may be lost during the 2-day illness. Abdominal cramps, nausea, vomiting, malaise, and fever can also commonly occur.

Diagnostic Approaches

DNA probes for genes associated with virulence are now available for use in large epidemiologic investigations.[65,66] At present DNA probes are the most practical method for screening (followed by tissue culture assays) for further differentiating enteroadherent strains. *E coli* serotyping is also useful but can only be performed in a few reference laboratories.

Recommendations for Therapy and Control

The treatment guidelines for ETEC infection can be used for EPEC infection.

Very little is known about animal reservoirs for enteroadherent *E coli*. During EPEC outbreaks, standard public-health and infection-control procedures are important for interrupting transmission. Isolation of cases, cohorting by area and nursing personnel, institution of strict handwashing procedures, and prevention of common exposure to equipment, bedding, or solutions are all indicated.

[David N. Taylor]

CAMPYLOBACTER ENTERITIS

Introduction and Military Relevance

Campylobacter organisms are one of the most common causes of acute bacterial diarrhea in the world. They affect children in developing countries and military personnel and travelers to developing countries. They are also one of the most common bacterial causes of diarrhea among all ages in developed countries and have an epidemiology and food-borne transmission similar to *Salmonella* organisms. *Campylobacter jejuni* and *C coli* have their natural reservoirs in the intestinal tracts of wild and domestic animals, predominantly chickens and cattle. Transmission of the infection to humans occurs through ingestion of contaminated chicken, other meats, or milk or by direct contact with infectious animal feces. The disease is characterized by acute watery diarrhea or dysentery, fever, and abdominal pain that is usually self-limited over a few days. Military units have been affected through eating improperly cooked chicken, and a large waterborne outbreak occurred on a military post when a water tower became contaminated from nesting birds.[67]

Description of the Pathogen

Campylobacter species are gram-negative, curved, rod-shaped bacteria with a polar flagellum. *C jejuni* is the species most commonly associated with diarrhea. Other species associated with diarrhea include *C coli*, *C laridis*, *C hyointestinalis*, and *C upsaliensis*.[68] These species can be distinguished biochemically from *C jejuni* by their inability to hydrolyze hippurate. These hippurate-negative or atypical hippurate-positive *Campylobacter* strains may account for 5% to 15% of the total *Campylobacter* isolated from patients with diarrhea.[69,70]

Campylobacter organisms are microaerophilic: they grow best in reduced oxygen concentrations of about 5%. They will not grow in atmospheres with ambient oxygen or under anaerobic conditions. The importance of *Campylobacter* species as human pathogens was overlooked until the 1970s because they do not grow on routine bacteriological media for stool pathogens.[71] Selective growth conditions are used in identifying *Campylobacter* organisms to take advantage of their microaerophilic and thermophilic (42°C) characteristics. *C jejuni* and *C coli* are naturally resistant to vancomycin, polymyxin, and the cephalosporins. These antibiotics can be incorporated into the media to further select these *Campylobacter* species from other enteric flora. Two different serotyping schemes are used to distinguish among strains of *C jejuni and C coli*.[72] Over 100 Lior serotypes based on the heat-labile flagellar proteins have been described, and a scheme based on heat-stable, or Penner, serotypes has identified 60 different serotypes.

Epidemiology

Transmission and Geographic Distribution

Transmission of infection to humans occurs by ingestion of the organism, usually in contaminated food. Outbreaks affecting both children and adults may be traced to contaminated sources of drinking water, poultry, eggs, unpasteurized milk, and raw hamburger meat.[73] Chicken bought in retail stores can be contaminated with *Campylobacter* organisms, and improper cooking can lead to infection. Direct contact with animal feces is probably important in areas of poor sanitation or close contact with domestic animals. Waterborne outbreaks have been associated with surface water contamination and contamination in water towers from bird droppings. Food handlers who are asymptomatic excretors of *C jejuni* are not a significant source of infection.

Campylobacter infection has a cosmopolitan distribution. It has been reported as a cause of infection on all continents. These bacteria have a zoonotic reservoir.[74] They inhabit the intestinal tracts of a variety of birds, including chickens, turkeys, and water fowl; farm animals, including pigs, cows, sheep, goats, and horses; domestic dogs and cats; and wild rodents and monkeys. Frequently, these animals are infected but do not usually show signs of illness.

Incidence

Campylobacter organisms are one of the most common bacterial causes of diarrhea in developed countries.[68,75,76] The isolation from fecal samples is almost always associated with diarrheal disease or other enteric symptoms. It affects all age groups and has the highest incidence in children under 5 years old. There is also a marked increase in incidence in young adults that makes *Campylobacter* a particularly important cause of diarrhea in this age group.

Campylobacter organisms are a common cause of diarrhea in travelers[77] and military personnel from developed countries going to the tropics.[78] In developing countries *Campylobacter* enteritis ranks with rotavirus infection, enterotoxigenic *Escherichia coli* infection, and shigellosis as a leading cause of acute diarrhea in children.[79] Surveys of childhood diarrhea in the tropics showed that *Campylobacter* organisms were isolated from the stool cultures of 4% to 35% of cases, with the highest rate of infection reported in infants with diarrhea. Older children and adults are infected less frequently because of immunity acquired in early childhood.[80] Healthy children in developing countries frequently show asymptomatic infection. Infections caused by *C coli* are more likely to be asymptomatic than ones caused by *C jejuni*. The ratio of cases of diarrhea to all persons infected with *Campylobacter* organisms is highest in infancy and declines with increasing age. Second infections may be due to different serotypes of *Campylobacter*. Immunity, which can be total or partial, serves to prevent illness or decrease the severity of illness.

In developed countries, there is an increased incidence of infection during summer months. In tropical developing countries, infection occurs during all seasons. In more temperate developing countries, such as in north Africa, there is a higher prevalence of infection during the wet, winter months.

Pathogenesis and Clinical Findings

The infective dose is estimated to vary from 800 to 10^6 bacteria.[81] *C jejuni* is killed by normal gastric acidity (pH 2.3), indicating that gastric acid is an effective barrier against infection and that ingestion of organisms with milk or other food that neutralizes acid may enhance infection by reducing the required inoculum. The incubation period varies from 1 to 7 days and is usually 2 to 4 days. During the incubation period, illness, and convalescence, *C jejuni* multiplies in the intestine and is excreted in feces in quantities of 10^6 to 10^9 organisms per gram of stool. The duration of fecal excretion varies from about 8 days in children 1 to 5 years old, to 14 days in infants, to up to 3 months in adults not treated with antibiotics.[68,73]

Pathogenesis

C jejuni invades epithelial cells, which leads to ulcerated mucosa and bloody diarrhea.[82] The regions of the intestine most affected are the jejunum, terminal ileum, and colon. Biopsies of infected intestines show inflammatory infiltrates in the lamina propria, crypt abscesses, and mucosal ulceration. Bacteria gain access to the bloodstream, but bacteremia is uncommon because most strains of *C jejuni* are susceptible to the bacteriolytic action of serum complement.[83] There is evidence for the presence of cytotoxins, enterotoxins, invasiveness, and adherence properties in some isolates, but as yet there is no well-defined association between specific clinical syndromes and any putative virulence characteristic.[82]

Clinical Findings

The characteristic clinical features of *Campylobacter* enteritis are fever, diarrhea, and abdominal pain.[84]

The diarrhea may be either watery or dysenteric, with the presence of blood or mucus in liquid stool. In developing countries, most children present with watery diarrhea rather than dysentery, whereas a larger portion of patients in developed countries report dysenteric disease. Fever, nausea, vomiting, and malaise may precede the onset of diarrhea by a day or more, and such nonspecific constitutional symptoms may be more severe than the diarrhea itself. The disease is usually self-limited and lasts 1 to 7 days. Severity of disease varies widely: stool frequency may vary from one to more than eight times a day. Most cases are mild, but about 20% of cases will have prolonged, severe disease with high fever, grossly bloody stools, and relapses. The abdominal pain may be severe, and, because it is sometimes localized to the right lower quadrant, patients with this infection have been subjected to laparotomy for suspected appendicitis. Cases of toxic megacolon, pseudomembranous colitis, and massive rectal bleeding have been reported.[85] Usually examination of stool reveals fecal leukocytes and sometimes red blood cells. Often, a Gram's stain of stool shows bacterial forms, including spiral or "seagull" shapes, suggestive of *Campylobacter* morphology.

Fatalities from this illness are rare in the developed world, but children in developing countries with severe diarrheal syndromes commonly die. In Bangladesh, *Campylobacter* organisms were the fourth most common cause of diarrhea in children who died, and most of those children showed severe colitis and the complicating conditions of pneumonia, septicemias with other organisms, and malnutrition.[86] Less common complications reported in patients with *Campylobacter* enteritis include hypoglycemia, pancreatitis, peritonitis, and cholecystitis. A reactive arthritis may develop in patients who have the HLA-B27 haplotype.[87]

C jejuni infection has been identified as one of the triggers of Guillain–Barré syndrome (GBS), and acute motor axonal neuropathy.[87,88] Between 20% and 40% of GBS cases have serological or microbiologic evidence of a *C jejuni* infection, usually within a month of the onset of neurological symptoms. GBS cases with *C jejuni* infection were significantly associated with a slower recovery and a poorer outcome than GBS cases not associated with a *Campylobacter* infection.[88]

Diagnostic Approaches

The diagnosis of *Campylobacter* enteritis requires isolation of the bacterium from stool cultures. This requires selective media, such as Skirrow's or Campy-BAP, incubation at 42°C, and a microaerophilic environment, such as a Gas-pak (BBL Microbiology Systems, Cockeysville, Md.) or, less optimally, a candle jar.[71,73] Identification follows standard bacteriological techniques. Fresh stool should be examined for the presence of leukocytes and to exclude the possible presence of trophozoites of *Entamoeba histolytica*. In the tropics, patients are frequently coinfected with more than one enteric pathogen. Endoscopy is not routinely advised; however, when inflammatory bowel disease is considered in the differential diagnosis, colonoscopy with biopsy may be useful. The colonic mucosa will show erythema, superficial ulcerations, and friability, and the biopsy will reveal characteristically acute inflammation and crypt abscesses.

Recommendations for Therapy and Control

Therapy

As in other diarrheal diseases, the most important therapeutic approach is rehydration, which can be carried out with either isotonic intravenous fluids or oral rehydration solutions. Severe dehydration due to this disease is infrequent. Use of antibiotics in *Campylobacter* infection is not routinely indicated, but they may be used to shorten illness when patients have bloody diarrhea.[73] In patients with bloody diarrhea, treatment with erythromycin should be considered. Most strains of *C jejuni* are susceptible to erythromycin, tetracyclines, aminoglycosides, clindamycin, chloramphenicol, and quinolones (eg, nalidixic acid, norfloxacin, ciprofloxacin, ofloxacin). Resistance to the fluoro-quinolone antibiotics can be a problem in treatment, particularly in the developing world. Azithromycin was evaluated as an alternative to ciprofloxacin for the treatment of ciprofloxacin-resistant *Campylobacter* acquired in Thailand by US military personnel.[78] In this study, nearly half of the *Campylobacter* infections were caused by ciprofloxacin-resistant organisms. Azithromycin was significantly more efficacious than ciprofloxacin in reducing the time of illness and the duration of shedding of the organism.

Control

Prevention of infection requires the provision of safe food and water. All meats, but especially poultry, should be handled with the assumption that they could be contaminated with *Campylobacter* organisms and other bacterial pathogens such as *Salmonella* organisms. Transmission of *Campylobacter* infection

can be reduced by cooking meats thoroughly and avoiding contamination of other foods by the juices of uncooked meats. Travelers to developing countries should take the usual precautions to avoid most uncooked foods and to ensure that their cooked food is served fresh, thoroughly cooked, and still hot. Handwashing before meals is a good preventive measure against most enteric infections. As discussed with enterotoxigenic *Escherichia coli* infections (see earlier in this chapter), prophylactic antibiotics are not usually recommended. The presence of immunity after natural infection suggests that a vaccine strategy might work. An oral, inactivated whole cell vaccine for *Campylobacter* is under development.

Reducing the hyperendemic transmission of *Campylobacter* infection in developing countries requires improvements in basic hygiene and living conditions of the people. Because children acquire infection in infancy and early childhood by ingesting contaminated food and by direct contact with animals, household methods of food preparation must be improved and animals, especially chickens, must be kept away from people's homes.

[David N. Taylor]

VIRAL GASTROENTERITIS

Introduction and Military Relevance

Diarrheal illness is one of the major causes of morbidity and mortality worldwide, especially in the developing world and among infants and young children everywhere. It is historically perhaps the most common cause of hospitalization and lost duty time for deployed military persons because of the difficulty in maintaining good hygienic standards in foreign and field environments. Diarrhea and accompanying gastrointestinal symptoms, such as bloating, cramping, and nausea, will be referred to here as gastroenteritis.

The first bacterial cause of gastroenteritis was discovered in 1883 when Koch isolated the cholera vibrio. Although many other bacterial sources have since been identified, the etiology of the majority of these illnesses has been elusive. Viruses were suspected but could not be etiologically confirmed, even during virology's golden age (the 1950s and 1960s) when tissue culture techniques lead to the discovery of hundreds of viruses.

The development of electron microscopic techniques permitted a quantum leap in understanding the etiology of diarrhea. In the single year from November 1972 to 1973, two of the most important diarrhea-causing viruses worldwide were discovered.[89] Immune electron microscopy—the direct visualization of antigen-antibody complexes—was used to detect the Norwalk virus, a primary cause of adult gastroenteritis. The following year, a thin section electron micrograph of duodenal mucosa revealed rotavirus, the single most important cause of severe diarrheal illness in infants and young children.

Further advances in electron microscopy and genomic sequencing have allowed the identification of other gastroenteritis-causing viruses that could not be detected with standard laboratory equipment and training. Special, well-resourced surveillance programs, including advanced laboratory capabilities, are necessary for definitive diagnosis of viral gastroenteritis. In the military, only some tertiary care centers, research facilities, and contracted laboratories currently have this capability.

These viruses' wide geographic distribution and high infectivity in typical military living environments make them a high military medical priority. For example, in 1998 US Army recruits at Fort Bliss, Texas, experienced an outbreak of viral gastroenteritis apparently associated with a particular dining facility. Twelve percent of the soldiers in one unit (99 soldiers) were hospitalized. The causative agent was a Norwalk-like virus.[90]

In a survey of more than 2,000 servicemembers deployed to the Persian Gulf War in 1990 and 1991, 20% admitted to being kept from their duties at some time by diarrheal disease.[11] Using a variety of methods to identify causal pathogens, epidemiologists found Norwalk-like viruses to be the primary agent in servicemembers with vomiting and diarrhea. They may also have been a widespread cause of gastroenteritis during the colder months before surveillance started.

In the spring of 1992, a large outbreak of acute gastroenteritis on a US Navy aircraft carrier was caused by a Norwalk-like virus. The outbreak lasted 35 days, and during that time 8% of the crew of 4,500 sailors reported to sick-bay. A questionnaire survey of two thirds of the crew identified 13% of respondents with symptoms. (The remainder of the crew had work conflicts on the days the survey was distributed.) The outbreak all but disappeared when most of the sailors went on shore leave but reappeared when they returned. This outbreak virtually exhausted some of the carrier's critical medical supplies even though only 58% of sailors with symptoms sought medical care.[91]

A group of Air Force and Army Special Forces

personnel deployed for 1 month (February 1993) to northern Thailand experienced a gastroenteritis outbreak with an attack rate of 28%.[92] Stool specimens were obtained from 24 of 95 patients. Among the pathogens recovered was rotavirus, the most common cause of infantile diarrhea but a less-common cause in adults. These findings indicate that military populations may be at risk of infection from viruses that typically affect young children.

Viral diarrhea has a worldwide sinister reputation for its morbidity and mortality among infants and young children, but it is often considered a relatively minor nuisance for adults. In military populations, however, which experience travel, crowded and austere living conditions, and large dining facilities as a way of life, epidemics of viral diarrhea are more potent risks. The dangers are amplified by the importance of having each member of a unit functional.

Description of the Pathogens

Viruses that cause gastroenteritis generally fall into three categories: small and round with surface structures, small and round but featureless, and larger, less uniformly shaped viruses. The first group (small, round, surface-structured) consists of those that are the principal causes of viral diarrhea in adults. Classification has matured recently as genomic sequencing and other new techniques have added to observations of external structure as bases for categorization (Table 37-3).

Small Round Viruses with Surface Features

This group, whose prototype is the Norwalk virus, comprises two families. *Caliciviridae* includes Norwalk, Norwalk-like, and classic caliciviruses, and *Astroviridae* includes the astroviruses. They are approximately 30 nm in diameter and contain a single strand of positive-sense RNA. The surface features seen in this group consist of either indentations (small round structured viruses or SRSVs), cup-like hollows with six-pointed stars (classic calicivirus), or five- or six-pointed stars with a central stain (astrovirus).[93]

The subgroup of SRSVs are also known as Norwalk and Norwalk-like viruses. Each virus in the subgroup is named for the place of the outbreak from which it was first isolated; for example, the prototype virus was first isolated from an outbreak in Norwalk, Ohio. Antigenic studies by immune

TABLE 37-3

SIGNIFICANT VIRUSES ASSOCIATED WITH HUMAN GASTROENTERITIS

Morphology	Family	Virus	Remarks
Small Round			
With surface features	Caliciviridae	SRSV (Norwalk, Norwalk-like)	≥ four serotypes (Norwalk, Hawaii, Snow Mtn, Taunton)
		classic calicivirus	
	Astroviridae	astrovirus	seven serotypes
Without surface features	Picornaviridae	enterovirus (Hepatitis A, polio, echo, coxsackie)	diarrhea is a minor symptom
	Parvoviridae	parvovirus	
Larger, less uniform			
	Reoviridae	rotavirus	groups, subgroups, serotypes
	Adenoviridae	adenovirus (serotypes 40, 41)	

SRSV small round structured virus

Sources: (1) Hyams KC, Bourgeois AL, Merrell BR, et al. Diarrheal disease during Operation Desert Shield. *N Engl J Med.* 1991,325:1423–1428 (2) Sharp TW, Hyams KC, Watts D, et al. Epidemiology of Norwalk virus during an outbreak of acute gastroenteritis aboard a US aircraft carrier. *J Med Virol.* 1995;45:61–67 (3) Belliot G, Laveran H, Monroe SS. Outbreak of gastroenteritis in military recruits associated with serotype 3 astrovirus infection. *J Med Virol.* 1997;51:101–106 (4) Matsui SM, Greenberg HB. Astroviruses. In: Fields BN, Knipe DM, Howley PM, et al, eds. *Fields Virology*. 3rd ed. Philadelphia: Lippincott-Raven; 1996: 979–1016.

electron microscopy have resulted in the identification of at least four serotypes (ie, Norwalk, Hawaii, Snow Mountain, and Taunton). Three genotypes have also been distinguished,[94] but they do not directly correlate with the serotypes, which suggests the need for further study and refinement of the classification.

The astroviruses and classic caliciviruses are relatively minor causes of adult gastroenteritis.[1] Astrovirus serotype 3 was found in an outbreak of gastroenteritis in French military recruits.[95] No serotypes have been identified for classic caliciviruses.[96]

Small Round Featureless Viruses

Unstructured, or featureless, small viruses associated with gastroenteritis are parvoviruses and enteroviruses. Infection with the latter (including hepatitis A, polio, coxsackie, and echo viruses) is not mainly manifested by gastroenteritis, although these viruses may cause an incidental, mild diarrhea.[97,98] Hepatitis viruses are discussed in Chapter 38.

Larger, Variously Shaped Viruses

This group contains, most notably, rotaviruses and adenoviruses.

The rotaviruses are members of the Reoviridae family and are distinguished by their wheel-like (rota means "wheel" in Latin) appearance in an electron micrograph.[99] Members of the rotavirus genus infect humans and many domestic and laboratory animals. The rotaviruses contain group, subgroup, and serotype antigens. The rotaviruses have been divided into seven groups, designated A thru G, of which groups A, B, and C have been recovered from humans. The VP6 protein, making up 50% of the virion, contains the group-specific antigen. The group A rotaviruses have been antigenically classified into 14 serotypes.

Adenoviruses are icosahedral particles 70 to 100 nm in diameter[100] with fiber projections. The human adenoviruses are classified into at least 47 serotypes, which fall into 6 subgroups. They cause a variety of illnesses in humans, including respiratory, ocular, and diarrheal diseases. The subgroup F adenoviruses, serotypes 40 and 41, are responsible for diarrheal disease in humans and have been referred to as the fastidious adenoviruses because of the difficulty of propagating them in cell cultures.

Torovirus, coronavirus, pestivirus, and picobirnavirus have all been associated with diarrhea in humans but require further evaluation before they are widely accepted as causes of the illness.[89,97,98]

Epidemiology

Transmission

All diarrhea-causing viruses are transmitted mainly through the fecal-oral route.

Of the small round structured viruses, the Norwalk and Norwalk-like viruses, or SRSVs, are the most important cause of epidemic, nonbacterial gastroenteritis in the world. They may be the most common cause (including bacterial) of gastroenteritis in the developed countries. They are the only gastroenteritis-causing viruses that predominantly affect adults. The SRSV group has been shown to cause outbreaks in such diverse environments as family settings, health care institutions, travel situations, nursing homes, and schools.

Transmission of SRSVs, as well as being between persons by the fecal-oral route, can also be through common-source outbreaks associated with contaminated food or water. Virus particles occur in vomit and feces and are infective in very low doses (10 to 100 virus particles). Spread of infection therefore can occur via aerosol droplets, although this is not true respiratory transmission because the droplets are aerosolized by vomiting, rather than by coughing, sneezing, or other respiratory acts. Movement of contaminated laundry can also aerosolize viral particles. Not surprisingly, the spread of disease is rapid, and the secondary attack rate is high: over 50%.[101] Some shellfish-associated outbreaks have attack rates of 90%.[102]

Many other viruses causing gastroenteritis are also transmitted via common sources. Major sources of foodborne viral gastroenteritis are bivalve mollusks (eg, oysters, clams, cockles, mussels) and other shellfish contaminated from raw sewage. Fruits and vegetables can be contaminated with polluted irrigation water or with untreated sewage sludge used as fertilizer. So far, however, outbreaks attributed to salad items have been thought to be caused by contamination during preparation from infected food handlers.[102]

Among the small featureless viruses, Parvovirus-like particles have been associated with shellfish-related outbreaks. They are also found in well persons,[98] though, so their transmission by contaminated food is less certain.

One of the larger viruses, rotavirus (group A), is the major cause of pediatric morbidity and mortality from diarrhea throughout the world. A high inoculum (eg, from close contact with an infected infant, from drinking heavily contaminated water) or lowered immunity can produce minor illness in older

children and adults. Waning immunity with age may also contribute to adult disease. Group B rotavirus has caused very large epidemics in adults in China but not elsewhere.[97]

Adenoviruses are not believed to be transmitted via food or water. Person-to-person transmission is probably the mechanism for spread of infection.

Geographic Distribution

All diarrhea-causing viruses are found worldwide, but there are differences in relative incidences among age groups and environmental settings. The SRSVs and enteric adenoviruses occur year-round, with peaks in the winter.[101] Rotavirus outbreaks occur during the cooler months in northern Europe and North America, where a yearly wave starts in the southwest in November and ends in New England in March.[97] The disease is year-round in areas within 10 degrees latitude of the equator.

Incidence

Figure 37-2 shows prevalences of the most common causes of viral gastroenteritis in school-aged children and adults in a developed country. In the United States, about 50% of adults have antibodies to Norwalk or Norwalk-like viruses by age 50.[102] In developing countries, however, SRSV antibody acquisition occurs in a similar fashion to that of rotavirus: neonates and very young children are more commonly affected.

SRSVs commonly circulate in communities and

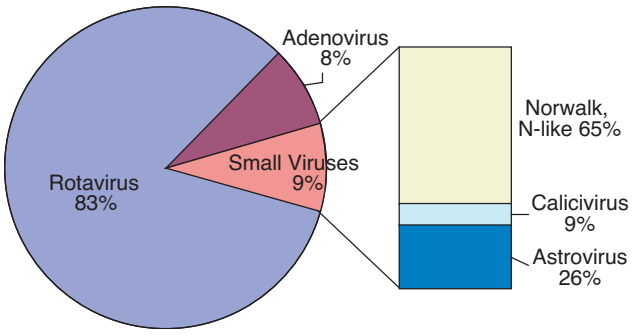

Fig. 37-2. The cumulative percentages of enteric viruses in the United Kingdom, 1990-1995.
Adapted from: Caul EO. Viral gastroenteritis: Small round structured viruses, caliciviruses and astroviruses, Part II: The epidemiological perspective. *J Clin Pathol*. 1996;49:960, with permission from the BMJ Publishing Group.

are believed to cause approximately 10% to 40% of gastrointestinal outbreaks in recreational camps, cruise ships, families, elementary schools and colleges, nursing homes, hospitals, cafeterias, and sports teams.[89,97,102] Although illness is relatively minor and short, the high attack rate causes a substantial loss of productivity at school and work.[93] For example, an SRSV outbreak associated with one infected bakery worker affected 3,000 persons and led to temporary closure of hospitals and schools in Minneapolis-St. Paul in 1982.[103] The similarities between the above settings and those found in military barracks, camps, and ships, along with the significance of lost productivity, suggests that the impact of SRSVs in the military may be substantial, but surprisingly little is known about viral gastroenteritis in these settings.

The other small structured viruses, calicivirus and astrovirus, are primarily found in the pediatric population. Calicivirus causes more pediatric diarrhea than any bacterial cause, but it is still less common than rotavirus. Calciviruses are rarely found in adults, except occasionally in nursing homes residents, where waning immunity may be a factor.[97,98,101] Enteric adenoviruses are considered the second-most important group of viruses associated with severe pediatric diarrhea.[89]

Pathogenesis and Clinical Findings

Gastroenteritis caused by SRSVs is usually a comparatively mild, self-limiting illness lasting approximately 12 to 60 hours. After an incubation period of about 24 to 48 hours, there is acute onset of nausea and vomiting (often explosive and projectile), abdominal cramping, and nonbloody diarrhea. Patients may have either vomiting or diarrhea or both, although vomiting is somewhat more prominent among children and diarrhea among adults. Symptoms, acuteness of onset, and a high secondary attack rate are characteristic enough to permit presumptive clinical diagnosis of SRSV.[89,104]

The SRSV seems to infect mature enterocytes of the proximal small intestine, causing malabsorption of D-xylose, lactose, and fat for up to 2 weeks after onset of illness. Gastric secretion of hydrochloric acid, pepsin, and intrinsic factor remain normal, but gastric emptying is slowed substantially. The latter finding probably accounts for the prominence of nausea and vomiting in this illness. Infection with SRSV induces both local gut and serum antibodies. The presence of serum antibodies, however, does not seem to protect against re-infection.

Classic calicivirus has an incubation period of 1

to 3 days, and illness lasts about 4 days. As in Norwalk-like illness, both vomiting and diarrhea may be present. Upper respiratory symptoms and fever occur less commonly. Unlike the case with SRSVs, antibodies to calicivirus may be protective.

In children, astrovirus disease is similar to but less severe than rotavirus.[105] Incubation is 24 to 36 hours, and illness lasts 1 to 4 days. Antibodies are probably protective.

Rotavirus has a 2-day incubation period. Watery diarrhea lasts 3 to 8 days and vomiting 3 days. Illness is often accompanied by fever and abdominal pain. Illness may be followed by temporary lactose intolerance. Infection confers long-term immunity to serious illness, but that immunity may wane with age.

The enteric adenovirus incubation period is 3 to 10 days, and illness lasts at least a week. Diarrhea is more prominent than vomiting or fever, and respiratory symptoms are often present. The long-term immunity conferred by infection may wane with age.

Viral gastroenteritis may be caused by multiple agents concurrently. This scenario is likely when shellfish or grossly contaminated water supplies are implicated. In outbreaks with mixed infections, differing incubation periods may create the impression that there is more than one outbreak.

Diagnostic Approaches

Except in instances where advanced laboratory capabilities (such as those found in the Theater Army Medical Laboratory or the Navy Joint Forward Laboratory) are deployed, field diagnosis usually depends on the clinical presentation of patients and the epidemiologic characteristics of outbreaks. Diagnoses based on these grounds are sufficient to initiate treatment and control measures.

Where laboratory confirmation of the diagnosis is available, it is valuable because it provides a better epidemiologic picture of the causes and illness patterns that are so disruptive to operations and training. Appropriate specimen collection, handling, and storage are crucial to establishing the etiology of gastroenteritis outbreaks. Particular care is necessary to prevent transmission of any agent to the personnel collecting or handling the specimens.

Since gastroenteritis-causing viruses are difficult to culture, other diagnostic tests are used. The tests include antigen and antibody detection by immunoassays, electron microscopy, and polymerase chain reaction. Electron microscopy is the classic procedure to detect viruses, and it is still the gold standard. These procedures are labor intensive, however, and few electron microscopes and experienced operators are available.

Fortunately for public health, the application of molecular biological procedures in the 1980s and 1990s resulted in determination of genome sequences and their product capsid proteins[106] that made many of the viral antigens available for rapid diagnostic tests. For example, commercial kits are available for the diagnosis of rotaviruses[107] and adenoviruses types 40 and 41.[108] The problem with these tests lies in their wide range of sensitivities (70% to 100%) and specificities (50% to 100%).[98]

Most individuals with viral gastroenteritis infection will have a rise in antibodies to that virus, but because these agents are so common, paired sera are necessary to demonstrate recent infection. At this time, though, antibody detection methods are available for Norwalk-like viruses only. Molecular studies are also permitting the application of reverse transcriptase polymerase chain reaction to SRSV diagnosis, although these procedures are not yet widespread.

Stool or serum specimens should be collected for diagnoses of suspected outbreaks of viral gastroenteritis, depending upon the tests to be used. The Centers for Disease Control and Prevention (CDC) recommends that stool specimens be collected within 48 hours of onset of symptoms (Exhibit 37-1). For outbreaks, electron microscopic examination or direct testing (antigen or reverse transcriptase polymerase chain reaction) requires that large volumes of stool be collected from at least 10 individuals who have unformed stool. Diagnostic yield is low if there are fewer specimens. These specimens should be refrigerated. If long-term storage is required, the stools should be stored at –70°C or colder. Stool samples to be sent to the CDC must be identified with a waterproof label and sealed in a plastic bag.

For antibody detection, serum is needed. Paired serum specimens should be collected during the first week and between the third and sixth weeks of illness.[98]

For the greatest yield, specimen collection should be accompanied by good clinical and epidemiologic information. Detailed directions for specimen collection and shipping are included in Exhibit 37-1.

Recommendations for Therapy and Control

The medical status of diarrhea patients should be assessed. Adults at risk for more severe illness[109] are those over 60 years of age, those who have a variety of chronic or immunosuppressive diseases or conditions, and those taking therapy that decreases gastric acidity (eg, hypochlorhydria, proton

EXHIBIT 37-1

CENTERS FOR DISEASE CONTROL AND PREVENTION GUIDELINES FOR COLLECTING SPECIMENS FOR VIRAL DIAGNOSIS

Stool

- **Collection in the first 48 hours.** Presently, viral diagnosis of a stool sample can be made only when the level of excretion is approximately 1 million particles/mL. For many viruses, this level of excretion is present only during the first 2 days of illness, and occasionally during the third. If specimens are not collected during the first 2 to 3 days of illness, an agent is unlikely to be detected. Thus, appropriate specimens should be collected as soon as an outbreak occurs. **Specimen collection should not await the results of epidemiologic and other investigations, since delay will almost certainly preclude a viral diagnosis.** If information gathered subsequently indicates that a viral etiology is unlikely, the specimens can be discarded before the cost of testing is incurred.
- **Ten diarrheal bulk specimens.** Bulk samples (enough to fill a large stool cup) are preferred, and only those specimens loose enough to assume the shape of their containers are likely to yield positive results. Serial specimens from persons with acute, frequent, high-volume diarrhea are particularly useful. The smaller the specimen and the more formed the stool, the lower the diagnostic yield. Rectal swabs are of little or no value. Specimens from at least 10 ill persons should be collected to maximize the chance that a diagnosis can be made. (The diagnostic yield is low when specimens from fewer than 10 persons are submitted.)
- **Storage at +4°C.** Because freezing may destroy the characteristic viral morphology that permits a diagnosis by electron microscopy, specimens should be kept at +4°C.

Paired Serum Specimens (essential for diagnosis)

- **Timing** Acute: during the first week of symptoms
  Convalescent: 3rd to 6th week
- **Number** 10 pairs from ill persons (the same persons submitting stool specimens)
  10 pairs from well persons
- **Quantity** Adults: 10 mL
  Children: 3 mL
- **Storage** Tubes containing no anticoagulant (tubes with red tops) should be used for collection. Sera should be spun off and frozen. If a centrifuge is not available, a clot should be allowed to form, and the serum should be decanted and frozen. If this step cannot be taken, the whole blood should be refrigerated, not frozen.

Other Specimens

Viruses causing gastroenteritis cannot normally be detected in vomitus, water, food, or environmental samples. Although British researchers report electron microscope detection of virus in shellfish, no successful effort has yet been reported in the United States.

Source: Centers for Disease Control. Viral agents of gastroenteritis: Public health importance and outbreak management. *MMWR*. 1990;39(RR-5):19.

pump or histamine type 2 inhibitors, antacids). Angiotensin-converting enzyme inhibitors and diuretics may also predispose those taking them to more serious gastrointestinal infections.

At the same time, severity of illness (as measured by fever, shock, hematochezia, concomitant illness, and number of stools per 24 hours) and hydration status, including urine output, should be assessed and monitored. Treatment, which is mainly supportive, involves hydration and maintenance of fluids and electrolytes.

Fluid replacement is best accomplished with an oral rehydration solution (ORS). These solutions were developed to be a simple, non-invasive, and inexpensive therapy for victims of severe cholera.[110] It was known that sodium absorption was linked

with other ions (eg, glucose, amino acids, dipeptides, tripeptides) at the intestinal brush border. However, early solutions contained higher levels of sodium than was optimal or even safe for less severe gastrointestinal infections and were associated with an increase in hypernatremia.

The need for a single ORS that could be administered to diarrhea patients regardless of age, etiologic agent, and initial serum sodium value resulted in a solution that contained the following (in mmol/L): sodium, 90; potassium, 20; chloride, 80; base, 30; and glucose, 111 (2%). This solution was approved by the World Health Organization and the United Nations International Children's Emergency Fund in 1975.[110] Oral rehydration solutions are available commercially and are encouraged for home use.

Patients with mild-to-moderate dehydration quickly improve clinically with simple rehydration. In these patients, the first 24 hours of illness should be managed with ORS as the only fluid intake (at least 2 L). Subsequently, 200 mL of ORS per loose stool should be given, along with unrestricted dietary and fluid intake.

Glucose-based ORS does not reduce the duration of illness or the volume of stool, but early feeding can reduce the severity and duration of illness.[110] It appears that glucose, in addition to providing the ORS sodium cotransport ion, also creates excessive osmotic load and therefore exacerbates diarrhea. More complex molecules, such as complex carbohydrates and larger proteins, are slowly digested by intestinal enzymes and then absorbed (as glucose or smaller peptides and amino acids, respectively) along with sodium. Therefore, a diet that emphasizes starches, cereals, yogurt, fruits, and vegetables is recommended after the first 24 hours. Foods high in simple sugars create too high an osmotic load and should be avoided.[110]

Symptoms of severe dehydration include profound apathy, weakness, confusion, or coma. Signs are tachycardia, rapid breathing, systolic blood pressure below 90 mm Hg, peripheral vasoconstriction (eg, cyanosis, cold extremities), uremia, and oliguria or anuria. If the patient is severely dehydrated or if ORS is not tolerated due to persistent vomiting, intravenous isotonic saline with potassium should be administered to replace fluid and electrolyte losses. In the event of acidosis due to severe dehydration, the replacement fluids should include 20% sodium bicarbonate (isotonic 1.26).

Antidiarrheal agents may be considered for treatment of symptoms. Bismuth subsalicylate may decrease abdominal cramping, but the reports are mixed on its effect on the duration of diarrhea.[98,105] Antimotility drugs, including opiates, loperamide, and diphenoxylate, may reduce symptoms but should be avoided in anyone with dysenteric symptoms, since they are harmful in patients with shigella (bacterial) infection.

Unfortunately, viruses that infect via the gastrointestinal tract are relatively resistant to inactivation. Since they are acid-stable, they survive food processing and preservation methods that use a low-pH environment to inhibit bacterial and fungal organisms. Temperatures required to inactivate viruses are not well established but are higher than those that kill bacteria. Viruses can remain infectious after freezing.[102]

These difficulties in eliminating viruses from contaminated food make prevention of contamination and outbreak control all the more important. The highest-risk foods are shellfish. Methods for optimal depuration (the self-cleansing actions of live shellfish after they have been moved to clean waters) are recommended, but they are less effective for viruses than for bacteria (and testing for contamination typically focuses on *Escherichia coli*, a bacterium). No satisfactory system has yet been devised for removal of viruses.[102]

All foods for US servicemembers should be approved according to military regulations. In areas where raw sewage is discharged into waters that contain shellfish, shellfish should be avoided altogether. The same is true for fruits and vegetables grown where raw sewage sludge is used as a fertilizer.

In outbreak situations in military settings, aggressive intervention is necessary. First the common source, such as water, ice, or shellfish, must be identified and eliminated. If water is contaminated with SRSVs, shock chlorine concentration of at least 10 mg/L for at least 30 minutes may help.[98]

Next, interpersonal transmission must be prevented, but implementing preventive measures in the field setting is challenging. Workers at risk for transmission are health care providers, daycare center staff, and food handlers. It has been suggested that for at least 2 days after the resolution of their illness, infected workers be excluded from contact with susceptible persons. Handwashing must be emphasized. Safeguards must be employed with soiled laundry (eg, transported in an enclosed container and in a sanitary manner, washed promptly in a machine at maximum cycle length, machine dried). Soiled surfaces should be promptly cleaned and disinfected with a germicidal product. Persons performing these tasks should wear protective barriers, including face masks. Nosocomial spread is minimized by these outbreak control measures.

Finally, contact between well and ill persons should be minimized, and in environments such as cruise ships and camps, renewal of a susceptible population should be interrupted. Population dispersal has been suggested as an effective control measure,[91] but in the very setting where it is likely to be of greatest benefit—crowded military barracks or ships—it is of greatest impracticality. In some circumstances, it could also spread the outbreak.

Only one vaccine now exists for the prevention of viral gastroenteritis (other than hepatitis A), and it is not currently available. Rotavirus vaccine was licensed in the United States for prevention of infantile gastroenteritis. After an excess of intestinal intussusception in vaccinated babies, however, the CDC withdrew the recommendation to vaccinate.[111] The vaccine was subsequently withdrawn from the market.

[Sharon L. Ludwig; Leonard N. Binn]

TYPHOID FEVER

Introduction and Military Relevance

Typhoid fever has historically had a major impact on military campaigns. In the Spanish-American War, one in five soldiers contracted typhoid fever, and more than 1,500 men died during the typhoid epidemic of 1898.[112] This prompted formation of a typhoid fever commission, composed of Walter Reed, Victor Vaughn, and Edward Shakespeare. Their study[113] resulted in an improved understanding of the mechanisms of transmission, including an appreciation for the role of asymptomatic carriers. Early British and American efforts to develop an effective typhoid vaccine were largely driven by the need to protect soldiers.

Despite advances in field sanitation and the development of effective vaccines, typhoid fever continues to pose a significant threat to service members, who are frequently deployed to areas where the disease remains endemic.[114–118] Changes in the global epidemiology of typhoid fever, including the emergence of multidrug-resistant strains, have intensified the threat to service members.

Description of the Pathogen

Typhoid fever is caused by the gram-negative bacterium *Salmonella enterica* serovar Typhi, hereafter referred to as *S* Typhi. More than 100 phage types have been identified.

Epidemiology

Transmission and Geographic Distribution

Humans are the only known reservoir for *S* Typhi, and typhoid fever is perpetuated in regions where fecal-oral dissemination of the organism continues unabated because of the lack of clean water or appropriate sanitation. Epidemiologic data from developing countries suggests that the incidence of typhoid fever is highest in regions where contaminated water supplies serve large populations. Foodborne illness in these countries is associated with high attack rates, resulting from large inocula of organisms, and may vary seasonally as contaminated water is used to irrigate or "freshen" vegetables.[119–121] Susceptible personnel deployed to regions of high endemicity may become infected through consumption of locally obtained, contaminated food or water, or when typhoid carriers are employed to prepare food for service members.[122,123] Infections in recent immigrants and international travelers represent most reported *S* Typhi infections the United States.[124–128]

Incidence

Although there is no precise estimate of the global incidence of typhoid fever, the World Health Organization estimates that worldwide the number of typhoid fever cases exceeds 16 million annually,[129,130] which results in more than 600,000 deaths.[130] In many developing countries, rapid increases in population density, especially in urban areas, combined with inadequate sanitation have led to an increased incidence of typhoid fever.[129]

Pathogenesis and Clinical Findings

The incubation period of typhoid fever ranges from 3 to 60 days or more, but is most commonly 7 to 14 days. The incubation period is in part dependent on the inoculum size, as well as the host's susceptibility and the strain involved.[131] Generally a larger infectious dose is associated with a shorter incubation period and a more severe illness. On average, an inoculum of at least 10^5 organisms is necessary to produce disease in healthy adults, but some may become ill with lesser exposures.[132] As with other gastrointestinal pathogens, the number of organisms required may be significantly lower in those suffering from achlorhydria or in individuals taking H2 blockers.

S Typhi produces a spectrum of illnesses that vary widely with respect to severity, clinical signs,

and symptomatology.[133–135] Classic typhoid fever often begins insidiously with nonspecific flu-like symptoms such as malaise, toxemia, fever, headache, anorexia, abdominal pain, and occasionally myalgias. One third to one half of patients present with diarrhea that varies in frequency from several to many stools per day.[136] Diarrhea appears to be more common in young children, while constipation occurs more commonly in adults.[136–139] Other symptoms that are less common and that may confound attempts at diagnosis are sore throat,[140] cough, dysuria, and bloody diarrhea.[141] Protracted diarrhea with few other symptoms may occur in young, malnourished children.[142] Many infections are mild and do not fit the classic description.

Physical signs ascribed to typhoid fever include a toxic appearance, dehydration, relative bradycardia, hepatosplenomegaly, abdominal tenderness, segmental ileus, rose spots (2- to 4-mm blanching, erythematous macules, frequently on the abdomen and chest), meningismus, and neuropsychiatric manifestations. Patients presenting early in the course of their illness may have relatively few signs or symptoms other than fever.[141,143] In travelers, typhoid fever is usually characterized by a persistent low-grade fever with headache.

In the preantibiotic era, many of the complications classically described in typhoid fever were appreciated after days of illness. These complications have taken on new importance with the emergence of multidrug-resistant strains, as patients fail to respond to antibiotics traditionally used to treat typhoid fever[144] and so have a greater tendency toward the complications that develop later in the course of the infection. Complications include intestinal perforation, gastrointestinal bleeding, pneumonia, pleural effusion, myocarditis, meningitis, sepsis, acute respiratory disease syndromes,[145] seizures, and coma.[146]

Intestinal perforation results from the proliferation of organisms in Peyer's patches of the small intestine and is one of the most feared complications of typhoid fever because of the high associated mortality rate. It occurs in approximately 3% of cases, particularly later in untreated cases.[147] With modern surgical techniques and antimicrobial therapy, the mortality rate has declined from nearly 100% in the preantibiotic era[148,149] to under 10% in a more recent study.[150]

Typical typhoid case fatality without treatment is 10%; with prompt treatment this can be reduced to less than 1%. Relapse rates as high as 20% may occur after therapy with appropriate antibiotics. Relapses occur in about 5% to 10% of untreated cases.

Immunity following natural infection with *S* Typhi is incomplete and may be overcome by a high inoculum of organisms or infection with different phage types. Although reinfection does occur, it is felt to be rare.[151]

Diagnosis

Isolation of *S* Typhi from either blood or bone marrow is required for a definitive diagnosis of typhoid fever. In the absence of antimicrobial therapy, the majority of patients will be bacteremic in the first week of the illness. Isolation of the organism from stool supports but does not confirm the diagnosis. Occasionally, the organism can be isolated from urine or cultures of skin obtained from rose spots. A significant rise in typhoid O-type agglutinins or Vi antibody is helpful in confirming the diagnosis.

Recommendations for Therapy and Control

Typhoid fever presents the clinician with some unique therapeutic challenges. First, *S* Typhi can invade the intestinal epithelial cell and penetrate the lamina propria. From there, the organism enters the bloodstream, where it may multiply within mononuclear phagocytes, which protect it from some antimicrobial agents. Therefore, in vitro resistance may predict clinical failure, but sensitivity of the organism does not always translate to clinical success.[152] Because of the poor correlation between in vitro sensitivity testing and clinical outcome and because there is currently no valid, reliable animal model for typhoid fever; therapies should be based on the results of well-controlled clinical studies. Previous studies have demonstrated that early treatment with effective antimicrobial therapy may not prevent relapse,[153] so close scrutiny during convalescence is necessary. Emerging resistance to several of the agents used as standard therapy in many areas, including the Arabian Gulf, Africa, India, and Egypt,[154] has prompted the use of antibiotics that are more costly and less readily available in developing countries.

A number of different classes of antibiotics have been shown to be effective in the treatment of typhoid fever. Chloramphenicol has been a mainstay in the treatment of typhoid fever since it was first employed by Woodward and colleagues[155] in 1948. It remains useful in cases caused by chloramphenicol-sensitive *S* Typhi. However, the rare association of chloramphenicol with drug-induced aplastic anemia and the emergence of resistance to chloramphenicol in the 1970s[156] led to the investigation of alternative agents for treatment. Ampicilllin[157] and trimethoprim-sulfamethoxazole[158,159] were later

shown to be effective therapies for typhoid fever. However, strains resistant to all of these traditional first-line therapies for typhoid fever have now emerged in many parts of the world,[154,160–166] leading to the introduction of different, newer antibiotics for treatment.

Fluoroquinolones are well suited for the treatment of typhoid fever and should be regarded as the agents of choice for adults in regions where multidrug-resistant strains of *S* Typhi are prevalent. These agents are highly active against salmonellae,[161,167] and they are concentrated in both macrophages and polymorphonuclear leukocytes, with intracellular levels as much as 10-fold higher than serum values.[168]

The third generation cephalosporins (eg, cefotaxime, cefoperazone, ceftriaxone, the orally administered cefixime) demonstrate excellent in vitro activity against many *Salmonella* species, including *S* Typhi.[169,170] Ceftriaxone and cefotaxime are effective against some ampicillin-resistant strains of *Salmonella*.[171] The minimal inhibitory concentrations for ceftriaxone are in the range of 0.05 μg/mL against most *Salmonella* species, and cellular penetration of ceftriaxone [172] indicates that it may be active against intracellular organisms. Its prolonged serum half-life and biliary excretion permit daily dosing.[173] Daily ceftriaxone for 3 [174], 5 [175], or 7 days [176] has compared favorably to standard 14-day courses of chloramphenicol in several randomized clinical trials. In a randomized clinical trial comparing ciprofloxacin to ceftriaxone, ciprofloxacin produced more rapid resolution of fever and had a higher success rate than ceftriaxone.[177] Although fluoroquinolones have been used successfully to treat typhoid fever in children, [178] there are persisting concerns about potential bone and cartilage toxicity of fluoroquinolones in young children.[179,180] The third generation cephalosporins are now considered the treatment of choice for children in regions where multidrug resistance is a problem.[181]

Patients presenting with severe toxemia from typhoid fever may benefit from the administration of corticosteroids. In a highly selected group of patients at high risk of death from typhoid fever in Jakarta, Indonesia, Hoffman and colleagues[182] demonstrated a significant reduction in mortality in patients treated with dexamethasone (3 mg/kg followed by 1 mg/kg every 6 hours) compared to placebo-treated controls. Others have suggested that patients receiving adjuvant steroids may have higher relapse rates.[183] Therefore, the use of corticosteroids in typhoid fever should be reserved for those cases complicated by profound mental status changes, severe toxemia, or impending shock.

Treatment of Typhoid Carriers

Between 1% and 5% of patients with typhoid fever become chronic carriers of *S* Typhi. The chronic carrier state is more common in women. The likelihood of becoming a carrier after having typhoid fever increases with age, paralleling an increased incidence of cholelithiasis. Infections with *Schistosoma haematobium* may result in chronic urinary carriage of *S* Typhi organisms,[184] which may reside in the gut of the worm or attached to the surface of the worm.[185] Antimicrobial treatment for acute disease does not prevent the development of the carriage state, and relapses have been reported as long as 24 months after initial therapy. Because humans are the only known reservoir for this organism, identification and treatment of carriers is of potential importance in interrupting the transmission of the organism to others.

Cure of typhoid carriers may be achieved with either antibiotics alone or through a combination of antimicrobial therapy and cholecystectomy. Most studies have demonstrated significantly lower cure rates for individuals with cholelithiasis, as calculi may serve as residual foci of infection. The finding of *S* Typhi in the bile of patients months after cholecystectomy supports the view that this organism may persist even after surgical intervention. Both intravenous ampicillin and oral amoxicillin, which is given with and without probenecid, have been employed successfully to eradicate the carriage state. Treatment with amoxicillin requires high doses (6 g daily) for 4 to 6 weeks and is frequently accompanied by intolerable gastrointestinal side effects.[186–188] Treatment with intravenous ampicillin has also been used, but prolonged intravenous therapy may be impractical. Oral trimethoprimsulfamethoxazole has been used with variable success.[189,190] Long-term followup examination is necessary to confirm successful clearance of the organism.

Fluoroquinolones have been used successfully to treat chronic carriers. Ciprofloxacin (750 mg orally twice a day for 28 days) eradicated the organism in 11 of 12 patients (92 %) with chronic *S* Typhi carriage.[191] Norfloxacin (400 mg twice a day for 28 days) was 86% effective in eradicating *S* Typhi from individuals without gallstones and 75% effective in those with cholelithiasis.[192]

Vaccines

The first successful US typhoid vaccine was developed by Colonel Frederick Fuller Russell and contributed significantly to the United States' dra-

matically lower incidence of typhoid fever in World War I than in the Spanish-American War. Later, volunteer trials of typhoid vaccines were initiated at the University of Maryland Hospital in collaboration with Joseph Smadel and others of the Walter Reed Army Institute of Research, Washington, DC.

Three vaccines for the prevention of typhoid fever are currently licensed for use in the United States[193] (Table 37-4). These include the live attenuated Ty21a oral typhoid vaccine and two parenteral vaccines: a heat-phenol inactivated vaccine and the recently licensed Vi capsular polysaccharide vaccine. A fourth vaccine, available only to the military, is the acetone-inactivated parenteral vaccine. The vaccines vary in their side effects, the time required for primary vaccination, and the need for booster immunizations.[194] Although each vaccine has been demonstrated to be effective in separate clinical trials, they have never been compared in prospective randomized studies. In clinical trials, the efficacy of the individual vaccines varies with the population studied and the intensity of exposure.

Parenteral killed whole cell typhoid vaccines, prepared by either heat-phenol or acetone inactivation methods, have been available for many years. In clinical trials, their efficacy varied from 50% to 88%.[194] Vaccination is often accompanied by side effects; nearly 25% of vaccinees develop fever, and 40% to 50% develop local side effects. The significant reactogenicity of these vaccines and the need to administer two doses more than 1 month apart for the primary immunization limit their utility, especially in comparison to other available vaccines.

Another parenteral vaccine, prepared from purified Vi capsular polysaccharide,[195] an essential virulence determinant of *S* Typhi, was licensed for use in the United States in the mid 1990s. In one clinical trial, more than 90% of healthy US adult males seroconverted following a single 25 μg injection of purified Vi antigen.[196] In the same study, antibody levels remained significantly elevated for up to 34 months following primary immunization. Following a single dose of vaccine, the number of cases of typhoid fever was reduced by 55% to 74% when the vaccine was tested in endemic areas.[197,198]

The Ty21a oral typhoid vaccine is a live vaccine composed of a strain of *S* Typhi that has been attenuated by chemical mutagenesis[199] and has an efficacy rate similar to parenteral vaccines.[200] Because this vaccine is administered every other day for four doses, compliance needs to be reinforced.[201,202] Mefloquine and antibiotics may inhibit the growth of Ty21a,[203,204] so vaccination should be delayed 24 hours after consuming these drugs. The vaccine should not be administered to immunosuppressed individuals.

Typhoid vaccination should be directed at those individuals anticipating prolonged exposure in endemic areas. By US military regulation,[205] typhoid immunization is to be given to all alert forces. This

TABLE 37-4

DOSAGE AND SCHEDULES FOR ADULT TYPHOID FEVER VACCINATION

Vaccine	Dose	Number of doses	Dosing interval	Boosting interval
Ty21a				
primary series	1 capsule*	4	2 days	—
booster	1 capsule*	4	2 days	every 5 years
Vi capsular polysaccharide				
primary series	0.5 mL†	1	—	—
booster	0.5 mL†	1	—	every 2 years
Heat-phenol-inactivated				
primary series	0.5 mL‡	2	4 weeks	—
booster	0.5 mL‡	1	—	every 3 years

*oral
†intramuscularly
‡subcutaneously

Adapted from: Centers for Disease Control and Prevention. Typhoid immunization—recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR*. 1994;43;RR-14:1–7.

generally includes Army personnel required to be ready for foreign deployment in 30 days or less, all foreign-deployed (except Canada) Navy and Marine Corps personnel, others subject to foreign deployment on short notice, and all Air Force rapid deployment personnel. It is also indicated for others deploying or traveling to high-risk areas. Vaccinees need to be reminded that typhoid vaccination does not obviate the need for caution in selecting food and drink in endemic areas because the vaccine is not 100% effective, immunity can be overcome by large inocula of organisms,[130] and the vaccine also offers no protection against other enteric pathogens.

Other Prevention Measures

In addition to vaccination, preventing cases of typhoid fever requires strict enforcement of measures designed to interrupt fecal–oral transmission of the organism. These include chlorination of water supplies, appropriate disposal of human waste, control of flies, strict attention to handwashing, and scrupulous management of food preparation. In endemic areas, local workers employed as food handlers should be closely screened using successive stool cultures to ensure that they are not typhoid carriers. Outbreaks of typhoid fever have often occurred after disasters, when disruption of water supplies and sanitation facilitate the transmission of *S* Typhi from infected carriers to a population of susceptible hosts. Mass vaccination of individuals at risk in this setting is of secondary importance to other efforts to halt transmission, such as restoration of clean water supplies and institution of appropriate levels of sanitation.

[James Fleckenstein]

NONTYPHOIDAL SALMONELLOSIS

Introduction and Military Relevance

Salmonellosis is an acute bacterial infection that can disrupt combat performance and readiness, most typically by causing cases of acute enterocolitis associated with fever, headache, abdominal pain, diarrhea, nausea, and sometimes vomiting. Salmonellosis has considerable impact in civilian and military arenas. It accounts for substantial health care expenditures, decreased productivity, and lost wages in Europe[206,207] and the United States. Annual health care costs in the United States resulting from these infections are estimated to exceed $50 million.[208] In the context of this chapter, salmonellosis will not include typhoid and paratyphoid fevers.

Salmonella organisms as a cause of enteric illness on deployments has been well documented[209–211] (Table 37-5). When good field sanitation is maintained, salmonella infections cease to be a major operational threat. When sanitation is compromised, though, the abrupt onset of salmonella infections and their tendency to present as epidemic case clusters can hinder readiness and performance. As was illustrated by an outbreak in US military personnel deployed to Croatia, personnel are at risk for salmonella infections when common dining facilities are used and hygienic practices are suboptimal.[212]

Description of the Pathogen

The salmonellae are nonspore-forming, gram-negative bacteria. Unlike *Salmonella typhi* and *S paratyphi*, for which humans constitute the only known reservoir, the nontyphoidal species of the genus are less host-adapted and may cause infections in multiple animal hosts. This large reservoir in lower animals constitutes a major source for infections in humans and in part accounts for the ubiquity of these infections. There are approximately 2,000 serotypes that can be distinguished by specific surface antigens. Their prevalence varies by region, with only a frac-

TABLE 37-5

INCIDENCE OF TYPHOID FEVER AND SALMONELLOSIS IN US ARMY TROOPS IN VIETNAM, 1965-1970

	Typhoid fever		Salmonellosis	
Year	No. of cases	Rate/1,000	No. of cases	Rate/1,000
1965	0	—	10	0.2
1966	1	0.01	17	0.01
1967	11	0.04	201	0.7
1968	8	0.02	70	0.2
1969	19	0.05	70	0.2
1970	23	0.08	30	0.1
Total	62	—	398	—

Reprinted from: Hedlund KW, Ognibene AJ. Typhoid fever and other salmonelloses. Ognibene AJ, Barrett O, eds. *General Medicine and Infectious Diseases*. Vol 2. In: *Internal Medicine in Vietnam*. Washington, DC: Office of the Surgeon General and Center of Military History, US Army; 1982: 365.

tion present at any time. These serotypes are grouped into four serogroups (A through D). Although serotype does not have significant implications for individual patient care, it has important public health significance with respect to surveillance and outbreak detection. This is particularly evident when an outbreak stems from widely distributed foods.

Epidemiology

Transmission

Transmission of *Salmonella* organisms may be direct or indirect. Nontyphoidal salmonellosis most commonly occurs after the consumption of contaminated food or water. *Salmonella* may be passed to humans because of a failure to cook food products thoroughly or by cross-contamination of salad or other uncooked foods. Sauces and custards that contain eggs are other potential sources. Cooked foods can be inoculated with salmonella when they are cooled (eg, by a food handler excreting organisms), and if the food is held improperly, multiplication of the organism may occur.

In the United States and other industrialized countries, the routine large-scale commercial preparation of food with national or international product distribution has served to disseminate *Salmonella* organisms and has resulted in massive outbreaks of nontyphoidal salmonellosis.[213,214] Outbreaks related to commercial food production are most frequently associated with consumption of dairy products,[214] eggs,[215] or meat[216]; however, the growing list of implicated food vehicles indicates that anything that can be contaminated and sustain growth of the organism can serve as a vehicle for transmission. International distribution of some foods has resulted in importation of novel strains of *Salmonella* and multinational epidemics on several occasions.[217,218]

In healthy volunteers, the median infective dose for salmonella infection is 10^7 organisms. This may be altered significantly by a number of important host factors that may increase the risk for the acquisition of salmonella infection, including reduced stomach acidity,[219] age, and depressed cell-mediated immunity. Exposure to antimicrobial agents increases the risk of infection by lowering natural colonization resistance through alteration of native colonic microflora.[220] Infection rates also appear to be dependent on the strain of *Salmonella,* and some infecting strains appear to cause more severe clinical manifestations.[221,222] Foods that buffer the effect of stomach acids, particularly fatty foods, may facilitate survival of the organism.[218,223]

Geographic Distribution

While *Salmonella* organisms are ubiquitous, certain serotypes may predominate in specific geographic or environmental niches, and these serotypes may evolve over time. In the United States, *S enteritidis* infections have spread from an initial focus in the Northeast to become a predominate serotype.[224] As in other countries, infections with *S enteritidis* largely can be traced to the distribution of infected eggs. Some strains may have an enhanced potential for spread, as has been evidenced by the rapid increase in *S enteritidis* phage type 4 in England and Wales[225] and the emergence of these strains in the United States.[226,227] Nontyphoidal salmonellosis is common in the developing world.

Incidence

Nontyphoidal *Salmonella* organisms cause numerous infections worldwide. While the incidence of typhoid fever in the United States has declined, the incidence of human nontyphoidal salmonellosis has steadily increased. In the United States alone, more than 40,000 cases are reported through passive surveillance to the Centers for Disease Control and Prevention annually.[228] It is estimated, however, that this represents only 1% to 5 % of the actual number of infections.

Pathogenesis and Clinical Findings

The incubation period for nontyphoidal salmonellosis is usually 12 to 36 hours. Approximately two thirds of all those with salmonella infections present with gastroenteritis and fever. These infections are often self-limited, require no therapy, and resolve over several days. Infected individuals may continue to excrete organisms for several weeks or months after the acute illness, but fewer than 1% of patients demonstrate carriage beyond 1 year.[229]

Bacteremia occurs in 3% to 10 % of all nontyphoidal salmonella infections,[230,231] and it has been reported to occur with most of the reported serotypes of *Salmonella*.[232] Some serotypes (eg, *S enterica* serovar Cholerasuis) may be more invasive than others, as is evidenced by their relatively frequent isolation from blood as compared with the number of stool isolates.[233]

At present, acquired immunodeficiency syndrome is the most common underlying condition associated with nontyphoidal salmonella bacteremia, followed by diabetes mellitus, malignancy, cirrhosis, chronic granulomatous disease, sickle cell disease,

and collagen vascular diseases.[231,233] However, nearly half of the bacteremias arise in patients without a recognizable underlying disease.[234] In otherwise healthy patients, salmonella bacteremia is often associated with a clearly defined episode of gastroenteritis. Conversely, the possibility of underlying immunosuppression should be considered in individuals presenting with primary nontyphoidal salmonella bacteremia without gastrointestinal symptoms.[235] Malaria appears to predispose patients to concurrent septicemia with gram-negative organisms, particularly *Salmonella*.[236] The possibility of dual infection should be entertained in febrile service members who have been deployed to endemic areas.

Nontyphoidal salmonellosis is an infrequent cause of endocarditis. It occurs more frequently in individuals over the age of 50 with underlying heart disease.[237–239] Salmonella infections of the aorta, particularly the abdominal aorta,[240] occur more frequently and usually in patients with preexisting atherosclerotic disease.[241]

Numerous extraintestinal foci of salmonella infection have been reported, a reflection of the organism's predilection for invasion of the bloodstream.[237] Intraabdominal infections caused by *Salmonella* organisms usually involve the liver, spleen, or biliary tract, commonly in patients with underlying structural abnormalities. Mesenteric lymphadenitis causing an appendicitis-like syndrome has been reported.[242] Salmonella osteomyelitis, originally described by Sir James Paget in 1876,[243] most frequently affects the long bones and vertebrae,[244] although virtually any bone may be infected.[245] Sickle cell disease remains an important predisposing factor for salmonella osteomyelitis and septic arthritis, particularly in early childhood. Multiple, often symmetrical, sites may be involved. Central nervous system infections with *Salmonella* species are rare. Brain abscess, subdural and epidural empyema, and meningitis have all been reported.[246] Urinary tract infections due to nontyphoidal *Salmonella* species occur rarely and are often associated with underlying immunosuppression or structural abnormalities.[247] Chronic urinary carriage of salmonella occurs commonly in the Middle East in those with bladder malformations and concomitant infection with *Schistosoma hematobium*. Pneumonia may result from hematogenous spread of nontyphoidal *Salmonella* organisms.[248]

Diagnostic Approaches

A diagnosis is usually made by isolating salmonellae from feces or blood through use of enteric media. Serologic tests are not useful. To screen for enteric infections in asymptomatic persons, multiple specimens of fecal material (3-10 g inoculated into enrichment media) should be obtained over several days because excretion may be intermittent. Investigation of close case contacts, especially those who may pose a significant ongoing risk to others, is indicated.

Recommendations for Therapy and Control

Therapy

The majority of nontyphoidal salmonella infections in immunocompetent hosts are cases of self-limited gastroenteritis and do not require treatment with antibiotics.[249,250] In most patients, antimicrobial therapy will serve to shorten the duration of symptoms by only 1 to 2 days and may extend the time of fecal excretion. Rehydration with oral electrolyte solutions is usually sufficient therapy.

In patients with particularly severe or protracted symptoms or in situations where performance is critical, antibiotic therapy is reasonable to speed recovery and return to duty. Because there is a higher risk of endothelial infection in older adults with bacteremia caused by *Salmonella*, some have suggested that patients older than 50 years receive antibiotic therapy for gastroenteritis.[251] In addition, immunosuppressed patients, particularly those with the human immunodeficiency virus,[252,253] may benefit from treatment of gastrointestinal infections to avoid subsequent bacteremia, which can be difficult to eradicate in this population. Infants younger than 2 months of age may also be candidates for antibiotic therapy.

For patients requiring therapy, initial treatment should ideally be based on some knowledge of local resistance patterns because of the emergence of strains resistant to multiple antimicrobial agents. Ampicillin, chloramphenicol, and trimethoprim-sulfamethoxazole have all been used successfully to treat nontyphoidal salmonellosis, but many strains are now resistant to these drugs. Alternatives are provided by newer agents, such as the fluoroquinolones and the third-generation cephalosporins, which demonstrate significantly more activity against *Salmonella* organisms in vitro.

Fluoroquinolones, in addition to being highly active against many salmonellae, possess favorable phamacokinetic parameters, including large volumes of distribution, long half lives, and good oral bioavailabilty.[254] High concentrations of fluoroquinolones are present in stool after oral dosing,[255] and fluoroquinolones also achieve high intracellular concentrations.[256] In double-blind trials of adults with diarrheal illness, ciprofloxacin shortened the

duration of diarrhea by 1.5 to 2 days.[257–259] These agents have been used successfully to treat salmonella infections caused by strains resistant to multiple other classes of antibiotics.[260]

In vitro studies have shown that many *Salmonella* species are sensitive to third-generation cephalosporins (eg, cefotaxime, ceftriaxone, cefoperazone, ceftazidime), and these drugs have been used successfully to eradicate nontyphoidal salmonellae.[261] Because fluoroquinolones are not approved for use in children, third-generation cephalosporins are often employed in treating younger patients.

Many investigators have cautioned that the use of antimicrobial agents in animal husbandry for growth promotion has led to the emergence of drug-resistant infections in humans.[208,262,263] While the use of antibiotics in animal feeds has been discouraged, the practice remains widespread, and new multidrug-resistant infections continue to emerge throughout the world.[221,222,264,265] Occasionally, resistance may emerge during the course of therapy, particularly in the treatment of chronic deep-seated infections such as osteomyelitis.[266]

Prevention

Given the many modes of transmission of salmonella infections, it is unlikely that all infections will be prevented even with strict adherence to measures designed to prevent transmission of these organisms. However, most infections can be prevented through careful attention to food handling, sanitation, and education of those in charge of food preparation and procurement. Irradiation of processed foods, particularly those of animal origin, should be encouraged. Fresh fruits and vegetables obtained from local sources are often used to supplement the diet of service members during extended deployments; such foods should be viewed as potentially contaminated with multiple enteric pathogens, including *Salmonella*.[11] Veterinary inspection of locally procured foods on deployments is essential to reduce the risk of nontyphoidal salmonellosis. The proper chlorination of water supplies is also an important preventive measure and can prevent large-scale outbreaks of salmonellosis. Handwashing should be emphasized for food handlers, those caring for patients, patients with enteric illness, and those caring for infants and incontinent adults.

Ill individuals should not participate in food handling or the care of immunocompromised or hospitalized patients, the elderly, or young children. Known carriers of *Salmonella* should be prohibited from handling food until they no longer shed the organisms. Carriers should have at least two negative stool cultures documented before being permitted to prepare food. Care should be taken especially when employing foreign workers in military mess facilities, as asymptomatic foodhandlers have been implicated as sources of infection despite screening.[267,268]

[James Fleckenstein]

SHIGELLOSIS

Introduction and Military Relevance

Shigellosis, often referred to as bacillary dysentery, is a febrile diarrheal syndrome manifested by the passage of frequent, scant stools that are bloody, mucoid, or both bloody and mucoid. Symptoms of abdominal cramps and tenesmus are present due to direct invasion of the colonic mucosa by members of the *Shigella* species.[269] Descriptions of this syndrome can be found in the Old Testament and a like disease played a major role in many military campaigns as far back as the year 480 BC. Shigellosis is endemic throughout the world and is hyperendemic in many developing countries. Infection with *Shigella* species is the most common cause of dysentery in children less than 5 years of age, especially in developing countries, where affected children experience a higher rate of stunting and mortality.[270]

Shigellosis has had a significant impact on military forces throughout history. According to the Greek historian, Herodotus, epidemics of dysentery plagued Xerxes' Persian army (500,000 men strong) during their unsuccessful invasion of Greece around 480 BC, especially during the battle for Salamis, the most important victory in Greek history.[271] In the 18th century, Prussian forces fighting under Frederick William II in France suffered 12,000 cases among a unit of 42,000, forcing his withdrawal from combat and retreat across the Rhine.[272] The British during the Crimean War (1854–1856) suffered ten times more casualties from dysentery than from all the Russian weapons.[273]

Acute diarrheal diseases, to include shigellosis, have continued to be an important medical problem for US military personnel operating in areas where sanitation has been inadequate. In the US Civil War, acute diarrheal diseases accounted for more than 25% of the deaths in the Union Army.[274] During World War II in the Middle East theater of operations, attack rates as high as 50% per month and noneffective rates as high as 3.5% per week were documented.[275] In North Africa, the British

Army was also reported to have sustained a significant number of casualties due to dysentery.[276] Shigellosis also proved to be the most common enteric infection identified among US military personnel in Vietnam, with an annual hospitalization rate as high as 8% documented in 1965.[277]

US troops deployed to Lebanon in 1958 to help in the evacuation of the Palestinian Liberation Organization were severely stricken with dysentery. Approximately 30% to 50% of a 10,000-man Marine landing force was affected; a total of 527 hospitalizations were recorded.[278] During Operation Bright Star in Egypt in July 1983, approximately 30% of the 82nd Airborne Division troops developed dysentery in a 1-week period.[116] From 1981 to 1990, diarrheal diseases have affected 15% to 20% of US troops participating in short-term military exercises in Egypt and Thailand; up to 5% of troops have lost duty time because of their illnesses.[25,279–281] Among US military personnel deployed to South America and western Africa, *Shigella* species have been isolated in up to 5% of diarrhea cases.[282]

In a sample of 2,000 US military personnel deployed to Saudi Arabia during the Persian Gulf War, 57% reported a significant diarrheal illness during the first 3 months of deployment (September–November 1990); 20% reported that they were not able to perform their duties while affected. Multidrug-resistant *Shigella* species (principally *S sonnei*) infections accounted for 26% of the cases of diarrhea evaluated, second only to enterotoxigenic *Escherichia coli*, which was found in 29% of cases. There were at least 3 outbreaks of shigellosis in the first 3 months of the operation.[11] Outbreaks were associated mainly with consumption of fresh fruits and vegetables and, to a lesser extent, with contamination of communal latrines, lack of handwashing facilities, and a high number of desert filth flies.[15] During Operation Restore Hope in Somalia (1992-1993), one outbreak of shigellosis involving 10 cases and additional sporadic cases were well documented.[283]

Shigellosis has also been well documented in foreign military contingents, most notably in Israel among kibbutz dwellers and recruits of the Israeli Defence Force.[284] Historically, military outbreaks of shigellosis have been associated with consumption of contaminated food items prepared by infected foodhandlers, as well as facilitation of transmission by common houseflies (*Musca domestica*) in this setting.[285] Uncontrolled epidemics of shigellosis, especially due to *S dysenteriae* type 1, are potential "war stopper" illnesses, which cause significant incapacitation and decrement in unit effectiveness.

Description of the Pathogen

Shigellae are slender, gram-negative, nonmotile rod bacteria belonging to the family Enterobacteriaceae. They are closely related genetically to *E coli*, and their origin from a common ancestor has been postulated. There are four clinically important species of *Shigella*: *S dysenteriae*, *S flexneri*, *S boydii*, and *S sonnei*, which are also known as subgroups A, B, C, and D, respectively. Strains of *Shigella* can be serologically characterized by the O (somatic) antigens, which are made up of cell wall lipopolysaccharide antigens. Numerous serotypes exist among *S dysenteriae* (12 serotypes), *S flexneri* (6 serotypes and 13 subserotypes), and *S boydii* (18 serotypes) species and are determined by agglutination with *Shigella*-specific antisera.

S dysenteriae type 1, also known as the Shiga bacillus, is a pathogen of developing countries. It exhibits several unique features compared to other members of the genus *Shigella*, including the production of Shiga toxin and the propensity for epidemic spread. It has been associated with major dysentery epidemics among refugees; a significant proportion of the deaths during the most recent Rwandan civil war were due to *S dysenteriae* type 1 (as well as and *Vibrio cholerae* O1) infections.[286]

The shigellae are highly host-adapted; their only natural hosts are humans and a few nonhuman primates.[260] There are no known environmental reservoirs of infection. Only small numbers of inocula are necessary. Experimental studies in volunteers have shown that disease can result from ingestion of as few as 10 viable *S dysenteriae* type 1 organisms or a few hundred *S flexneri* 2a or *S sonnei* organisms.[287,288]

Epidemiology

Transmission

Direct, person-to-person contact is the most important mode of *Shigella* transmission. In regions with inadequate excreta disposal facilities, flies may also be an important vector.[285,289] The small inocula required to cause shigellosis facilitates transmission of the disease and explains the frequent failure of routine sanitary and hygienic measures to prevent shigellosis. Strict attention to handwashing after defecation[290] and measures to control houseflies[285] have been shown to reduce the incidence of shigellosis in military field studies.

Water and food also appear to be important vehicles of transmission of *Shigella* in developing countries.[291] Epidemics of waterborne shigellosis

caused by fecally contaminated wells, lakes, ponds, pools, and other sources of surface water have been documented. In the United States during the 2-year period of 1993 to 1994, for example, 3 outbreaks of *S sonnei* associated with swimming in lakes (a total of 437 cases) and 4 outbreaks involving untreated water from wells dug and maintained by individuals and an individual cistern (a total of 279 cases) were documented.[292] Foodborne transmission, on the other hand, is not as common but, when it occurs, is associated with large outbreaks.[293] Shigellae are known to grow very well in food items such as rice, lentil soup, milk, cooked beef, cooked fish, mashed potato, raw cucumbers, and vegetables.[294,295]

Secondary cases during outbreaks of shigellosis are common, especially in households of index patients. The attack rate is higher if (*a*) the index case is a young, non–toilet-trained child, (*b*) the contacts are younger (rates of 40% to 60% in those 1 to 4 years of age but less than 20% in adults), (*c*) the houses have privies, and (*d*) improper handwashing practices are noted.[293,296] Other risk factors associated with secondary transmission are contact with a person with dysentery, sharing of latrines with other households, storing of water at home and hand-dipping with a hand-held cup, and consumption of food from street vendors.[297]

In industrialized countries, *Shigella* organisms are readily transmitted in certain populations at high risk where abnormal behavior or poor hygienic practices facilitate fecal-oral contamination.[298,299] High-risk groups include Native American populations,[298] children in childcare centers,[300,301] those in institutions for the mentally retarded,[302] those aboard ships,[303] those in penal institutions,[304] military units training under field conditions,[286] and those who practice anal-oral sex.[305]

Geographic Distribution

Shigellosis has a global distribution, but the prevalence of the various species and types varies geographically. In industrialized countries, such as the United States, endemic shigellosis is primarily a pediatric disease caused by *S sonnei*.[298] In developing countries, *S flexneri* is the most common species, with *S flexneri* 2a being a prominent serotype; *S boydii* is common in the Indian subcontinent.[306]

Incidence

It is estimated that 3 to 5 billion diarrhea cases occur worldwide every year; average rates range from 5 to 12 illnesses per child per year, with rates as high as 19 illnesses per child per year in the poorest areas. Approximately 5% to 10% of these diarrhea cases may be caused by *Shigella* organisms.[306] Diarrheal disease, including dysentery, also constitutes one of the leading causes of mortality, accounting for an estimated 5 to 10 million deaths per year. Most of these deaths (estimated at 12,600 deaths per day) occur in children less than 5 years of age in Asia, Africa, and Latin America.[307,308] The annual worldwide incidence of shigellosis is estimated at 200 million cases, with an annual death toll estimated at 650,000.[309]

Epidemics of Shiga dysentery, due to multidrug-resistant *S dysenteriae* type 1, caused an estimated 500,000 cases and 20,000 deaths between 1969 and 1973 in Central America.[310,311] Likewise, during major epidemics in Africa and the Indian subcontinent, a significant proportion of the population (up to 10%) were affected, with mortality rates as high as 10%.[297,312–314]

Pathogenesis and Clinical Findings

Shigellae cause disease by direct mucosal invasion of the distal small bowel and colon with concomitant inflammatory reaction. Enterotoxin production facilitates invasion and destruction of epithelial cells, which explains the findings of white blood cells and blood in stools. The incubation period for shigellosis is usually 12 to 96 hours, although *S dysenteriae* type 1 infections can take up to 1 week to manifest clinically.[315p451–455] Onset of fever, abdominal cramping, and malaise is followed by a variable amount of watery diarrhea before dysentery begins. In severe cases, it is not uncommon for an infected person to have 20 or 30 bowel movements per day, consisting of scant volumes of mucus or blood or both mucus and blood, often accompanied by severe abdominal cramping, tenesmus, and urgency. Depending on the infecting strain, a large proportion of patients may have only watery diarrhea, and some patients may have fever without intestinal symptoms. In general, *S sonnei* causes the mildest disease and *S dysenteriae* the most severe.

Most cases of shigellosis in well-nourished and healthy people are self-limited and resolve without sequelae. This is frequently not the case, however, in severe infections caused by *S dysenteriae* type 1 or by other serotypes in malnourished populations. In malnourished children, *Shigella* infection, particularly with *S dysenteriae* type 1, may result in a

chronic type of relapsing diarrhea and a protein-losing enteropathy. Other complications in children can include convulsions, meningismus, and secondary spread with vaginitis. Intestinal complications of shigellosis include toxic megacolon, which carries a high fatality rate, and rectal prolapse, which requires early manual reduction. Intestinal perforation is rare.[316]

There are a number of unusual but important extraintestinal complications of *Shigella* infections. Peripheral leukocyte counts in excess of 50,000 have been seen in approximately 4% of patients during outbreaks caused by *S dysenteriae* type 1.[317] Having a leukemoid reaction carries a poor prognosis.[318] Hemolytic-uremic syndrome, consisting of the triad of microangiopathic hemolytic anemia, thrombocytopenia, and renal failure, occurs in a small percentage of cases of shigellosis, mostly those with *S dysenteriae* type 1 infections and mainly in children. Although the pathogenesis of hemolytic-uremic syndrome is not completely understood, there is an association between circulating endotoxin and the development of the syndrome.[314] Early dialysis to eliminate this toxin may be lifesaving.

Shigella bacteremia is generally considered an unusual occurrence.[319] Nevertheless, it has been documented to occur in as many as 4% of cases of *S dysenteriae* type 1 infections in a Bangladeshi population and was found to be associated with a high incidence of other complications and death.[320] In this study, young age and malnutrition were risk factors. Reiter's syndrome or reactive arthritis follows shigellosis in 1% to 2% percent of cases, usually 2 to 4 weeks after the acute illness. Persons with the HLA-B27 histocompatibility antigen are at much higher risk of this complication.[321]

A great majority of *Shigella*-infected patients will clear their infections within 2 weeks, more than 90% will clear within 1 to 4 weeks without antibiotic therapy. Even though long-term *Shigella* carriage has been well documented in less than 5% of cases, it may be important in the perpetuation of infection in the household and in the spread of infection to close contacts and by infected foodhandlers.[322] Carriage is reduced significantly (to less than 1 week) by antibiotic therapy.

A large body of evidence indicates that there is effective acquired immunity to *Shigella* infections. Introduction of a new strain in a previously nonimmune population, for example, is often followed by high attack rates greater than 5% to 10% in all age groups. Prospective studies among children in endemic areas, such as Guatemala[323] and Chile,[324] have shown that a prior bout of shigellosis elicits about 75% protection against reinfection with a homologous serotype. Likewise, serological studies among Israeli military recruits have shown that preexisting anti-lipopolysaccharide (somatic antigen) antibodies protect individuals from subsequent *Shigella* infection.[325] Volunteer challenge studies done in the 1970s have also demonstrated that a previous bout of shigellosis confers 64% to 78% protection against dysentery caused by *S flexneri* type 2a and *S sonnei*.[326,327] Clearly, there is significant but by no means complete protection from clinical shigellosis caused by the same serotype. Unfortunately, such immunity can often be overcome with a large dose of *Shigella* organisms.[328]

Diagnostic Approaches

The definitive diagnosis of shigellosis depends on the isolation or identification of the organism from a stool specimen. In the near future, techniques such as rapid immunoassays for antigen detection, mononuclear antibody-based dipstick assays, DNA probes, and polymerase chain reaction kits may be used routinely for rapid diagnosis. *Shigella* rapidly loses viability in an acid environment and thus may be difficult to recover from stool specimens that are not processed within 2 to 4 hours. When direct plating from a stool sample is not possible, microbiologic recovery can be improved by the use of proper transport media; buffered glycerol saline has been reported to be the best.[329] Cary-Blair medium can also be used for transport but is not as good as buffered glycerol saline.[330] Although mucus or blood-flecked portions of stool samples are the preferred specimens for culture,[331] a properly obtained rectal swab, which samples the material in contact with the mucosal epithelium, can also be used for culture provided it is gathered from at least 2 cm past the anal sphincter. The specimens of choice are, in order of decreasing productivity, stool, rectal swab specimens, and anal swab specimens.[332]

A combination of nonselective media (eg, MacConkey's agar) and selective media (eg, Hektoen enteric agar, *Salmonella-Shigella* agar) are suggested for isolation.[329,331] Additionally, xylose-lysine-deoxycholate medium has been found to be especially good for isolating *Shigella* species.[333] Identity can be confirmed by agglutination tests using group-specific anti-lipopolysaccharide antibodies [334] against the four major serogroups: A (*S dysenteriae*), B (*S flexneri*), C (*S boydii*), and D (*S sonnei*).

In patients with febrile diarrhea or in those with mucoid, bloody stools but without fever, examination for fecal leucocytes by methylene blue staining of a

fresh stool sample is indicated. The finding of fecal leukocytes in the stool strongly suggests, but is not diagnostic of, *Shigella* infection and should prompt stool culture for specific diagnosis.[335] The stool should also be examined for motile amoebic trophozoites containing ingested erythrocytes to rule out infection with *Entamoeba histolytica*.

Recommendations for Therapy and Control

Therapy

As in other diarrheal diseases, restoration of fluid deficit and maintenance of hydration status and serum electrolyte balance is indicated. Antimicrobial therapy has been shown to shorten the duration of symptoms in shigellosis,[336,337] and its use is justified in cases of moderate or severe disease. Throughout most of the world, *Shigella* organisms are resistant to multiple antibiotics that were previously useful in treatment. This makes effective therapy difficult, especially in countries where shigellosis is endemic and where the high cost of newer antibiotics prohibits their use.[338] In addition, major dysentery outbreaks since 1969 have increasingly involved multidrug-resistant strains of *S dysenteriae* type 1,[297,310–312,339–345] creating therapeutic difficulties. Interestingly, the first significant evidence of multidrug resistance occurred in 1967 and 1968 in Vietnam where widespread resistance to tetracycline, chloramphenicol, and ampicillin was found.[277,346] This rapid emergence of antibiotic resistance has been mediated by a drug-resistance (R) plasmid.[269]

The choice of an antimicrobial agent depends on the resistance patterns of *Shigella* in a particular geographic area.[269,293] Five-day regimens with ampicillin (100 mg/kg per day for children; 500 mg every 6 hours for adults) or trimethoprim-sulfamethoxazole (TMP-SMX, TMP: 10 mg/kg per day and SMX: 50 mg/kg per day in two divided doses) are good choices only in areas with sensitive strains. Tetracycline as a single oral adult dose of 2.5 g has been used successfully and may be effective even against antibiotic-resistant strains.[347] Short-course therapy with a quinolone (eg, norfloxacin 400 mg twice a day, ciprofloxacin 500 mg twice a day) or with TMP-SMX (TMP 160 mg and SMX 800 mg, 2 times a day) for 3 days is an alternative that has been useful in several military settings.[283,348] Single-dose therapeutic regimens with quinolones (eg, norfloxacin 800 mg, ciprofloxacin 1 g) have also been found to be effective in treating shigellosis in adults in developing countries.[349–351] Tetracycline and quinolones are not recommended for use in children younger than 8 years old. In such cases, nalidixic acid (55 mg/kg per day in 4 equally divided doses), TMP-SMX (TMP 10 mg/kg per day and SMX 50 mg/kg per day in 2 equally divided doses), or cefixime (8 mg/kg per day) for 5 days is indicated.[293,352] Antiperistaltic agents, such as diphenoxylate hydrochloride (Lomotil), may prolong clinical illness and could play a role in the development of toxic dilatation of the colon and, therefore, should not be used.[353] In contrast, a study done in Thailand among hospitalized patients with dysentery found that the addition of loperamide (Imodium) to a 3-day course of therapy with ciprofloxacin (500 mg twice a day) shortened the duration and frequency of diarrhea by more than 50%.[354]

Control

During acute illness, enteric precautions should be followed. Because of the low infecting dose, patients with *Shigella* infections should not be employed to handle food or to care for children until at least 2 successive fecal sample or rectal swab cultures are negative. The samples should be taken more than 24 hours apart and more than 48 hours after antimicrobial therapy ends. Patients and medical staff should be advised to always wash their hands with soap after defecation, before eating, and after patient contact. Fecally contaminated articles, such as clothing and linen, should be disinfected. Feces and vomitus should be disinfected with calcium hypochlorite or carbolic acid.[315] Active detection of other personnel infected with *Shigella* and treatment of close contacts of cases is not routinely indicated except in the case of foodhandlers, employees of child-care centers, hospital staff, and military personnel known to be exposed to a common source of infection during an epidemic. There is an urgent need to report all suspected outbreaks of shigellosis; early treatment of suspected cases with antibiotics is essential to limit transmissibility in the field setting.

Transmission of shigellosis can be decreased significantly in military populations by following some simple control measures (Exhibit 37-2).

Much effort has gone toward developing vaccines to prevent shigellosis in the past 30 years by many military and civilian investigators. Despite all this effort and despite the fact that *Shigella* was discovered almost a century ago, there are yet no licensed vaccines for the prevention of shigellosis.[355] Development of these vaccines has been hindered because there are no valid animal models for these pathogens and because there is no consensus about what constitute

EXHIBIT 37-2

SIMPLE AND EFFECTIVE MEASURES TO CONTROL TRANSMISSION OF SHIGELLOSIS IN MILITARY POPULATIONS

- Frequent effective handwashing with soap and water, especially after defecation and immediately before eating or preparing food
- Sanitary control and disposal of feces
- Provision of a safe water supply and protection from contamination, to include effective chlorination at the distribution point in military camps
- Avoidance of swimming in potentially contaminated bodies of fresh water (swimming in seawater is considered to be acceptable)
- Control of the vector (fly) populations in and around excreta disposal and dining facilities by use of insecticides, yeast-baited fly traps, garbage collection, and proper disposal of wastewater and sewage
- Proper cooking and subsequent refrigeration of potentially infected food items; leafy vegetables should be washed or chemically treated if they are to be eaten uncooked; all leftover food should be discarded, reheated to more than 60°C, or refrigerated or frozen immediately
- Avoidance of high-risk food items, such as food and drinks from street vendors
- Removal of persons with diarrhea from jobs as foodhandlers
- Early detection and treatment of cases to limit secondary transmission to other unit members
- Selective antibiotic prophylaxis of close contacts or potentially exposed personnel; doxycycline (100 mg/day for 14 days) has been found to protect contacts from clinical shigellosis;* in areas where *Shigella* organisms are antibiotic-resistant, ciprofloxacin (500 mg/day) or norfloxacin (400 mg/day) may be used as an alternative

*Ben-Yehuda O, Cohen D, Alkan M, Greenbaum A, Jelin N, Steinherz R. Doxycycline prophylaxis for shigellosis. *Arch Intern Med*. 1990;150:209–212.

the host protective immune factors.[356] Some scientists feel that protective immunity to shigellosis is mediated by mucosal factors, especially secretory immunoglobulin A (sIgA), and that only live, attenuated strains of bacteria are capable of eliciting an effective intestinal sIgA response. Under the hypothesis that antibodies secreted in the gut have an important role in protection against shigellosis, oral, enteroinvasive *Shigella* vaccines were developed in the 1980s and 1990s.[357]

Other investigators, though, feel that protection can be achieved by serum IgG and mucosal sIgA antibody response conferred by conjugate vaccines that elicit high levels of antibodies to the O-specific lipopolysaccharides of *Shigella* species.[358] Phase I and II studies among United States Army and Israel Defence Force soldiers has indicated that these injectable conjugate vaccines are safe and induce protective immunity that is equivalent to that present after shigellosis.[359,360] Moreover, a phase III study of a single-dose *S sonnei* conjugate vaccine conducted in Israel among male military recruits demonstrated a significant level (74%) of protective efficacy against culture-proven shigellosis caused by *S sonnei*.[361] Testing of other candidate oral, enteroinvasive, *Shigella* vaccines and subunit vaccines (part of the bacteria, administered parenterally, intranasally, or orally) is ongoing. A candidate oral, live, attenuated *S flexneri* 2a vaccine is presently undergoing trials in military personnel in the United States and among civilians in Bangladesh.[362]

[Jose L. Sanchez]

CHOLERA

Introduction and Military Relevance

The disease known as cholera has probably been endemic for over 2,000 years in the Indian subcontinent,[363] and the term "cholera" is first seen in the works of the great Greek physician Hippocrates.[364] The first well-documented clinical descriptions of cholera date back to 1503 in Gaspar Correa's book, *Lendas da India*.[365] The first recognized pandemic of the disease originated around 1817 in India. Since

then, there have been an additional six pandemics. Nonimmune military forces, especially from Europe and India, have been repeatedly plagued by this dreaded disease. Infected military personnel have played a major role in the spread of what is now called classical cholera during the first six pandemics, in the 19th and early 20th centuries. Bengal troops traveling to Oman from Bombay in 1821 were principally responsible for the spread of classical cholera outside of the Indian subcontinent during the first pandemic. Death rates among British troops in India reached 21 per 1,000 in 1822.[366] During the second pandemic, Polish and French troops spread the disease in their homelands and in Austria in the spring of 1831.[367] In the largest recorded military outbreak, 350,000 cases occurred in Europe in 1866 among Austrian, Italian, and German forces. In the United States, Union troop movements during the Civil War were a key factor in spreading the disease to major Midwestern cities. During World War I, an epidemic affected 66,000 Russian prisoners in camps in Hungary, Austria, and Germany.[363]

Cholera caused by the El Tor biotype was first described at the El Tor quarantine station on the Sinai Peninsula in 1905 among pilgrims returning from Mecca. This same strain 55 years later gave rise to the seventh pandemic in 1960 and 1961 in Sulawesi, Indonesia.[363,368] Since then, the El Tor biotype has quickly replaced the classical as the predominant biotype worldwide.

Four important events in the 1990s have placed cholera high on the list of emerging infections. First among them was the reintroduction of cholera into Latin America in January 1991 after nearly 100 years of absence. This outbreak spread from Peru to Mexico within 2 years and in 5 years caused more than 1 million cases and 10,000 deaths.[367]

Second, during late 1992 a new serogroup, *Vibrio cholerae* O139 synonym Bengal, appeared in India and Bangladesh. This Bengal strain (initially detected in the countries bordering the Bay of Bengal) produced major epidemics of cholera-like illness (up to 200,000 cases from 1992 to 1996) in India, Bangladesh, and five other countries in Southeast Asia.[369–371] Travel-associated (ie, imported) cases have also been reported in the United States, the United Kingdom, Denmark, Germany, Japan, Hong Kong, and Singapore.[371–374]

Third, the massive outbreak of El Tor cholera in Rwandan refugees in Goma, Zaire, resulting in 70,000 cases and 12,000 deaths in July 1994, showed that during times of crisis cholera can be catastrophic.[375,376] The very high death rates caused by cholera (approximately 15 per 1,000), with case fatality ratios as high as 48% recorded at one camp, were principally due to the rapid waterborne spread of cholera (as well as shigellosis), which quickly overwhelmed the existing medical support capabilities and the capacity for oral rehydration therapy at diarrhea treatment centers.[376] The Rwandan refugee experience contrasts sharply with the Peruvian experience during the peak of the Latin American epidemic (1991-1993). In Peru, case fatality ratios were kept consistently at or below 1% in comparison to significantly higher case fatality ratios for Africa (approximately 9%) and Asia (approximately 3%).[377]

Fourth, the resurgence of cholera has had an impact on nonimmune military personnel, expatriates, and travelers to endemic areas. During the Peruvian epidemic, for example, attack rates as high as 2% to 10% occurred among Peruvian military recruits (Sanchez JL, unpublished data). An increased incidence of cholera was also noted among Americans at the United States Embassy in Lima.[378] In the United States at the same time, a 10-fold increase in cholera cases was noted by Centers for Disease Control and Prevention investigators caused by the proximity of the Latin American outbreak and increased awareness.[379]

Description of the Pathogen

Cholera is caused by *Vibrio cholerae*, a motile, curved, gram-negative bacillus, first described in 1854 in Italy by Filippo Pacini. Subsequently, Robert Koch demonstrated in 1883 that cholera is caused by this organism, which he called *Kommabazillen*.[368] It is a well-defined species on the basis of biochemical tests and DNA homology studies.[380] The species can be subdivided into 139 different serogroups, based on the composition of the major surface antigen of the cell wall (the O somatic antigen). Only two of these 139 serogroups, O1 and O139, have been associated with epidemics of cholera; these two serogroups have been the only ones consistently found to produce cholera toxin (CT), the toxin responsible for fluid secretion into the bowel lumen.[381] Non-O1, non-O139 serogroups have been associated with only sporadic cases and small clusters of noncholera diarrheal illness.[382] Serogroup O1 can be further subdivided into 3 antigenic forms (or serotypes) named Ogawa, Inaba, and Hikojima based on quantitative differences of factors A, B, and C of the O antigen.[383] *V cholerae* O1 strains are also subdivided into 2 biotypes: classical and El Tor.

V cholerae O139 strains appear to be genetically related to the *V cholerae* O1 strains that caused the seventh pandemic. This non-O1 strain, identified in late 1992, is most likely an O antigen mutant with an array of virulence determinants typical of *V*

cholerae O1, biotype El Tor.[384] The high attack rates of severe cholera from O139 seen among adults in areas long endemic for *V cholerae* O1 would seem to indicate that there is no cross-protection from previous infection by O1 serogroup strains. In contrast to O1 strains, these O139 strains have the capacity to produce a polysaccharide capsule and demonstrate an increased capacity for cholera toxin production, as well as for spread and proliferation within the environment.[385] These strains are also known to survive well in environmental water (eg, ponds, lakes, rivers, canals) unlike O1 and other non-O1 strains.[371,386]

V cholerae has, since the early 1980s, been identified as an integral part of the normal, free-living (autochtonous) bacterial flora in estuarine areas. The persistence of *V cholerae* within the environment (for months and probably years) is facilitated by its ability to enter a viable, nonculturable "dormant" state where the organism's requirements for nutrients and oxygen are markedly decreased.[387] It is also able to bind to chitin, a component of crustacean shells, and is able to colonize the surfaces of algae, phytoplankton, and copepods (zooplankton), in addition to the roots of aquatic plants such as water hyacinths. Environmental factors—such as increased water temperature, decreased salinity, increased pH, and an increase in the seawater's nutrients, among others—may trigger conversion of the organism from the viable, nonculturable phase to the culturable, and therefore infectious, phase. These environmental factors, in turn, may also lead to increases in the crustacean populations, with associated increases in the population of free-living *V cholerae*. The periodic introduction of such infectious environmental isolates into the human population, through ingestion of undercooked shellfish and seafood, is probably responsible for isolated foci of endemic disease on the US Gulf Coast and in Australia, as well as for the initial case clusters that gave rise to the Latin American epidemic.[378,388]

In addition, *V cholerae* O1 strains have been recently found to shift to a "rugose" form associated with the production of an exopolysaccharide that promotes cell aggregation. This form has been found to be resistant to disinfectants such as chlorine.[389] Chlorination of the water supply has been a key, effective intervention in controlling cholera outbreaks in the past.[390] If these rugose strains become prevalent in the potable water supply, they may serve as an important factor contributing to the waterborne transmission of cholera.

Epidemiology

The epidemiology of cholera can be roughly divided into two phases or patterns: the epidemic and the endemic[391,392] (Table 37-6).

Transmission

Cholera is caused by the ingestion of cholera bacilli in food or water that has been previously contaminated by feces or vomitus of infected persons.[315p100–110]

TABLE 37-6

EPIDEMIOLOGIC FEATURES OF CHOLERA

Feature	Epidemic phase	Endemic phase
Level of immunity	None, all susceptible	High, increasing with age until adulthood
Ages at greatest risk	All ages	Children 2–15 y, mothers of children < 2 y
Attack rates	Higher (1%-10%)	Lower (< 1%)
Primary transmission	Single food/water sources	Exposure to contaminated water, shellfish, seafood
Secondary transmission	Variable, intra-familial spread	Multiple food items, contaminated water sources, intra-familial spread (family clusters)
Asymptomatic infections	Less common	Very common
Principal reservoirs	Ill individuals and close contacts	Aquatic and environmental* asymptomatic shedders
Seasonality	Variable	Summer and monsoon months, times of algae blooms in coastal areas

*Viable, nonculturable (VNC) vibrios found in algae, phyto/zooplankton, estuarine waters, and roots of aquatic plants.
Sources: Colwell RR, Huq A. Vibrios in the environment: Viable but nonculturable *Vibrio cholerae*. In: Wachsmuth IK, Blake PA, Olsvik O, eds. Vibrio cholerae *and Cholera: Molecular to Global Perspectives*. Washington, DC: American Society for Microbiology; 1994: 117–133; Glass RI, Black RE. The epidemiology of cholera. In: Barua D, Greenough III WB, eds. *Cholera*. New York: Plenum Medical Book Co; 1992: 129–154; Shears P. Cholera. *Ann Trop Med Parasitol*. 1994;88:109–122.

Epidemics have followed the introduction of *V cholerae* into nonendemic areas and have been characterized by explosive outbreaks. Asymptomatically infected individuals have not played an important role in transmission in epidemic cholera, except for close household contacts (such as infected children or mothers), unit contacts, or foodhandlers. Control of transmission during the initial epidemic phase can be achieved more effectively than later, when the endemic phase is established.

The transition from the initial epidemic phase to a more protracted, chronic endemic phase is attained by the establishment of natural human reservoirs of infection in the population and in the aquatic environment. Once this occurs, cholera tends to settle into a clear seasonal pattern, with peaks of transmission during or at the end of the summer months or after the monsoon (rainy) season.

Contamination of food, whether at home, at common gatherings, in markets, or by street vendors, is common in areas that are endemic for cholera. *V cholerae* O1 can survive for 2 to 14 days in foods and can persist for many weeks in shellfish and mollusks.[388] Widespread contamination of surface water sources, such as lakes, rivers, streams, canals, springs, and wells, also contributes to the transmission of cholera.

The transmission patterns of O139 strains are similar to those of O1 strains.[371] The secondary infection rates among family members approximate 25% within 10 days of the index case. Household water (eg, from tubewells) has often been found to be the principal source of infection in Bangladesh. It appears, thus, that the predominant mode of transmission of *V cholerae* O139 is waterborne.

Geographic Distribution

Cholera is present worldwide and is particularly endemic in India and Bangladesh (surrounding the Bay of Bengal), as well as in South America.

Incidence

Attack rates of epidemic cholera occurring in nonimmune populations can be as high as 10%, affecting all age groups similarly. Considerable morbidity and mortality occur at the time of these outbreaks. For example, the introduction of cholera into West Africa in 1970 resulted in more than 150,000 cases and more than 20,000 deaths reported within 1 year.[393] Likewise, the introduction of cholera in Peru in 1991 resulted in more than 420,000 cases and more than 3,300 deaths reported within the first 15 months of that epidemic.[394]

Once cholera becomes endemic in an area, immunity is acquired early in life; higher attack rates occur in children 2 to 15 years of age and in women of childbearing age who are exposed to large inoculums of *V cholerae* organisms while caring for the very young.[395] Because of this relatively higher level of immunity, lower overall attack rates take place in the adult population (< 1% per year). Secondary transmission of cholera occurs principally by intra-familial spread, with usual rates of infection among family contacts in the range of 4% to 22% and sometimes as high as 50%.[395–397]

Diagnostic Approaches

Cholera is principally a clinical diagnosis. Any patient with watery diarrhea, especially if severely dehydrated, who is in or has traveled within the previous 5 days to an endemic area for cholera should be suspected of having cholera and treated accordingly. Definitive means of diagnosis is by isolation of the organism from culture of stool or rectal swab specimens. If processing is going to be delayed beyond 4 to 6 hours, the sample should be placed in Cary-Blair transport medium; *V cholerae* can be recovered from it for up to 4 weeks after sampling.[398] It is important not to refrigerate or freeze such samples because vibrios are more vulnerable to refrigeration or freezing than other enteric bacilli. Cultures in TCBS agar are detected as large, yellow, smooth colonies. Confirmation is done by slide agglutination in the presence of polyvalent O1 antisera in a microbiology laboratory.

Field Antigen Detection Tests

Rapid, reliable field identification methods are available. The most commonly used is darkfield microscopy, which relies on the identification of motile vibrios and their immobilization with specific O1 antisera. This method can identify cholera infections in 2 to 5 minutes in about 50% of cases.[399] Rapid diagnosis of both *V cholerae* O1 and O139 infections in the field has been made possible since 1992 by simple, rapid, field-expedient, immunological methods.[400–402] Direct detection of bacterial antigen in stool samples is done with coagglutination tests using monoclonal antibodies against the O1 and O139 antigens (CholeraScreen and BengalScreen, New Horizons Diagnostics Corp, Columbia, Md) or with colloidal-based colorimetric immunoassay kits (CholeraSMART and BengalSMART, New Horizons Diagnostics Corp, Columbia, Md). The cholera toxin can also be detected in stool samples by coagglutination tests using anti-cholera toxin (anti-

CT) antibodies.[403] DNA probes and polymerase chain reaction methods have been used in the 1990s in research laboratories for the detection of cholera toxin genes and to detect toxigenic *V cholerae* O1 in food and environmental samples.[380]

Serologic Antibody Detection Assays

Serologic assays can be useful in three settings: (1) in making a retrospective diagnosis of cholera, (2) in conducting epidemiologic investigations, or (3) in identifying infected contacts, (ie, cases where stool samples are unavailable or where many infections may be mild or asymptomatic). Antibacterial (or vibriocidal) and anti-CT antibody tests are described in detail in references 404 and 405. They tend to be used mostly in research settings. Serum vibriocidal antibodies have been associated with protection against disease in studies in endemic areas, as well as in volunteer studies.[380] This protection is related to the inhibition of vibrio colonization by secretory immunoglobulin A in the gut rather than as a result of a direct protective effect of serum (mainly IgG) antibodies. Vibriocidal antibody levels are seen to increase in only 50% to 60% of infected patients and remain elevated for 3 to 6 months after infection. By comparison, anti-CT antibodies are detected in more than 90% of patients and remain elevated for up to 2 years after initial infection. Therefore, anti-CT antibodies are more sensitive and useful in the serologic diagnosis of acute cases and for epidemiologic investigations in previously nonimmune populations, such as soldiers and travelers from developed countries. Serologic diagnosis is assisted by collection of acute phase (within 3 to 5 days of onset of illness) and convalescent phase (3 to 4 weeks thereafter) paired serum specimens. A 4-fold or greater rise in titers is considered diagnostic of recent infection with *V cholerae*.[405]

Pathogenesis and Clinical Findings

The toxin produced by *V cholerae* causes fluid secretion in the bowel lumen. The incubation period of cholera ranges from several hours to up to 5 days.[315] This is greatly determined by the inoculum size[391,406] and whether food serves as the vehicle of transmission because food protects vibrios from the action of stomach acid. As few as 100 to 1,000 organisms in food or in a bicarbonate buffering agent (as in volunteer studies) can cause disease.[406,407] Other host factors that increase the risk of cholera are the use of antacids or medications that reduce gastric acid secretion, the use of cannabis, and a history of gastric surgery.[408] It has also been found that individuals in the O blood group, while not at increased risk of infection, are at increased risk of developing severe cholera illness.[409,410] Breast-feeding appears to protect infants from developing cholera because of the protective effect of immunoglobulin A antibodies in breast milk.[411]

Only a minority of patients infected with *V cholerae* O1 develop severe cholera (cholera gravis). In Bangladesh, for example, it has been estimated that only 11% of classical infections and 2% of El Tor infections result in severe cholera.[412] Studies conducted among Peruvian military units (Sanchez J, unpublished data) and civilian populations [413] have documented that only 5% to 10% of diarrhea cases associated with *V cholerae* O1 infection resulted in severe disease or hospitalization.

The most marked features of severe cholera are the voluminous output of watery stool and the dehydration that results (Table 37-7). The rate of diarrhea can reach 500 to 1,000 mL per hour, leading rapidly to hypotension, tachycardia, and vascular collapse. The patient becomes lethargic or stuporous with sunken eyes and cheeks and dry mucous membranes. Decreased skin turgor (measured by the skin-pinch sign) is found in all such cases. Urine flow is decreased or absent, and serum specific gravity is consistently elevated. Clinical illness that goes untreated resolves in 4 to 6 days in most cases, unless circulatory collapse occurs. More than 90% of *V cholerae* O1-infected persons will be vibrio-free within 8 to 10 days, and rarely does excretion extend beyond 2 weeks.[396,397] Long-term carriers are exceedingly uncommon and do not play a significant role in disease transmission.

Detailed information regarding the clinical aspects of *V cholerae* O139 infections is limited.[371,414,415] Dhar and colleagues[416] have found in Bangladesh that the illnesses caused by O1 and O139 serogroups seem to be similar and that important clinical features, such as the duration of diarrhea and the degree of dehydration before hospital admission, were no different. In addition, they also found that patients with O139-serogroup infections responded to standard O1 serogroup cholera therapy.

Recommendations for Therapy and Control

Rehydration Therapy

The key to the treatment of cholera is the rapid rehydration of the patient, either with oral rehydration therapy (ORT) for mildly dehydrated patients or with a combination of ORT and intravenous re-

TABLE 37-7

GUIDELINES FOR CLINICAL EVALUATION OF DEHYDRATION AND RECOMMENDATIONS FOR REHYDRATION AND MAINTENANCE FLUID THERAPY

Parameter	Degree of Dehydration		
	Mild or none	Moderate	Severe
Mental status	Alert	Restless or lethargic	Lethargic, stuporous, or comatose
Thirst	Present	Present	Marked
Radial pulse	Normal	Rapid	Rapid and feeble or impalpable
Respirations	Normal	Tachypneic	Tachypneic, deep, labored
Skin-pinch sign	Skin retracts immediately	Skin retracts slowly (1 to 2 s)	Skin retracts very slowly (> 2 s)
Eyes	Normal	Sunken	Dramatically sunken
Urine flow	Normal	Scant and dark	Scant or absent
Serum specific gravity	≤ 1.027	1.028-1.034	> 1.034
Fluid deficit*	20 to 50	51 to 90	91 to 120
Preferred method of rehydration	ORT in 4-6 hrs	ORT or IVRT or both, depends on presence of vomiting and stool losses	IVRT, 2L in 30-60 m, remainder in 3-4 h
Preferred type of rehydration	WHO ORT (all ages) Rehydralyte (adults) Pedialyte (children) Infalyte (infants)	WHO ORT or IVRT or both, Normal saline†‡	Lactated Ringer's†
Maintenance	ORT for as long as diarrhea persists	NA	NA

ORT: Oral rehydration therapy, IVRT: Intravenous rehydration therapy, WHO: World Health Organization, NA: Not applicable.
*mL/kg of body weight
†Dextrose-containing solutions (2%–5%) are preferred because of the risk of hypoglycemia in cholera patients.
‡Addition of potassium chloride (10 mEq/L) is recommended to reduce risk of hypokalemia.
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hydration therapy for moderate or severely dehydrated patients. The development of a practical, simple, and safe mode of oral rehydration in the 1960s has been lauded as one of the most important medical discoveries of this century.[417] Fluid therapy is divided into the rehydration phase and the maintenance phase.[418] Table 37-7 presents guidelines to follow for both phases of therapy.

Severely dehydrated patients have a major fluid deficit to make up in the first 4 hours (91 to 120 mL/kg of body weight). Intravenous rehydration therapy with a dextrose-containing solution of Ringer's Lactate (RL) or normal saline (NS) is indicated. In their absence, plain Ringer's Lactate or normal saline supplemented with potassium is indicated. Once the patient is alert and can tolerate oral fluids, ORT should be started. Stool losses, fluid intake, and serum-specific gravity should continue to be monitored closely at the patient's bedside on at least an hourly basis for the first 4 to 6 hours. Serum-specific gravity is the best objective parameter to evaluate success of rehydration; it can be measured using a simple and inexpensive hand-held refractometer. Once ORT is begun, the patient should be encouraged to drink freely to at least equal one and a half times the volume of stool losses. ORT should be continued for as long as the patient has diarrhea. Management of diarrhea can be easily done at the first or second echelon of care (eg, unit aid station, field clinic, hospital). Several ORT formulations are available in the United States and include: (*a*) World Health Organization (WHO) ORT (Janis Brothers Packaging Co., Kansas City, Mo.), (*b*) Rehydralyte (Ross Products Division, Abbott Laboratories, Columbus, Ohio), (*c*) Pedialyte (Ross Products Division, Abbott Laboratories, Columbus, Ohio), and (*d*) Infalyte (Mead Johnson Nutritionals, Bristol-Myers Squibb Co., Evansville, Ind.). Sports drinks (eg, Gatorade) and other high-sugar solutions (such as soft drinks) are not appropriate.[379]

Antimicrobial Therapy

Antimicrobial therapy is an important adjunctive therapy in cholera, whether caused by O1 or O139 strains [371,418] (Table 37-8). Duration of illness and stool volume losses can be cut in half with oral (not parenteral) antibiotics. In addition, the duration of excretion of *V cholerae* is also shortened to an average of 48 to 72 hours with antibiotics.[418] Tetracycline or doxycycline are the recommended first-line drugs. For children less than 8 years of age and pregnant women, erythromycin, furazolidone, or trimethoprim-sulfamethoxazole (TMP-SMX) are indicated. In areas where there has been significant resistance reported, quinolones such as norfloxacin or ciprofloxacin can be used.[416,419–422] Quinolones have great advantages in that they are effective as single-dose therapy and the rate of clearance of *V cholerae* from stools is faster than with tetracycline or furazolidone treatment.[419,420] This rapid clearance of the stools may help to reduce secondary transmission of cholera, especially in hospitals, treatment centers, and refugee settings where increased transmission is a serious problem.[419] Use of bismuth subsalicylate, albeit beneficial for traveler's diarrhea, has not been adequately evaluated in patients with cholera. Antiperistaltic agents, such as loperamide (Imodium) and diphenoxylate hydrochloride (Lomotil), should be avoided. Antiemetic agents, likewise, are of doubtful benefit and should be avoided because they may cause severe dystonic reactions in dehydrated patients.[418]

Control

Some strategies for the prevention and control of cholera follow. They are discussed in more detail in references 315, 378, 423, 424, and 425.

Early detection of incipient epidemics by establishing a continuous surveillance system for diarrheal diseases and investigating severe cases and clusters is crucial. All cases of watery diarrhea, especially if associated with severe dehydration or

TABLE 37-8

ANTIMICROBIAL THERAPY AND RESISTANCE PROFILE OF CHOLERA

Drug	Adult Dosage	Pediatric Dosage	Areas with Resistance
Tetracycline	500 mg four times daily for 3 days or 1 g single dose	50 mg/kg body weight divided in 4 daily doses for 3 days	Bangladesh, India, Thailand, Ecuador, eastern Africa, Zaire
Doxycycline	300 mg as a single dose	4–6 mg/kg as a single dose	Same as for tetracycline
Erythromycin	250 mg four times daily for 3 days	30 mg/kg body weight divided in 3 daily doses for 3 days	Bangladesh, India, Thailand, eastern Africa
Furazolidone	100 mg four times daily for 3 days	5 mg/kg body weight divided in 4 daily doses for 3 days or 7 mg/kg as a single dose	Bangladesh, India, Thailand, eastern Africa
TMP-SMX	320 mg TMP and 1.6 g SMX twice daily for 3 days	8 mg TMP and 40 mg SMX per kg body weight divided in 2 daily doses for 3 days	Bangladesh, India, Thailand, Ecuador, eastern Africa
Quinolones	Norfloxacin 400 mg twice daily for 3 days, or ciprofloxacin 250-500 mg, 1-2 times a day for 3 days or 1 g single dose	Not recommended	Not reported

TMP-SMX: Trimethoprim-sulfamethoxazole

Sources: Bennish ML. Cholera: pathophysiology, clinical features, and treatment. In: Wachsmuth IK, Blake PA, Olsvik O, eds. Vibrio cholerae *and Cholera: Molecular to Global Perspectives*. Washington, DC: American Society for Microbiology; 1994: 229–255; Swerdlow DL, Isaacson M. The epidemiology of cholera in Africa. In: Wachsmuth IK, Blake PA, Olsvik O, eds. Vibrio cholerae *and Cholera: Molecular to Global Perspectives*. Washington, DC: American Society for Microbiology; 1994: 297–307; Khan WA, Bennish ML, Seas C, et al. Randomised controlled comparison of single-dose ciprofloxacin and doxycycline for cholera caused by *Vibrio cholerae* O1 or O139. *Lancet*. 1996;348:296–300; Gotuzzo E, Seas C, Echevarria J, Carrillo C, Mostorino R, Ruiz R. Ciprofloxacin for the treatment of cholera: A randomized, double-blind, controlled clinical trial of a single daily dose in Peruvian adults. *Clin Infect Dis*. 1995;20:1485–1490; Yamamoto T, Nair GB, Albert MJ, Parodi CC, Takeda Y. Survey of *in vitro* susceptibilities of *Vibrio cholerae* O1 and O139 to antimicrobial agents. *Antimicrob Agents Chemother*. 1995;39:241–244; Mitra R, Basu A, Dutta D, Nair GB, Takeda Y. Resurgence of *Vibrio cholerae* O139 Bengal with altered antibiogram in Calcutta, India. *Lancet*. 1996;348:1181.

hospitalization, should be investigated. A simple clinical case definition—for example, watery diarrhea of sudden onset in a person of any age—is appropriate and can reliably predict *V cholerae* O1 or O139 infections in approximately 90% of cases.[424] Clustering in time or place or both (ie, spot mapping of cases) may suggest common modes of transmission amenable to control.

Good personal hygiene will limit spread within the unit or household. Proper handwashing with soap after defecation and before eating or preparing food is key, along with avoiding consumption of high-risk items prepared by the local population, such as food or drinks from street vendors, seafood or shellfish products (especially if raw), vegetables, uncarbonated drinks, and ice. Bathing in potentially contaminated bodies of water should also be prohibited.

Construction and proper maintenance of excreta disposal facilities will reduce the risk of spread of cholera in bivouacked units and refugee camp settings. Defecation on the ground and in or near drinking water sources should be avoided.

Provision of safe and plentiful water, as well as its protection and appropriate storage in the home, unit, or food serving areas, is important. Appropriate care in the preparation and handling of food items and consumption of cooked food while still hot are important. Foodborne spread of *V cholerae* is facilitated by bacterial multiplication in food kept at ambient temperatures after cooking.[388] Although the role of flies in cholera transmission is controversial, it is conceivable that they could represent a risk by inoculating food with *V cholerae.*[426] Therefore, fly-proofing of food service and fecal disposal facilities, as well as fly control by bait-traps or use of insecticides, is indicated.

Chemoprophylaxis

The use of tetracycline (500 mg twice a day for at least 2 days, half dose for children aged 8 to 13 years) or doxycycline (300 mg single dose, half dose for children aged 8 to 13 years) chemoprophylaxis reduces the rate of secondary transmission for household or unit contacts of cases.[423] For children younger than 8 years of age, pregnant women, and persons with kidney disease, tetracycline should be avoided; erythromycin or TMP-SMX may be used in the same dosages as for treatment (see Table 37-8). The use of single-dose ciprofloxacin (250 mg), on the other hand, has not been found to be effective in preventing *V cholerae* O1 infections among household contacts of cases.[427] It should be noted that mass chemoprophylaxis of a community or unit is usually contraindicated, due to the risk of drug resistance and the appearance of potentially serious side effects.[381,423,428] It is indicated only when an outbreak of cholera has occurred in a closed group that has had a common exposure, and it is effective only if given within the first 5 days after exposure. Surveillance for cases among exposed personnel should be conducted for 5 days from the last exposure. No special isolation precautions are needed for cholera patients. Effective measures to limit nosocomial and intra-unit spread include handwashing with soap after each patient is seen, use of gloves for specimen handling, laundering of soiled clothing or bed linen, and disinfection of feces and vomitus with calcium hypochlorite or carbolic acid.[315]

Vaccines

Parenteral, whole-cell cholera vaccines have been in use since the late 19th century. Controlled trials in the 1960s in cholera-endemic areas demonstrated that parenteral vaccines were only 60% efficacious for the first 3 months, declining to 30% 4 to 6 months after vaccination.[429] Parenteral, phenol-inactivated vaccine (Wyeth Laboratories, Marietta, Penn), the only cholera vaccine licensed in the United States, has to be given in 2 doses at 1- to 4-week intervals and is associated with significant local reactions in up to 30% of vaccinees. A booster dose is recommended every 6 months. In addition, this vaccine does not reduce asymptomatic carriage of *V cholerae* O1, and its protective efficacy is very low (< 30%) in children.[430] Simultaneous administration with yellow fever vaccine can decrease subsequent antibody response to both vaccines. The cholera vaccine's usefulness for military forces or travelers to endemic areas is very limited.

The resurgence of cholera has renewed interest in vaccine development. In the past 15 years, inactivated oral cholera vaccine candidates have been developed and found to be protective in challenge studies. An oral vaccine, consisting of the B subunit of cholera toxin (1 mg) and 10^{11} cholera whole cells (WC/BS, Cholerix, SBL Vaccin AB, Stockholm, Sweden), was found to protect against diarrheal illness caused by *V cholerae* O1 and enterotoxigenic *Escherichia coli* in Bangladesh.[431] This vaccine provided 85% efficacy against cholera in the first 6 months and a cumulative efficacy of 50% over 3 years when 2 or 3 doses were given 6 weeks apart.[432] Protection, however, was evident only for the first 3 years of follow-up and was found to be better against classical than El Tor cholera, especially among children younger than 5 years of age.[432,433] A

less expensive, recombinantly produced formulation of this vaccine (WC/rBS; Dukoral/oral cholera vaccine, SBL Vaccin AB, Stockholm, Sweden) was developed in the late 1980s and was subsequently found to be safe and immunogenic.[434] Immunity is conferred within 7 to 10 days of the second dose. This WC/rBS oral vaccine, given in 2 doses 1 to 2 weeks apart, provided 86% efficacy for 3 months against cholera among Peruvian military personnel immediately preceding an epidemic of El Tor cholera with attack rates of 2% to 3% in the summer of 1994.[435] Its efficacy in endemic areas where El Tor Ogawa is prevalent (eg, in Peru), however, has been limited. No efficacy was noted after two doses and 61% efficacy noted after a booster dose given a year later.[436] A similar inactivated oral cholera vaccine manufactured in Vietnam has shown a protective efficacy of 66% against El Tor cholera.[437] Protection in this study was found to be similar for young children (1 to 5 years old, 68%) as for older people (older than 5 years, 66%). It remains to be resolved whether this vaccine will be useful for travelers or military personnel without naturally acquired immunity.[438]

The oral, inactivated vaccines recently developed represent an unquestionable advance over the currently licensed parenteral vaccines. However, the need for two doses 1 to 2 weeks apart may make them a difficult option for rapid immunization of military forces or travelers and may limit their usefulness in the control of incipient or ongoing epidemics of cholera. Single-dose, live, attenuated, oral cholera vaccines would be ideal for these needs. The most well-studied of these vaccines is CVD 103–HgR (Mutacol Berna, Berna, Swiss Serum and Vaccine Institute, Bern, Switzerland). This vaccine confers an immune response (and protection in challenged volunteers) within 8 days of administration.[439] Volunteers attain 90% to 100% protection against subsequent challenge with El Tor and classical strains.[440] Unfortunately, this vaccine was not shown to protect against cholera in a recently completed, randomized, placebo-controlled, double-blind field trial in Indonesia.[441] This vaccine is licensed for use in Europe, Canada, and certain countries of Latin America. A booster dose is recommended after 6 months and chloroquine or antibiotics should be administered no sooner than 1 week after administration of this vaccine.

The rapid spread of *V cholerae* O139 among all ages in areas where *V cholerae* O1 is endemic indicates that immunity to O1-serogroup cholera is not protective against O139-serogroup infections.[369,381] Epidemiologic and laboratory studies suggest that natural immunity to *V cholerae* O1 is not protective against *V cholerae* O139.[433] This has been confirmed in recent studies in rabbits and in human volunteers.[371,442] The high rates of severe illness seen with this new strain and its potential impact in causing large epidemics among nonimmune adults predicate an urgent need to develop live, attenuated *V cholerae* O139-serogroup vaccines.

As of 2000, several O139-serogroup vaccine candidates have been developed and are in various stages of analysis.[443–446] Improved preparations of oral killed vaccines are also being developed, including combination *V cholerae* O1 and O139 vaccines and new parenteral cholera vaccines consisting of O antigens conjugated to a variety of proteins, including cholera toxin.[447]

The hope is that in the future, oral cholera vaccines, killed and live, will become readily available for use in vaccination programs in developing countries,[448] as well as for travelers, expatriates, and military personnel at risk. Another possibly important, although somewhat controversial, scenario is the use of these vaccines during acute emergencies (eg, famines, typhoons, floods) and among refugees in both primitive and well-established camps where the risk of impending cholera outbreaks is considered to be very high.[449] Such mass vaccination with the two-dose WC/rBS vaccine has been accomplished,[450] and cost-effectiveness evaluation performed by Naficy and colleagues found that this vaccine could be used for mass vaccination in refugee settings if the price per dose was low (< $0.22 per dose).[451]

[Jose L. Sanchez]

AMEBIASIS

Introduction and Military Relevance

Throughout history, soldiers involved in military campaigns have suffered from diarrheal illnesses, from Napoleon's troops invading Russia to Civil War soldiers along the banks of the Chickahominy River in Virginia. *Entamoeba histolytica* was first recognized as a diarrheal pathogen among US troops during the Philippine Insurrection in 1899, and since then it has been documented in every major war fought in the developing world. In World War II, for example, admission rates for amebic dysentery in the China-Burma-India theater were 22.39 per 1,000 per year.[452] Amebic dysentery, or amebic colitis, is the most common manifestation of *E histolytica* infection, but the protozoa can also gain

access to the liver, presumably via the portal vein, where it causes liver abscesses. Less common target organs include the lung, brain, and skin, but wherever it invades, it demonstrates the lytic destruction of tissue befitting its species name. In the mid 1990s, *E histolytica* was separated from the nonpathogenic species *E dispar*. This reclassification has important ramifications for diagnosis and treatment because the two protozoa have identical morphology under the microscope but only *E histolytica* infection requires antiprotozoal therapy.

Description of the Pathogen

E histolytica is a pseudopod-forming protozoan parasite in the Sarcodina subphylum. *E histolytica* is the most invasive *Entamoeba,* a group that includes such other species that infect humans as *E hartmanni, E polecki, E coli, E gingivalis*, and *E dispar.* Only *E histolytica* causes dysentery and liver abscess. Its motile trophozoite form invades and causes disease, but the cyst form transmits disease from host to host (Figure 37-3). The quadrinucleate cyst averages from 10 to 15 mm in diameter, is excreted in the feces of an infected host, and is stable for weeks to months in an appropriately moist environment. In the small intestine, the cyst excysts to form eight trophozoites, mononucleate ameboid cells measuring from 10 to 60 mm in diameter. These trophozoites may then colonize the intestine as harmless commensals or invade into the colonic epithelium, causing inflammation and destruction of the bowel wall.

While *E histolytica* trophozoites may either colonize or invade host intestine, *E dispar* can only colonize and has never been documented to invade host tissue. As early as 1925, Brumpt suggested that the pathogenic and nonpathogenic types should be classified into two separate species.[453] However, the inability to distinguish morphologically between these two proposed species caused this proposal to languish until 1978, when differences in patterns of isoenzymes between "pathogenic" and "nonpathogenic zymodemes" of *E histolytica* suggested that two different species did in fact exist.[454] Since that initial observation, evidence has accumulated for the reclassification of *E histolytica* into pathogenic *(E histolytica)* and nonpathogenic *(E dispar)* species based on differences in monoclonal antibody epitopes,[455] Southern blot patterns of genomic DNA,[456] and ribosomal RNA sequences.[457] This reclassification is especially satisfying in that it helps to explain what was long a central conundrum in the study of amebiasis: of all the people who could be demonstrated by microscopic examination of stool samples to be carriers of *"E histolytica"* in the days before the two species were separated, only 10% manifested symptoms of amebiasis. Since *E dispar* is the more common organism and the two species are identical morphologically, it seems likely that most of the asymptomatic infections with *"E histolytica"* detected were actually caused by *E dispar.*

Epidemiology

Transmission

E histolytica cysts are transmitted by ingestion of fecally contaminated water and food or through direct fecal-oral contact; the trophozoite is not infectious because it is too fragile to resist the harsh pH and enzymatic conditions in the stomach. The

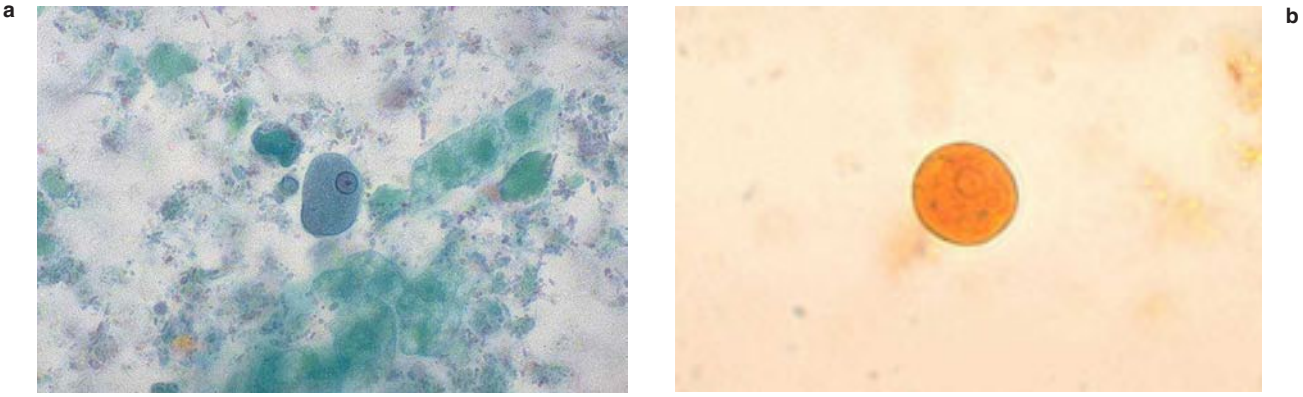

Fig. 37-3. *Entamoeba histolytica* or *E dispar* trophozoites (**a:** in a blue stain) and cyst (**b:** in an orange stain). Note that it is not possible to distinguish *E histolytica* form *E dispar* morphologically.
Photographs: Courtesy of the Centers for Disease Control and Prevention.

cyst, however, passes unscathed through the stomach to the small intestine. Intestinal trophozoites may also encyst and be excreted in the feces of the host, so that the cycle of infection is continued. The disease is considered communicable for as long as cysts are being passed, a situation that can last for years.[315p11–15] The incubation period for the development of amebic dysentery is variable but most commonly lasts from 2 to 4 weeks.

Geographic Distribution

Although *E histolytica* can be found throughout the world, it is endemic in the developing world where sanitary conditions allow infection to spread; examples include Central and South America, Africa, and the Indian subcontinent, where it is the third leading parasitic cause of death.[458]

Incidence

More than 10% of the world's population is thought to be infected by *E dispar* and *E histolytica*, with the approximately 50 million cases of invasive disease in the world each year resulting in as many as 100,000 deaths a year.[459] A 1988 survey in Mexico demonstrated that 8.4% of the population was seropositive for *E histolytica* as measured by the indirect hemagglutination assay, with a peak incidence occurring in the 5- to 9-year-old age group.[460] That year, there were an estimated 1 million cases of amebiasis and 1,216 deaths caused by *E histolytica* infection in Mexico.[461] In Bangladesh, studies using the stool antigen detection test showed that city-dwelling children with diarrhea had a 4.2% prevalence rate of infection with *E histolytica*.[462]

In developed countries, such as the United States, amebiasis is predominately a disease of recent immigrants and travelers returned from the tropics. One study in Germany documented that 0.3% of travelers abroad acquired invasive amebiasis, with the risk of infection increasing with the length of the trip.[463] One dramatic example was 160 Italian travelers who went on a 5-day trip to Thailand where 72% were infected; consumption of certain foods (ie, ice, ice cream, raw fruit) was significantly linked to *E histolytica* infection.[464]

Pathogenesis and Clinical Findings

E histolytica is thought to invade the colonic epithelium directly, adhering to host cells via the Gal/GalNAc lectin.[465] In vitro studies have demonstrated that lectin-mediated adherence is necessary for cytolysis, but the exact mechanism of cell killing is not known.[466] Tissue destruction begins as small foci of necrosis that progress to ulcers. The characteristic amebic lesion is a flask-shaped ulcer extending through the mucosa and muscularis mucosa into the submucosa. Factors that might influence the invasiveness of infection experienced by the host may include the particular strain of *E histolytica* present, the presence of anti-ameba antibodies, and the host's bacterial flora in the intestine, genetic predisposition, and nutritional state.

TABLE 37-9

HISTORY, SYMPTOMS, AND SIGNS OF AMEBIC COLITIS

Male/female	1/1
Immigrant from or traveler to endemic area	Most
Gradual onset	Most
Length of symptoms > 1 wk	Most
Heme (+) stools	100%
Diarrhea	94-100%
Dysentery	94-100%
Abdominal pain	12-80%
Weight loss	44%
Fever > 38°C	10%

The most common clinical manifestation of intestinal amebiasis is amebic colitis, characterized by liquid stools (up to 25 a day) containing bloody mucus and accompanied by abdominal pain and tenderness (Table 37-9). The onset is usually gradual, building over the course of 1 to 3 weeks; when the diarrhea is severe, signs of dehydration and electrolyte imbalance may also be present. Essentially all patients have heme-positive stools, but fecal leukocytes may not be present, presumably due to the cytotoxic effect of amebic trophozoites on human neutrophils.

Acute necrotizing colitis, or fulminant colitis, is a more unusual and more severe manifestation of intestinal amebiasis, with a predisposition for occurring in debilitated hosts. These patients are severely ill with fever, leukocytosis, profuse bloody mucoid diarrhea, and abdominal pain and distention; the mortality rate is greater than 40%. Surgical intervention is often necessary to perform a partial or total colectomy.[467] Other uncommon results of intestinal invasion include ameboma, a carcinoma-like annular lesion of the colon, toxic megacolon, peritonitis, and cutaneous amebiasis.

TABLE 37-10

HISTORY, SYMPTOMS, AND SIGNS OF AMEBIC LIVER ABSCESS

Male/female	9/1
Immigrant from or traveler to endemic area	Most
Length of symptoms > 4 weeks	21-51%
Fever	85-90%
Abdominal tenderness	84-90%
Weight loss	33-50%
Hepatomegaly	30-50%
Diarrhea	20-33%
Cough	10-30%
Jaundice	6-10%

From the intestine, invasion of submucosal venules can allow trophozoites to disseminate through the portal vein to the liver, where they can cause amebic liver abscess. Presenting symptoms of amebic liver abscess are usually fever and abdominal pain, often in the right upper quadrant (Table 37-10). On physical exam, there is often point tenderness over the liver, with or without hepatomegaly. Laboratory findings may include leukocytosis, mild anemia, and elevated alkaline phosphatase levels; hepatic imaging studies, such as ultrasound or computerized tomography, reveal an oval-shaped defect. Most patients do not experience concurrent diarrhea, although a history of dysentery within the past year is common.

Complications of liver abscess occur when the abscess expands to involve adjacent structures, such as the peritoneum, pericardium, diaphragm, pleural cavity, or lungs. Clinical manifestations of pleuropulmonary amebiasis are cough, pleuritic pain, and dyspnea. Less frequently, amebae spread to the brain by a hematogenous route, forming large necrotic lesions that rapidly prove fatal.

Diagnostic Approaches

Because *E histolytica* is endemic in the developing world, heme-positive diarrhea, especially in the absence of fever, in persons living in or returning from these areas should immediately raise the suspicion of amebic infection. Other invasive pathogens that should be included in the differential diagnosis are *Shigella* species, *Salmonella enteritidis, Campylobacter jejuni, Yersinia enterocolitica,* and the invasive species of *Escherichia coli.* Additionally, since amebiasis can mimic inflammatory bowel disease, care must be taken to distinguish between these two diagnoses because steroid administration can cause amebic dysentery to develop into fulminant colitis.

The standard method for diagnosing intestinal amebiasis is to identify *E histolytica* trophozoites or cysts in the stool. This method, however, is flawed for two reasons. The first is that microscopic examination of a single stool specimen has a sensitivity of no more than 33% to 50% and, according to one study, a specificity of 79%. The second major problem is that this method fails to distinguish between the pathogen *E histolytica* and the morphologically identical *E dispar,* an organism that has never been documented to cause colitis or liver abscess. While it is true that hematophagous trophozoites are more likely to be *E histolytica,* they can also be *E dispar*.[468]

Taking advantage of the fact that *E histolytica* and *E dispar* possess divergent surface proteins, a stool antigen detection test that is specific for *E histolytica* has become available for clinical use from TechLab, Inc (Blacksburg, Va.). This test uses monoclonal antibodies specific for the *E histolytica* lectin in an enzyme-linked immunosorbent assay. Sensitivity and specificity are very high for this kit, at 93% and 98% respectively.[468] Another diagnostic test is the indirect hemagglutination test for anti-amebic antibody. This test is approximately 80% to 90% sensitive for amebic colitis and liver abscess but is problematic because it can be negative early in the course of infection and remain positive for years after an episode of amebiasis.[469] In endemic areas where a substantial number of residents have anti-amebic antibodies as detected by this test, a positive serologic test may reflect current or prior invasive amebiasis.[470]

If liver abscess is suspected, hepatic imaging can quickly establish the presence of a cavitary defect in the liver. However, because comparative studies using ultrasound, computerized tomography, and magnetic resonance imaging have shown that it is not possible to differentiate amebic from pyogenic abscess based on imaging alone,[471–473] information from epidemiologic risk factors must be used to suggest a diagnosis. Patients with amebic liver abscess tend to be younger in age (less than 45 years), predominantly male, and recent travelers or immigrants. Pyogenic liver abscess patients, on the other hand, often present with concurrent biliary tract disease. Serum anti-amebic antibodies can also be useful for establishing a diagnosis, and, if necessary, ultrasound-guided fine needle aspiration can be used to investigate the lesion. The stool antigen detection test is less effective for liver abscess, with a sensitivity of only 67%.[474]

Recommendations for Therapy and Control

Asymptomatic colonization with *E histolytica* can be treated with diloxanide furoate (500 mg three times a day for 10 days in adults) or with paromomycin (30 mg/kg in three divided doses for 7 days). Another luminal agent, diiodohydroxyquin, can cause optic atrophy and vision loss in children receiving chronic treatment and is not commercially available in the United States. All three of these agents are generally well tolerated.

Both amebic colitis and liver abscess can be treated with metronidazole (500-750 mg three times a day for 10 days) plus one of the luminal agents. Although metronidazole has some unpleasant side effects, such as headache, nausea, metallic taste, and a disulfuram-like reaction to alcohol, reaction is rarely severe, and treatment efficacy is greater than 90%. Uncommon neurologic side effects, such as vertigo, encephalitis, or neutropenia, may require discontinuation of treatment. Tinidazole, a nitroimidazole not available in the United States, is also an effective treatment. If patients with liver abscess fail to respond after 3 days, chloroquine or dehydroemetine may be added to the regimen. Needle aspiration of liver abscess is usually not required and has not been shown to speed recovery.

Control of amebic infection can be achieved by eradicating fecal contamination of food and water. Human feces must be disposed of in a sanitary manner, and persons working in endemic areas must be educated in personal hygiene and safe handling of locally obtained food and water supplies. Since cysts are resistant to low doses of chlorine or iodine, water can be boiled to make it safe to drink, and raw vegetables should be washed with soap and then soaked in vinegar for 15 minutes to ensure eradication of the cysts. Public water supplies can be protected from contamination by sand filtration, which removes most cysts.[315]

Although diarrheal pathogens such as *E histolytica* have long been a scourge of army encampments, recent military operations, such the Persian Gulf War, where the percentage of personnel treated for gastroenteritis per week dropped to below 1% after the first month, demonstrates that with proper precautions diarrheal disease does not have to be a major player in future military campaigns.

[William A. Petri, Jr.; Joanna M. Schaenman]

GIARDIASIS

Introduction and Military Relevance

Since the time of the Israelites fighting the Hittites, prevention of diarrheal disease has been a key factor in the successful mobilization of troops. A passage in Deuteronomy (23:9) exhorts the Israelites: "As part of your equipment have something to dig with, and when you relieve yourself dig a hole and cover up your excrement."

Giardiasis is an important parasitic cause of diarrheal disease. It is the most common parasite identified in stool samples of individuals in the United States, present in about 4% of stool specimens submitted to clinical laboratories.[475] The disease is quite common in developing countries, especially in urban slums where a substantial number of children are infected. Waterborne and foodborne transmission are the most frequent mechanisms of spread, with person-to-person spread important in daycare settings and among sexually active homosexual males.

In the military, giardiasis will most often be encountered in personnel during or after return from deployment to developing countries. In addition, it may be seen by those caring for native populations, refugees, and peacekeeping forces from developing nations. An example of the increased risk for giardiasis in developing countries is the experience with diarrheal illness in expatriate residents and tourists to Nepal, where 9% to 16% had *Giardia lamblia* identified in their stools.[77] In Operation Restore Hope in Somalia from 1992 to 1993, 0.8% of personnel sought care for diarrheal illness each week and less than 3% of all personnel reported a diarrheal illness per week. *G lamblia* was isolated from 4% of personnel with diarrhea, making it the third most common eneteropathogen identified (*Shigella* species were isolated from 33% and enterotoxigenic *Escherichia coli* from 16%). The relatively low overall attack rate of diarrhea (compared to previous deployments in developing countries) likely was due to the lack of consumption of local food products because of the economic devastation and security threats within Somalia. As in previous deployments, personnel drank bottled water from approved vendors and preprepared food from the United States.[283] A survey of 422 Marines returned from Operation Desert Storm similarly revealed a 2% prevalence of *G lamblia* cysts.[476] The risk of contracting giardiasis is not restricted to developing countries, however. In a Utah Army National Guard field training exercise in the Rocky Mountains of the United States, 15% of all personnel reported symptoms consistent with giardiasis, and symptoms were reported in 62% of personnel who supplemented their water supply with raw water from lakes, streams, and a cattle watering trough.[477]

Description of the Pathogen

Giardia lamblia has also been called *G intestinalis* and *G duodenalis.* The infective form of the parasite is the cyst, which is 7 to 10 μm wide and 8 to 12 μm long, with a refractile cell wall and 2 to 4 nuclei. Trophozoites are the motile form of the parasite, which emerge from the cyst in the small bowel lumen. They contain 2 nuclei and 4 flagella and are 12 to 15 μm long by 5 to 10 μm wide. The nuclei have a characteristic central karyosome, which gives the trophozoite its face-like appearance in stained specimens. The dorsal surface of the trophozoite is round and smooth, while the ventral surface has a concave anterior disc that is thought to help the trophozoite adhere to the intestinal epithelium.

Epidemiology

Transmission

Giardiasis is highly infectious—ingestion of as few as 10 to 25 cysts produces disease in human volunteers. Waterborne transmission is an important route of acquisition of giardiasis. Consumption of improperly treated surface water (as opposed to well water) is the most important risk factor. Military personnel, hikers, and campers who consume untreated stream or other surface water are at risk for infection with giardia. Surface water may be contaminated not only with giardia from human sources, but also with giardia from beavers, muskrats, and possibly other animals that have the potential to transmit giardia to humans.[478]

Foodborne transmission occurs. In one instance, 32 employees of a public school system developed symptomatic giardiasis after eating home-canned salmon. The salmon had been prepared by a grandmother who had just diapered her grandson, and the grandson was subsequently shown to have giardia infection.[479] Outbreak investigations need to consider the possibility of foodborne transmission, although waterborne transmission is more common.

Person-to-person spread of giardia infection is documented in children and employees in daycare centers, in sexually active male homosexuals, and in residents of institutions for the mentally handicapped.

Geographic Distribution

Giardiasis occurs in all parts of the world and is a common cause of waterborne outbreaks of diarrhea in the United States. Waterborne outbreaks have occurred in the Rocky Mountain areas of the United States and Canada and in the northwestern and northeastern United States. Even seemingly pristine mountain streams in North America can be contaminated with giardia; the infectious giardia cysts are extremely stable in cool water. In some urban slums in developing countries, rates of giardia infection approach 100%.[480]

Incidence

Surveys of children under the age of 3 years in daycare centers have measured giardia infection rates as high as 25% to 50%.[481] Most of these infections are asymptomatic: studies demonstrated that children with giardia infection had normal nutritional status and were not more likely to have enteric symptoms. Parents of children in day care and daycare workers have a higher rate of giardia infection than the overall population. Homosexual men seen in sexually transmitted disease clinics have rates of giardia infection as high as 10%.[482]

Pathogenesis and Clinical Findings

Pathogenesis

Infection is initiated by the ingestion of *G lamblia* cysts. Excystation follows ingestion, with the trophozoites multiplying in the small bowel. The infection remains luminal in almost all cases, with rare exceptions of mucosal invasion by the trophozoites. The parasite may adhere to the intestinal epithelium via its ventral disk or via a parasite carbohydrate-binding adhesin protein. Trophozoites encyst in the bowel lumen, with an encystation-specific secretory vesicle system implicated in synthesis of the cyst wall.[483]

The pathogenesis of diarrhea is not clear. No enterotoxin has been characterized, and the organism is normally not invasive. Damage to intestinal epithelial cells and atrophy of microvilli have been shown in biopsies of some patients with giardiasis. Malabsorption of protein, D-xylose, and fat soluble vitamins, as well as disaccharidase deficiency, occurs in some patients with giardiasis.

Different strains of the parasite differ in their ability to cause infection and diarrhea, as has been shown in human challenge studies. Parasite surface antigen variation has been documented in vitro and in experimental human infections, and the antibody response has been shown to be isolate-specific, suggesting that antigenic variation may be a mechanism of immune evasion.[484]

Evidence for acquired immunity to giardiasis includes the lower incidence of infection in adults than in children and the observation from epidemiological and human experimental challenge stud-

ies that symptomatic infections with giardia are more common with the first episode of infection than with later infections.[480,484]

Clinical Findings

Infection can be manifest after return from an endemic or high-risk area, as the average incubation period from infection to onset of diarrhea is 7 days and can be as long as 28 days. The typical patient with symptomatic giardiasis will have an illness lasting 7 days or more with some combination of symptoms including diarrhea, flatulence, foul-smelling stools, nausea, abdominal cramps, and excessive tiredness (Table 37-11). The most notable feature of the illness is the prolonged nature of the diarrhea and the malabsorption that may be present.[485] Lactase deficiency and malabsorption of D-xylose, protein, fat, and fat-soluble vitamins may all occur to varying degrees. Stool specimens are semiformed or loose, lack occult blood, and may contain mucus or fecal leukocytes or both. Especially in endemic settings, such as daycare centers in the developed world and urban slums in developing countries, most giardia infection is asymptomatic. Protection against symptomatic infection in children under 18 months of age has been associated with breast feeding.

Diagnostic Approaches

The diagnosis of giardiasis should be considered in outbreaks or individual cases of diarrheal illnesses lasting 5 to 7 days or more. Travel to a developing country, exposure to children in day care or to institutionalized individuals, and sex between male homosexuals should all increase the suspicion of giardiasis. Common source outbreaks can be either waterborne or foodborne.

Historically, giardiasis has been diagnosed by identification of the trophozoite or cyst in stool specimens. The motile trophozoite can sometimes be identified in a saline wet mount of fresh stool. Cysts can be stained with iodine; stools preserved in polyvinyl alcohol need trichrome or iron hematoxylin stains. Antigen detection assays are now available from at least six companies in immunofluorescent and enzyme immunoassay formats. These tests have comparable, and in many cases improved, sensitivity and specificity compared to microscopy. Sampling of duodenal contents for giardia by aspiration, biopsy, or string test is almost never necessary if careful examination of stool with antigen detection tests or stool microscopy is performed.

TABLE 37-11

PERCENTAGE OF PATIENTS WITH GIARDIASIS WHO HAVE SPECIFIC SYMPTOMS AND SIGNS OF GIARDIASIS

Prolonged diarrhea	100%
Fatigue	97%
Abdominal cramps	83%
Bloating	79%
Malodorous stool	79%
Flatulence	76%
Weight loss	59%
Fever	21%
Vomiting	17%

Reprinted with permission from Oxford University Press: Hopkins RS, Juranek DD. Acute giardiasis: an improved clinical case definition for epidemiologic studies. *Am J Epidemiol*. 1991;133:402–407.

Recommendations for Therapy and Control

Metronidazole is the drug of first choice for treatment of giardiasis, although it does not have a Food and Drug Administration indication for this use; tinidazole is also effective but is unavailable in the United States. Metronidazole (250 mg three times a day for adults or 15 mg/kg a day in three divided doses for 5 days for children) is 80% to 95% effective. Side effects of treatment include a disulfiram-like reaction when taken with alcohol, nausea, dry mouth, and headache. Dizziness, vertigo, paresthesias, and, rarely, encephalopathy or convulsions can be neurologic side effects and warrant discontining the drug. Neutropenia has been associated with metronidazole but is reversible after discontinuing the drug. There is no evidence of carcinogenicity or mutagenicity of metronidazole in humans, although use during the first trimester is not indicated. Alternative drugs include furazolidone, which can cause hemolysis in individuals with glucose-6-phosphate dehydrogenase deficiency; quinacrine, which is poorly tolerated because of nausea, vomiting, and cramping and is unavailable in the United States; and paromomycin, for which clinical experience in the treatment of giardiasis is limited.[486] In patients with a history of exposure and clinical findings consistent with giardiasis but with negative stool diagnostic studies for *G lamblia* and other enteropathogens, many authorities recommend empiric treatment with metronidazole because of the historic difficulties with sensitivity of the diagnostic tests.

Prevention of waterborne outbreaks requires proper flocculation, sedimentation, filtration, and chlorination of water supplies. Filtration is the single most important step of water purification for removal of the chlorine-resistant giardia cysts from community water supplies, as the cysts of giardia are not completely inactivated by the other steps. Good personal hygiene is required to prevent transmission by food handlers and in daycare centers. For military personnel in the field, all surface water should be considered to be contaminated with giardia. Approaches to field water purification include bringing the water to a boil for 1 minute, filtration through a 2 μm filter (but a 1 μm filter is best to also eliminate other cyst organisms), or treatment for 30 minutes with halazone (5 tablets per liter for 30 minutes), Globaline (tetraglycine hydroperiodide, 1 tablet per quart), or saturated crystalline iodine (12.5 mL/L for 30 minutes). Halazone or iodine treatment of water is less effective at 3°C than at 20°C.[487]

[William A. Petri, Jr.]

ENTERIC COCCIDIA INFECTIONS

Cryptosporidium

Introduction and Military Relevance

Cryptosporidium parvum, an intracellular coccidian protozoan, is an important emerging enteric pathogen associated with large waterborne outbreaks and cases related to person-to-person and zoonotic transmission. The control of this organism is challenging because of its high resistance to chlorine and other chemical disinfectants, small size (making filtration of the organism from potable water sources difficult), low infectious inoculum, and ubiquitous presence in various animal hosts and surface-water sources worldwide.[488]

Cryptosporidium was described in 1907 but first became recognized as an important human pathogen during the 1980s among immunocompromised persons, especially those infected with human immunodeficiency virus (HIV). Since then, the organism has increasingly been recognized as a common cause of diarrhea among immunocompetent persons in both developed and developing countries. *Cryptosporidium* is a well-recognized cause of traveler's diarrhea[489,490] and should be specifically considered in any water purification strategy used during a military deployment.

Description of the Pathogen

At least 20 species of *Cryptosporidium* have been reported, with *C parvum* the species associated with clinical illness in humans.[488] *C parvum* is found in a variety of mammals, including livestock and pets. It has a complex life cycle, which includes sexual and asexual stages and the ability to auto-infect and complete its development within a single host. The infectious inoculum has been proven to be as low as 30 organisms and theoretically may be as low as one organism.[491,492] Infectious oocysts, excreted by persons or animals, can exist in the environment for prolonged periods.

Epidemiology

Transmission. Fecal-oral transmission of oocysts can occur through person-to-person contact, animal-to-person contact, and ingestion of water or food that has been contaminated by human or animal feces.[493] Because of the widespread prevalence of the organism in animals, *Cryptosporidium* is ubiquitous in a variety of environmental water sources. Municipal drinking water outbreaks in the United States and other countries have occurred when *Cryptosporidium* has passed from surface-water sources (eg, lakes, rivers, and streams) through municipal treatment systems that met regulatory standards for filtration and chlorination.[493–495] The largest known *Cryptosporidium* diarrheal outbreak linked to public water occurred in 1993 and affected more than 400,000 residents of the Milwaukee, Wis., area.[495] In addition to common-source outbreaks linked to drinking water, outbreaks linked to public swimming facilities have also been well documented.[493,496]

Recent studies suggest that *Cryptosporidium* oocysts are present in 65% to 97% of surface water in the United States and that small numbers of oocysts regularly breach filtration systems; oocysts have been found in tap water in 27% to 54% of communities evaluated.[493]

Because of the low infectious inoculum, *Cryptosporidium* organisms are easily passed from person to person in a variety of settings, such as within families, at childcare and health care centers, at other institutional settings, and between sexual partners.[488,493,497] Animal-to-human transmission has been documented, especially from calves but also from other livestock, laboratory animals, and, occasionally, household pets.[488,493] There has been at least one case of cryptosporidiosis thought to be related to aerosol transmission.[498]

Geographic Distribution. *Cryptosporidium* has a world-wide distribution. However, the widespread nature of *Cryptosporidium* is often not well appreciated because of the lack of routine testing for this organism in clinical microbiology laboratories and research laboratories that specialize in enteric diseases.

Incidence. The organism has been estimated to cause 5% to 10% of diarrheal cases in developing countries and 1% to 3% of diarrheal cases in the United States and Europe,[488] but reported rates vary widely.[499] The high seroprevalence of *Cryptosporidium* that has been documented even in developed countries, where 17% to 58% of adults have detectable antibodies,[494,499,500] attests to the widespread exposure to the organism.

Pathogenesis and Clinical Findings

Sporozoites released from ingested oocysts invade and replicate in intestinal epithelial cells in both the small and large intestine. The exact mechanism of how the organism causes diarrhea is unknown. The average incubation period is 7 days, with a relatively wide range (1 to 28 days).[488,501,502]

In normal as well as immunocompromised hosts, infection can range from asymptomatic to severe, cholera-like diarrhea. Acute, watery diarrhea is the most common symptom and may be accompanied by loss of appetite, abdominal cramps, fatigue, malaise, nausea, vomiting, fever, and other symptoms.[488,495] Clues that may suggest a *Cryptosporidium* infection include prolonged diarrhea and diarrhea that is unresponsive to standard antibiotic treatment. In the Milwaukee outbreak, the mean duration of illness was 9 to 12 days for persons with laboratory-confirmed infection.[495,501] In normal hosts, the illness is self-limited, whereas immununocompromised hosts are predisposed to chronic *Cryptosporidium* infections.

Cryptosporidium can be excreted well after the resolution of symptoms. Although oocyst shedding for up to 2 months has been documented, the mean duration of shedding after resolution of symptoms is 7 days.[502] In the Milwaukee outbreak, 39% of patients developed recurrent episodes of watery diarrhea after 2 to 14 days of being free of symptoms.[501] The explanation for these recurrences, which lasted an average of 2 days (range 1 to 14 days), is uncertain but may relate to persons reinfecting themselves with oocysts that they are shedding.

Diagnostic Approaches

Cryptosporidium infection should be considered in the differential diagnosis of diarrheal episodes among US service members stationed in developing and developed countries. It is important for clinicians to determine whether routine ova and parasite examinations performed at their laboratory facilities include evaluation for *Cryptosporidium*. The diagnosis in a field setting is the same as in garrison. The diagnosis can be made in a field setting if there are capabilities for performing routine microscopy by a concentration procedure such as Sheather's sugar flotation or modified acid-fast staining.[488] Stool specimens may be examined fresh or after formalin fixative under routine light microscopy. Using the Sheather's sugar flotation method, *Cryptosporidium* species display a pink-tinged spherical shape under high-power light microscopy. Oocysts stain red or pink using the modified acid-fast procedure. Because other coccidia have similar microscopic and staining characteristics, it is important to measure the size of organisms detected. *Cryptosporidium* species are typically 4 to 6 μm in size, compared with 8 to 10 μm for *Cyclospora* and 20 to 30 μm for *Isospora*.[503] Newer assays using monoclonal antibodies, immunofluorescence, and enyzme-linked immunosorbent assay methods have been developed that may offer increased sensitivity in detecting *Cryptosporidium* in fecal specimens.[488,504]

Recommendations for Therapy and Control

Numerous drugs have been tried against *Cryptosporidium* with poor or limited success, although data from one study suggest that paromomycin, a poorly absorbed aminoglycoside, is effective in reducing oocyst excretion and improving clinical condition of patients with acquired immunodeficiency syndrome and cryptosporidiosis.[505] No treatment has been proven to shorten the course of infection in normal hosts.

Although data are limited on the risk of *Cryptosporidium* in military populations, based on data from civilian communities and travelers, *Cryptosporidium* may pose a significant threat of causing outbreaks related to the waterborne and person-to-person modes of transmission. The Centers for Disease Control and Prevention's (CDC's) strategy for prevention of infection [506] combines optimal potable water treatment with improved diagnostic and surveillance methods. The risk associated with low levels of oocysts, such as are commonly found in publicly treated water, is unknown but is generally not considered to be a serious hazard for immunocompetent persons unless other data suggest that water quality is not acceptable. Such data include epidemiologic evidence of an increase in the number

of cases, water turbidity measurements, fecal coliform counts, and particle counts or turbidity measurements on filters. When evidence suggests that water quality may not be adequate, the CDC recommends boiling drinking water as the most reliable method of killing oocysts.[506] Bringing water to a boil for any length of time is adequate.[507] If a filtration system is used, only a filter capable of removing particles less than or equal to 1 μm should be used.[506] Filters in this category include those that produce water by reverse osmosis, those labeled as "Absolute" 1 μm filters, and those meeting American National Standards Institute (ANSI) (formally the National Sanitation Foundation) International Standard #53 "Cyst Removal." Systems that only employ ultraviolet light, activated carbon, or pentiodide-impregnated resins are not effective against *Cryptosporidium*. Bottled water does not guarantee that the water is free of oocysts unless it was distilled or filtered by methods that meet the criteria indicated above. Bottled-water labels have not been standardized regarding water source and whether treatment methods are adequate to remove oocysts. Generally, groundwater sources (eg, springs and wells) are much less likely to contain *Cryptosporidium* oocysts than surface-water sources, but the exclusive source of water is often not specified. Use of the terms "microfiltration" or "Nominal" 1 μm filters may not ensure that the filters used were effective against *Cryptosporidium*. Ozonation can kill oocysts, but the appropriate concentration and contact time relative to the allowable level of ozone has not been established for bottled water. Carbonated canned or bottled beverages are considered safe.

In addition to assuring adequate water treatment, secondary transmission through person-to-person spread needs to be carefully controlled because of the low infectious inoculum. Patients with *Cryptosporidium* infections should be instructed to wash their hands frequently (especially after using the toilet and before eating), avoid preparing food, avoid contact with hospitalized or institutionalized persons, and refrain from swimming in public bathing areas (such as swimming pools) while they have diarrhea. They should follow these precautions for 2 weeks after symptoms have resolved because of the likelihood that they will continue to shed viable organisms.[506]

Cyclospora Species

Introduction and Military Relevance

Cyclospora species (previously referred to as cyanobacterium-like bodies) has been associated with prolonged diarrhea among travelers [508–513] and indigenous persons living in developing counties.[514–517] Like *Cryptosporidium, Cyclospora* is also a cause of chronic diarrhea in HIV-infected persons.[511,512,518] Although the organism was first described in 1979,[519] it was not recognized as an important pathogen until the late 1980s and early 1990s.[508–514] Traveler's diarrhea cases caused by *Cyclospora* have been reported from all over the world, and a particularly high incidence of the infection has been documented among tourists and expatriate residents in Nepal.[508,509]

Description of the Pathogen

Initial reports in the 1980s and early 1990s described the organism either as resembling a cyanobacterium (blue-green algae), based primarily on the morphology in formalin-preserved specimens, or a coccidia, based on staining characteristics that were similar to *Cryptosporidium parvum*. [508,510–513,520] The organism, collected in potassium dichromate, was conclusively shown in 1993 to be a coccidia. Based on its sporulation characteristics, it was identified as a *Cyclospora,* a coccidia found in certain animals, and the name *Cyclospora cayetanensis* was proposed.[514,521] A *Cyclospora* oocyst, when induced to sporulate, develops four sporozoites within two sporocysts.

Epidemiology

Transmission. Studies provide compelling evidence that *Cyclospora* is a waterborne disease. In a case-control study of expatriates and travelers in Nepal, consumption of untreated water was significantly associated with disease.[509] *Cyclospora* infections in Nepal and other locations are highly seasonal, with virtually all cases occurring during the warm, rainy months.[508,509] This suggests that environmental factors are important in the life cycle of this organism. In 1990, an outbreak of diarrhea caused by *Cyclospora* occurred among 21 house-staff physicians and other staff working at a hospital in Chicago.[522] An epidemiologic investigation identified tap water in the physicians' dormitory as the most likely source, and an environmental investigation suggested that stagnant water in a rooftop storage tank may have contaminated the water supply after a pump failure. A 1995 outbreak of *Cyclospora*-induced diarrhea at a country club in New York was also traced to contaminated drinking water.[523]

Like *Cryptosporidium, Cyclospora* is difficult to

identify in water sources; the concentration of oocysts in water is likely to be low. However, there are at least three reports of the organism being identified in epidemiologically implicated water sources.[509,524,525] *Cyclospora* may be similar to *Cryptosporidium* in being resistant to chlorine. In 1994, an outbreak of diarrhea caused by *Cyclospora* occurred among British soldiers stationed at a Gurka military training camp in Pokhara, Nepal.[524] The organism was found in camp drinking water despite adequate chlorine levels.

In addition to the waterborne route of transmission, there is increasing evidence that *Cyclospora* is transmitted by food sources.[526–529] In the case-control study from Nepal, consumption of untreated water accounted for only 28% of cases studied,[509] suggesting that additional modes of transmission, such as by food or person-to-person contact, were likely. In one report from Nepal, *Cyclospora* was identified on a head of lettuce from which a patient had eaten 2 days before the onset of symptoms.[526]

In 1996 and 1997, large outbreaks of *Cyclospora* infection were detected in the United States and Canada.[529,530] Evidence implicated consumption of fresh raspberries from Guatemala and led to widespread recognition of the importance of this pathogen.

Geographic Distribution. A growing number of reports suggest that *Cyclospora* has a worldwide distribution. These include case reports of diarrhea among travelers and indigenous persons in numerous developing countries,[508–519] as well as reports of *Cyclospora* outbreaks and sporadic cases occurring in developed countries.[522,523,528–531]

Incidence. Although there have been many case reports throughout the world, there have been very few systematic studies of prevalence or incidence of *Cyclospora* in defined populations. Among expatriates and tourists in Nepal, the organism is identified in more than 10% of diarrhea cases occurring during the rainy season, and an annual incidence of 7% was documented among US Embassy personnel and dependents there in 1992.[509] In a subsequent year-long active-surveillance study of expatriate residents, an annual incidence of 32% (16 cases per 50 person-years) was detected.[532] Among Nepalese children younger than 5 years of age presenting to a clinic for treatment of diarrhea, 5% had *Cyclospora* identified in their stool.[515] There was a pronounced age variation, with a 12% prevalence among those children who were 18 months of age or older.

In a prospective study in Peru, 6% to 18 % of children younger than 2 years of age were found to have *Cyclospora* organisms at some time during a 2-year period when stools were examined on a weekly basis.[514] Because the vast majority of stools were collected during times when children were well, only 22% of detected infections were associated with symptoms.

Cyclospora is likely to be a cause of low-level endemic disease in the United States, based on reports from the CDC and a prevalence study from Lahey Clinic in Massachusetts.[531] Of 1,042 consecutive stool samples examined at the Lahey Clinic's microbiology laboratory, 3 (0.3%) were positive for the organism. These three patients had no history of recent travel and presented with relapsing watery diarrhea that lasted from 12 days to 8 weeks.

Pathogenesis and Clinical Findings

Cyclospora causes a syndrome characterized by prolonged diarrhea and high morbidity if untreated. The largest case series that characterized the natural history of infection and small intestinal pathology was among adult travelers in Nepal.[508,509,533] Case-control data comparing patients with diarrhea to well controls provide strong evidence that *Cyclospora* is pathogenic.[509]

In the first few days of *Cyclospora* infection, symptoms can be indistinguishable from those caused by bacterial enteric pathogens, including the abrupt onset of watery diarrhea, fever, nausea, vomiting, and abdominal cramps. A protracted course of intermittent diarrhea, fatigue, upper intestinal symptoms (eg, loss of appetite, nausea, increased gas), and weight loss follows.[508,509] Among adult travelers in Nepal, the diarrheal illness associated with *Cyclospora* lasted a median of 7 weeks, compared with 9 days for persons with other causes of diarrhea.[509] Patients with *Cyclospora* averaged six diarrheal stools per day, which was similar to the number of stools seen in patients with bacterial diarrhea. Malabsorption of D-xylose is characteristic.[508] Without treatment, the disease is eventually self limited, and the disappearance of the organism from stool specimens is highly correlated with the resolution of symptoms.[508,509]

The incubation period is not well characterized but is likely to be as short as 1 or 2 days, based on data from studies in Nepal and the Chicago outbreak. Travelers in Nepal have acquired the infection within 2 days of arriving in country.[508] In the Chicago hospital outbreak, most cases occurred 1 to 8 days (with a peak at 2 days) after a water pump failure that was thought to be related to contamination of the water storage tank implicated in the

outbreak.[522]

Little is known about the life cycle of *Cyclospora* or the pathogenic mechanisms responsible for symptoms. It is likely, however, that sporozoites released from ingested oocysts invade and replicate in upper intestinal enterocytes in a similar manner as other coccidia. Small intestinal biopsies from patients with the disease have shown inflammatory changes, villous atrophy, and crypt hyperplasia.[533,534] The organism has also been identified within jejunal enterocytes using electron microscopy.[534]

Diagnostic Approaches

Unsporulated *Cyclospora* oocysts are easily recognized in a fresh stool preparation using regular light microscopy.[514] However, up to 50% of infections will not be detected unless a concentration procedure, such as with formalin ethyl acetate, is used (Rajah R, Shlim DR, unpublished data, 2000). Like *Cryptosporidium,* the organism floats in Sheather's sucrose solution and can be detected using a modified acid-fast staining procedure.[514,520] Staining does not increase the rate of detection compared with a regular, concentrated, wet preparation (Rajah R, Shlim DR, unpublished data, 2000). Although most organisms appear red or pink on a modified acid-fast stain, some organisms resist the stain and appear white on the blue background.[520] It is important to measure the size of *Cyclospora* oocysts to make sure that they are in the 8- to 10-μm range, because they are morphologically similar but approximately twice the size of *Cryptosporidium* oocysts. *Cyclospora* organisms remain viable in potassium dichromate preservative for several months and will undergo sporulation within 5 days in vitro when incubated at 25°C to 32°C.[514] Formalin preservation tends to distort the internal structure of the unsporulated oocyst,[520] which is seen as round on examination of fresh stool (Figure 37-4).

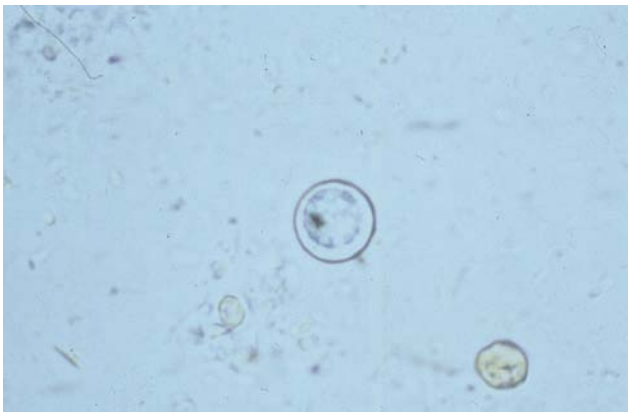

Fig. 37-4. This is a *Cyclospora* oocyst detected from a fresh stool preparation. Cell walls measuring 8 to 10 μm in diameter surround a single round unsporulated morula. Photograph: Courtesy of Lieutenant Colonel Charles W. Hoge, Medical Corps, US Army.

Recommendations for Therapy and Control

Cyclospora infections in immunocompetent persons respond rapidly to a standard dose of trimethoprim-sulfamethoxazole (TMP-SMX) [535,536] and in this manner resemble *Isospora* infections. Immunocompromised persons with *Cyclospora* infections also respond to TMP-SMX treatment, but the dose used in patients with HIV infection is twice the dose used in healthy travelers in Nepal. In addition, chronic suppressive therapy is necessary to prevent relapse in HIV-infected persons.[518] There is evidence that ciprofloxacin is an effective alternative, but its efficacy is less than that of TMP-SMX.[537]

Further studies are needed to determine optimal water purification strategies for *Cyclospora*, as well as the optimal methods to decontaminate suspect food. The outbreak in Nepal involving British soldiers suggested that *Cyclospora* is similar to *Cryptosporidium* in being resistant to chlorine.[524] Until additional data are available, the same strategies used to prevent *Cryptosporidium* oocyst transmission should be used to prevent transmission of *Cyclospora* oocysts.

Isospora belli

Isospora belli is mentioned in this chapter for completeness but is not considered an important military infectious disease. In contrast to *Cryptosporidium, Isospora* is strictly a human parasite. This characteristic, combined with its large, easily filterable size, limits or precludes chances of acquiring this organism from environmental or zoonotic sources. *Isospora* is a very rare cause of traveler's diarrhea,[538] but it is an important cause of chronic diarrhea in immunosuppressed (especially HIV-infected) persons living in developing countries.[503,539] The clinical features of illness and methods of diagnosis are similar to the two other intestinal coccidia. Like *Cyclospora, Isospora* infections respond to treatment with TMP-SMX.[539,540]

[Charles W. Hoge]

HELMINTHS

Introduction and Military Relevance

The world abounds in parasites and the majority are helminths. In 1947, Stoll [541] estimated the human population to be 2.16 billion and the number of helminthic infections in humans to be 2.25 billion. The human population in 2000 will be about 6 billion, and, based on current data, helminthic infections are keeping pace; at the end of the 20th century humanity's worm burden was 6 billion infections or more.

Military personnel are often assigned or deployed to areas of the world that are endemic for helminthic infections, have poor sanitation, or are scenes of unrest and devastation where public health facilities have been destroyed and good public health practices are absent. Soil and water may be contaminated with human and animal excrement, and safe water supplies may be cut off. In the past, military personnel have acquired helminthic infections directly from fecally contaminated soil, from food by eating raw or poorly cooked meat and vegetables, and from water by ingesting helminth eggs, larvae, or intermediate hosts harboring larval stages of the parasites. Some helminths relevant to military personnel and transmitted by food, water, and soil are presented here and helminths transmitted by snail and arthropod vectors, such as those that cause schistosomiasis and filariasis, are covered elsewhere.

Infections caused by *Strongyloides* worms, hookworm, and a number of other soil-transmitted helminths have been reported in US military personnel. Hookworm infection caused by *Ancylostoma duodenale* was documented in personnel deployed to Assam and Burma during World War II. Specific studies were also done on 50 selected hookworm-infected soldiers admitted to a hospital in Burma during World War II, and 80% of them had significant symptoms.[542] This parasite was also reported in personnel returning from the Pacific theater during World War II;[543] fortunately, little hookworm disease was seen in these cases. Ground troops were exposed to infection sleeping in foxholes, crawling through the jungle, and occupying native villages surrounded by soil previously contaminated with human excreta. A number of soldiers developed what was termed "trench cough" while in the foxholes. This was caused by the migration of hookworm larvae through the lungs. Coughing in the foxholes was a hazard since it could give the soldiers' position away. There were 22,238 cases of hookworm treated during the years 1942 to 1945.[544] In an earlier publication covering the same years, Swartzwelder [545] reviewed the numbers of nematode and cestode infections and reported 1,242 admissions for strongyloidiasis, more than 5,000 cases of ascariasis, 285 hospital and quarters admissions for trichuriasis (most had been acquired in the United States), and approximately 2,000 cestode infections caused by *Taenia solium, T saginata,* and *Hymenolepsis nana*. In another review,[546] a number of infections with *Ascaris lumbricoides* were reported, especially in American troops in the vicinity of Manila. *Strongyloides stercoralis* was reported in 7.4% of 633 stools from troops in the Pacific theater. Trichuriasis, trichinosis, and even taeniasis were reported. Many Australian, British, and American ex–prisoners of war who worked on the Thai-Burma railway acquired strongyloidiasis, which was only detected years later in Veterans Administration hospitals.[547] Hookworm, *S stercoralis*, and *A lumbricoides* infections were also seen in US troops in Vietnam,[548] and these parasites, along with *Trichuris trichuria*, were diagnosed in patients with diarrhea seen at the Naval Support Activity Hospital in Danang, Vietnam.[549] Although many other helminthic infections were endemic in the Vietnamese, such as paragonimiasis, clonorchiasis, and fasciolopsiasis, none of these was seen in US service members.[550]

Helminthic infections among military personnel deployed to areas outside of Southeast Asia have also been reported. Dutch troops who had been in New Guinea became infected with *Ancylostoma ceylanicum* (erroneously reported as *A braziliensis*).[551] US military personnel stationed in Panama and troops going through jungle training there experienced eosinophilia, which was attributed to soil-transmitted helminths.[552] Hookworm infection was also associated with US military operations in Grenada in 1983.[553] More recently, hookworm and *S stercoralis* have been associated with gastrointestinal illness in troops returning from jungle training in Panama.[554] The eating of uncooked foods can also lead to infections during training exercises. During survival training on Okinawa, three US Marines acquired angiostrongyliasis by eating wild snails raw; others in the group ate only cooked snails and did not become ill.[555]

Description of the Pathogens

The worms that parasitize humans belong to three main groups: nematodes (or roundworms) and two within the flatworms: cestodes (or tapeworms) and trematodes (or flukes) (Table 37-12).

TABLE 37-12

HELMINTHS TRANSMITTED BY FOOD, WATER, AND SOIL

Parasite	Reservoir	Means of Transmission	Presenting Clinical Manifestations
Nematodes			
Ascaris lumbricoides	Humans	Eggs in soil	Vague intestinal symptoms, cough, pneumonitis, intestinal obstruction
Trichuris trichuria (whipworm)	Humans	Eggs in soil	Mucous diarrhea, abdominal discomfort, prolapsed rectum
Necator americanus (New World hookworm)	Humans	Larvae in soil	Dermatitis, eosinophilia, cough, abdominal pain, weakness, anemia
Ancylostoma duodenale (Old World hookworm)	Humans	Larvae in soil	Dermatitis, eosinophilia, cough, abdominal pain, weakness, anemia
Ancylostoma braziliense (hookworm)	Dogs	Larvae in soil	Cutaenous larva migrans, serpingineous tracts, dermatitis, pruritis
Ancylostoma ceylanicum (hookworm)	Dogs, cats	Larvae in soil	Anemia
Strongyloides stercoralis	Humans, dogs	Larvae in soil	Cough, eosinophilia, abdominal discomfort, larva currens
Trichinella spiralis	Pigs	Larvae in meat	Periorbital edema, muscle pain, eosinophilia, fever
Gnathostoma spinigerum	Dogs	Larvae in fish, frogs, tadpoles	Epigastric pain, vomiting, fever, edema, erythema, pruritis, rash, pain
Capillaria philippinensis	Birds	Larvae in fish	Diarrhea, abdominal pain, borborygmus
Anisakis simplex	Marine mammals	Larvae in marine fish, squid	Abdominal pain, eosinophilic granuloma, diarrhea, vomiting
Angiostrongylus cantonensis	Rats	Larvae in snails, slugs	Headache, eosinophilic meningitis, paresthesia
Angiostrongylus costaricensis	Cotton rats	Larvae in slugs	Abdominal pain, eosinophilia, palpable abdominal mass
Dracunculus medinensis	Humans	Larvae in copepods	Pruritis, blisters, ulcers, eosinophilia
Cestodes			
Diphyllobothrium latum	Fish-eating mammals	Fish	Anemia, vitamin B_{12} loss
Spirometra spp.	Dogs, cats	Frogs, tadpoles, snakes	Larval migrans, pain, periorbital edema, eosinophilia
Taenia saginata	Humans	Cysticercus larvae in beef	Vague gasterointestinal symptoms, anorexia
Taenia solium	Humans	Cysticercus larvae in pork	Vague gastrointestinal symptoms, anorexia
Taenia solium (Cysticercosis)	Humans	Eggs in soil	Epileptic seizures, nodules, muscle pain, visual disturbances
Hymenolepsis nana	Rodents, beetles, fleas	Cysticercoid larvae in insects or eggs	Diarrhea, abdominal pain, anorexia, enteritis
Hymenolepsis diminuta	Rats, beetles	Cysticercoid larvae in beetles	Diarrhea, abdominal pain, anorexia, enteritis
Trematodes: Liver			
Clonorchis sinensis	Humans, fish-eating mammals	Larvae in fish	Diarrhea, jaundice, hepatomegaly, eosinophilia, cirrhoses

(**Table 37-12** *continues*)

Table 37-12 *continued*

Opisthorchis viverrini	Humans, fish-eating mammals	Larvae in fish	Diarrhea, jaundice, hepatomegaly, eosinophilia, cirrhoses
Opisthorchis felineus	Humans, fish-eating mammals	Larvae in fish	Diarrhea, jaundice, hepatomegaly, eosinophilia, cirrhoses
Fasciola hepatica	Sheep, goats, humans	Water plants, watercress	Abdominal pain, cirrhoses, jaundice, eosinophilia
Trematodes: Lung			
Paragonimus westermani	Crab-eating mammals	Larvae in crabs and crayfish	Cough, fever, hemoptysis, eosinophilia
Trematodes: Intestinal			
Fasciolopsis buski	Pigs, humans	Water plants	Abdominal pain, edema, diarrhea, eosinophilia, ascites
Metagonimus yokogawai	Fish-eating mammals	Fish	Vague abdominal pain, diarrhea, nausea
Heterophyes spp.	Fish-eating mammals	Fish	Vague abdominal pain, diarrhea, nausea
Echinostoma spp.	Rats, birds	Snails, tadpoles, fish	Abdominal pain, diarrhea, inflammation, ulcers

Nematodes

The nematodes are cylindrical and tapered at both ends. Their outer covering or skin consists of many layers of proteinaceous material that forms a cuticle. The size of these worms varies from a few millimeters to more than 50 cm. The mouth, at the anterior end, leads to a digestive tract and an anus at the posterior end. The sexes are separate: males have copulatory spicules and testes; some also have bursae, which are used to hold females during copulation. The females have one or two ovaries, a uterus, a vagina, and a vulva. The females produce eggs, larvae, or, rarely, both eggs and larvae.

Cestodes

The adult cestodes are flat and ribbon-like, consisting of chains of individual segments or proglottids collectively known as a strobila. The anterior end has a holdfast organ or scolex, with suckers and sometimes hooklets, followed by a neck. The neck is the area of growth or strobilization. Behind the neck region, the proglottids are of various sizes and stages of maturation: immature proglottids are followed by mature proglottids, with gravid proglottids filled with eggs at the extreme posterior. Tapeworms do not have a digestive tract and absorb nutrients through the integument or skin. Each proglottid possesses male and female sex organs. Tapeworms vary in length from millimeters to meters. Their width also varies depending on the location on the stroblia and may range from a few millimeters to a centimeter. Eggs may pass individually or within detached gravid proglottids.

Trematodes

Trematodes are flat or leaf-like and vary in size from a few millimeters to several centimeters; their width is variable. They possess two suckers or ascetabula, the anterior or oral sucker and the imperforate ventral sucker located along the median ventral line. The mouth is in the oral sucker and leads to a pharynx and two ceca (blind digestive tracts). Except for the schistosomes, all trematodes possess both male and female reproductive organs. They produce eggs of various sizes and shapes. Eggs may be embryonated when discharged from the human body or they may require a period of embryonation after they are deposited in water.

Epidemiology

Transmission

Helminthic infections in humans number in the billions. Animal and plant life, particularly when eaten raw or partially cooked, serve as major sources for human helminthic infections. Nearly one half of helminthic infections are acquired from the ingestion of fecally contaminated soil, water, or

vegetation or by contact with the soil. Others are acquired by the ingestion of animal intermediate hosts containing infective stages of the parasites or by drinking water containing intermediate hosts. The life cycle and means of transmission of human helminthiasis is variable, depending on the species.

Nematodes. *Ascaris lumbricoides*, the giant intestinal roundworm, 20 to 35 cm long, resides in the small intestine, and the eggs pass with the feces. The eggs reach the soil, embryonate in a few weeks, and become infective. The hardy egg shell offers good protection, and the embryonated egg can withstand drying and other hazardous conditions for very long periods depending on conditions. When soil or vegetation contaminated with the eggs is ingested, the eggs hatch in the intestines and the liberated larvae penetrate the mucosa and migrate to the liver, heart, and lungs. After a period in the lungs, the young worms migrate up the pulmonary tree, are swallowed, and grow into adults in the small intestine. The prepatent period is 60 to 75 days.

Trichuris trichura or the whipworm, 30 to 55 mm long, lives in the large intestine, and eggs laid by females pass in the feces. The egg embryonates in the soil and is ingested with soil or contaminated vegetables or water. The eggs hatch in the intestine, and the larvae migrate down the bowel and develop directly into the adult stage in the large intestine. The prepatent period is 3 months.

There are several hookworm species that may infect humans, but the most important are *Ancylostoma duodenale*, the Old World hookworm, and *Necator americanus*, the New World hookworm. Adults of both species are about 8 to 13 mm in length and inhabit the small intestine. Eggs produced by the female worms pass in the feces into the environment. In the soil, rhabditiform larvae develop inside the eggs. The larvae hatch out of the eggs and, after a few days, develop into infective filariform larvae that are able to penetrate human skin. *A duodenale* larvae may also penetrate buccal mucosa with the drinking of contaminated water. In the soil, the filariform larvae will climb to the highest elevation on the grass and soil and congregate, a process called thigmotrophism, waiting to infect a victim through exposed feet or skin elsewhere on the body that contacts the contaminated area. *A duodenale* may also have a dormant stage in humans, called hypobiosis or arrested development, whereby the parasite remains in the larval stage somewhere in the body until it is ready to complete development. The larvae in the host migrate through the body to the lungs. After a period of further development in the lungs, the worms move up the respiratory passages to the throat, are swallowed, and mature in the small intestine. The prepatent period is 4 to 5 weeks.

Strongyloides stercoralis, only found as females in the definitive host, produces thin-shelled eggs containing larvae. The rhabditiform larvae hatch quickly from the eggs, pass in the feces, and develop into infective-stage filariform larvae. The larvae, like those of the hookworm, penetrate the skin and migrate through the body to the lungs and, eventually, to the small intestine. The prepatent period is 1 month. The larvae usually penetrate skin in contact with contaminated soil, but, like *A duodenale*, the larvae may also enter the body in drinking water and penetrate the buccal mucosa. Strains of *S stercoralis* may have a free-living cycle in the soil in which both male and female worms develop and reproduce. Furthermore, autoinfection can occur with certain strains of this parasite. Larvae may become infective while in the host, penetrate the gut, and migrate throughout the body, particularly in the immunosuppressed. This can lead to massive, disseminated infections decades after the initial infection.

Trichinella spiralis causes a widespread zoonotic parasitosis acquired by eating larva-laden muscle from infected pigs, wild game animals, or other carnivores. The meat is digested in the stomach and intestine; this releases the larvae, which enter the intestinal mucosa to mature. Adult worms reenter the gut and females release larvae, which enter the intestine wall, are picked up by the lymphatics or mesenteric venules, and are carried throughout the body to become encysted in striated muscle cells. The larvae remain in the musculature until eaten. Several other species of *Trichinella* have been described,[556] but *Trichinella spiralis* is considered the most important and the species that usually causes human infection. The other species are rarely reported in humans and are geographically limited. There are a plethora of carnivorous animal species scattered worldwide that serve as sources of infection.

Other exotic worms are acquired by humans who eat raw or poorly cooked animal life. *Gnathostoma spinigerum* is a parasite that is associated with eating raw freshwater fish and other aquatic animal life, especially in Southeast Asia. Adult worms are parasites of dogs, cats, and other carnivores; in the worm's life cycle, copepods are first-intermediate hosts and aquatic vertebrates are second-intermediate hosts. Larvae in the tissues of the second-intermediate host animals are released when the host's flesh is digested, and the larvae then migrate from the intestine to various parts of the body. Adult

worms usually locate in the stomach wall and form tumors in the gastric mucosa of dogs and other carnivores. Humans are abnormal hosts in which the parasites do not mature. The larvae become migratory, wandering throughout the body, and cause disease. Raw or poorly cooked freshwater fish are the most common source of infection in humans.

Freshwater fish are also a source of a recently recognized parasite of humans, *Capillaria philippinensis*, reported primarily from the Philippines, Thailand, and a few other countries mostly in Asia. When humans eat small fish containing infective-stage larvae, the larvae are released after digestion of the fish and develop into adults in the intestine. Fish-eating birds are considered the natural host. If not treated early enough in humans, the parasitosis can cause death. Eggs passed in the feces embryonate in soil or water; eggs are eaten by the tiny fish and hatch in the fish intestine. The larvae become infective in about 3 weeks. In bird and human intestines, the larvae become adults, and females produce eggs or larvae. The larvae can also reach maturity in the host's gut, leading to autoinfection and hyperinfection.

Anisakiasis is another helminthiasis acquired from fish. *Anisakis simplex* is an intestinal parasite of marine mammals, with small marine crustaceans serving as the first-intermediate host and a variety of marine fish serving as the second-intermediate host. The infective larvae are usually in the mesenteries of the fish but migrate to the muscle when the fish dies. Humans acquire the infection by eating the fish raw in such dishes as ceviche, sashimi, or sushi. Larvae released from the fish muscle after digestion penetrate the intestinal mucosa of humans, provoking eosinophilic granulomas. Most cases of anisakiasis are reported from Japan.

Mollusks serve as intermediate hosts for rodent parasites of the genus *Angiostrongylus.* The rat lungworm, *Angiostrongylus cantonensis*, is found in the pulmonary vessels of *Rattus* species. Larvae produced by female worms leave the lungs, reach the intestine, and pass with the feces. These larvae enter land snails and develop into the infective stage. When the snails are eaten by rats, the larvae migrate to the brain, mature, and migrate to the pulmonary vessels. When humans eat infected snails, the larvae reach the brain, die, and cause an eosinophilic meningitis. The giant African snail, *Achatina fulica*, and *Pila* species are major sources of infection in Southeast Asia (mostly in Taiwan and Thailand). *Angiostrongylus costaricensis* is found in mesenteric arteries of cotton rats (*Sigmodon* species), and the slug *Vaginulus plebeius* serves as the intermediate host. Humans eat this tiny slug accidentally with vegetation, and the parasite, after being digested out of the slug's tissues, penetrates the gut and causes eosinophilic granulomas in the cecum. Most infections are reported from Costa Rica.

Dracunculus medinensis, the longest nematode to parasitize humans, is acquired by ingesting infected copepods in drinking water. The larvae released from the arthropod as it is digested migrate through the tissue and usually settle in subcutaneous tissue in areas of the body that have contact with water. Female worms cause blisters to form in the skin through which they release larvae. The larvae are then taken up by the copepods. Dracunculiasis is endemic in African and some Middle Eastern and Southwest Asian countries.

Cestodes. Tapeworms are a common source of foodborne helminthic infections occurring worldwide. Infections are acquired in most cases by the ingestion of larvae in fish, meat, or arthropods. The large fish tapeworm *Diphyllobo*th *rium latum* is acquired from fish, usually salmonoids, containing the pleurocercoid or sparganum stage of the worm. When the fish is eaten, the larva emerges from the fish tissue and attaches to the intestinal mucosa by a sucking groove or bothria at the head of the worm. Growth occurs at the neck region and segments form continuously. Eggs produced pass in the feces, which are deposited into water. A ciliated coracidium develops in the egg, hatches, swims around in the water, enters a copepod, and forms into a procercoid larva. The copepod is eaten by the fish, and the procercoid larva moves into the fish tissue and develops into a pleurocercoid larva. Pleurocercoid larvae or spargana of *Spirometra* species, which are parasites of canines and felines, may infect humans. The infections become visceral larva migrans or sparganosis. The life cycle and means of transmission of these parasites are similar to the fish tapeworms, with copepods and a variety of aquatic vertebrates serving as intermediate hosts or sources of infection. Sparganosis results from ingesting infected copepods or other aquatic animal life containing spargana or by using animal poultices infected with the parasite. The larvae emerge from the poultice and enter the body through the eye or wound upon which the poultice is placed.

Taenia saginata and *T solium* are tapeworms acquired by eating beef or pork containing cysticercus larvae. The larvae are released from the meat during digestion and attach to the intestinal mucosa with suckers and hooklets. Growth occurs in the neck region, with the developing proglottids or segments reaching sexual maturity as they move

posteriorly. Eggs containing hexacanth embryos pass in the feces. The eggs are ingested by cattle and pigs and hatch in the intestine; the hexacanth then migrates to the tissues, usually muscle tissue. If eggs of *T solium* enter the intestinal tract of humans, the hexacanth embryos may enter tissue and develop into cysticercus larvae, causing the disease cysticercosis.

Other tapeworms that infect humans are the rodent cestodes *Hymenolepsis nana* and *H diminuta*. Both species are transmitted by the accidental ingestion of arthropods (eg, beetles, fleas) infected with cysticeroid larvae. *H nana* infections may also be acquired by ingesting eggs, and immunity to infection may develop in the definitive host. Infections caused by eating infected arthropods, however, do not confer immunity, and eggs produced by the adult worms hatch in the intestines and lead to autoinfection and hyperinfection.

Trematodes. There are myriad trematodes that infect humans. Most are foodborne and invade the liver, lungs, and intestines. These parasites are acquired by eating raw or partially cooked animal or plant life. Liver flukes, such as *Clonorchis sinensis* (Chinese liver flukes) in China and Korea and *Opis*th *orchis viverrini* in Thailand, are acquired by eating freshwater fish. The metacercaria is digested from the fish muscle and migrates into the bile passages. Eggs pass in human feces into water and are eaten by snails. The larvae in the snails multiply and release cercariae, which leave the snail, enter fish, and encyst in the fish musculature. In Eastern Europe and Russia, the cat liver fluke, *O felineus*, which also infects humans, has a similar life cycle.

The sheep liver fluke, *Fasciola hepatica*, found in sheep- and cattle-raising countries worldwide, will also invade the liver of humans. The adult flukes live in the bile ducts, the eggs pass with feces into a body of water, and a ciliated miracidum is released that enters snails. Cercariae emerge from the snail and encyst on aquatic vegetation as metacercariae. When humans eat the vegetation uncooked, the metacercariae migrate through the gut wall, enter the peritoneal cavity, penetrate the liver capsule, and migrate to the bile ducts. Human infections are frequent in European, African, and Latin American countries where people eat water plants (eg, watercress, water lettuce) uncooked.

There are approximately 40 species of *Paragonimus* worldwide, but the most important is the lung fluke *P westermani,* which is commonly found in China, Japan, Korea, Taiwan, and the Philippines. Other species are also found in Asia, North and South America, and Africa, but the prevalences are low. The worms, usually in pairs, are present in cystic cavities in lung parenchyma. Eggs are passed with sputum, but when they are swallowed, they pass in feces. A miracidium hatches from the egg in fresh water and penetrates a certain species of snail. The parasite multiplies in the snail, and the released cercariae encyst as metacercariae in crabs and crayfish. When humans eat these second-intermediate hosts raw or improperly cooked, the larvae migrate through the gut wall, into the peritoneal cavity, through the diaphragm, and into the lung tissue.

There are also a number of intestinal flukes of humans, such as *Fasciolopsis buski*, the giant intestinal fluke. It is only known to occur in certain parts of Asia, where pigs are the usual reservoir hosts. This large worm resides in the intestine and produces eggs that pass in the feces into water. The miracidia from the eggs enter snails, and the released cercariae encyst as metacercariae on a variety of water plants (eg, water caltrop, water chestnuts, water bamboo, water lettuce). The water plants are eaten, and the metacercariae encyst and grow into adults in the intestine.

Other intestinal flukes, such as *Metagoninus yokogawai* and *Heterophyes heterophyes*, are acquired from eating fish; *Echinostoma* species are acquired from eating fish, clams, snails, tadpoles, and other aquatic animal life. Most of these parasitoses are endemic in Asia, with sporadic reports from elsewhere in the world.

Geographic Distribution and Incidence

Human helminthic infections are found worldwide, with the highest prevalences in tropical countries where sanitation is poor or nonexistent and the population eats food that is raw or insufficiently cooked. Countries in Africa, Asia, the Middle East, and South and Central America are considered the most highly endemic. Warm climates foster helminthic infections. Intestinal roundworms infections are most common in Southeast Asia and Latin America, while trichinosis is more common in areas with a temperate climate and in the northern rather than in the southern hemisphere. Cestode infections are highly prevalent in Latin America, except for *H nana,* which is the most common tapeworm in North America. *Diphyllobo*th *rium latum* infections are more common in temperate climates and are seen in populations living around the Great Lakes in North America and in Scandinavian countries. Other diphyllobothrid species are reported from Japan and South America. Trematode infections abound in Asian countries; they are associated with

the habit of eating a variety of foods raw. Some trematode infections are common in Eastern Europe and in sheep-raising countries. Exotic parasitoses such as capillariasis, angiostrongyliasis, anisakiasis, and gnathostomiasis are also associated with eating raw freshwater and marine fish, snails, tadpoles, aquatic vegetation, and other aquatic life in Southeast Asia.

Pathogenesis and Clinical Findings

Helminths have intricate life cycles, and pathology is associated with their migratory pathways and final habitat in the host. Most humans have few worms and are free of disease, but there are occasions when there are massive infections and severe illness develops. It is usually the zoonotic parasites that cause serious disease. Most worms are commensals, but they can cause disease by (*a*) competing for essential nutrients, (*b*) obstructing, blocking, or perforating the intestinal tract or biliary tree, (*c*) sucking blood, (*d*) inducing inflammation and malabsorptive changes in the gut, and (*e*) inducing hypersensitivity reactions, usually caused by migrating larvae that secrete and excrete antigens that induce antibodies and cellular immune responses. In reinfection, host antibodies and memory cells respond and may affect the development of new infections.[557] Eosinophilia and pneumonitis are common, especially in helminthic infections with migrating larvae. Symptoms include abdominal pain and diarrhea, as well as malabsorption, iron deficiency anemia, and protein-losing enteropathy.

Nematodes

Intestinal infections involving *Ascaris lumbricoides* may cause allergic manifestations, gut obstruction, intussusception, blockage of bile ducts and cholangitis, perforation of the gut, and erratic ascariasis (worms passing out the nose, mouth, anus, or umbilicus).

Trichinella trichuria worms, especially in heavy infections, may affect intestinal integrity by burying their anterior ends in the mucosa, causing the bowel to appear villose. Sufficient edema develops to cause obstruction, and straining at defecation causes rectal prolapse. Whipworms are also known to suck blood, but the amount of blood loss is small.

Adult hookworms bite into the mucosa of the small intestine and suck blood. Large numbers of worms feeding at the same time may lead to iron deficiency anemia. Hookworm disease potentiates the effects of other intestinal parasitoses and contributes to malnutrition. There may be minor gut lesions with hemorrhage. The blood loss, depending on the species, is estimated to be 0.03 to 0.3 μL per day per worm. Larvae migrating through the lungs may cause pneumonitis. Larvae penetrating the skin may permit secondary bacterial infection, and hookworm larvae that are parasites of other animals, such as dog hookworms, may cause cutaneous larva migrans in humans (Figure 37-5).

Adult female *S stercoralis* worms buried in the mucosa of the small intestine damage the absorptive surface, causing chronic enteritis and sprue-like enteropathy, malabsorption, weight loss, and diarrhea. Hypersensitivity develops in some persons, and larvae may cause urticarial eruptions, larva currens, pneumonitis, and eosinophilia. Autoinfection in immunocompromised persons often leads to hyperinfections, disseminated strongyloidiasis, and death. In these individuals, the parasites may be present in undetectable levels for years, but when the host becomes immunosuppressed, the parasite multiplies rapidly. In many cases the sputum may contain rhabditiform larvae, indicating adult females in the lungs. The larvae spread to the liver, heart, adrenals, kidneys, and central nervous system (CNS). Persons with human t-cell lymphotrophic virus type I (HTLV-I) are highly susceptible to strongyloidiasis.

When muscle from an animal infected with *Trichinella spiralis* is eaten, the larvae enter the intestinal mucosa and cause a transitory enteritis and

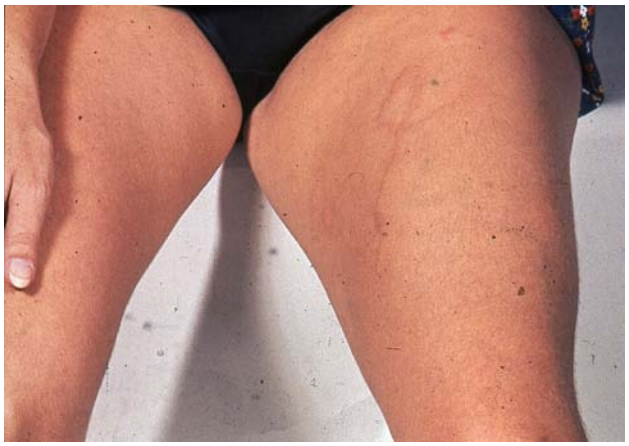

Fig. 37-5. This is an example of creeping eruption. Note the tract made by a migrating larva of dog hookworm on the thigh of family member of an American service member. She was sun bathing on a beach in Taiwan.
Photograph: Courtesy of Dr. John H Cross, Uniformed Services University of the Health Sciences.

malabsorption. Adults in the intestine reproduce, and the larvae migrate throughout the body to striated muscle. Once in the muscle, the larvae enter a cell, eventually die, and become calcified. Typhoidal-like symptoms occur early in the infections, and when the larvae are migrating, eosinophilia, muscle soreness and pain, and periorbital edema result. Cell destruction may cause acute inflammatory changes and an interstitial myocarditis. Trapped larvae in the lungs are known to precipitate edema, focal hemorrhage, and eosinophilia.

Gnathostoma larvae migrate to various parts of the human body. Larvae in subcutaneous tissues may cause transient, warm, erythematous swelling or migrate through the tissues, producing serpingenous tracts. The wandering larvae may also enter the eye and CNS, causing death. Eosinophilic neuritis, meningitis, and encephalitis may develop. In the eye, the infection may result in uveitis, hemorrhage, retinal detachment, and blindness.

Abdominal pain, diarrhea, and borborygmy are characteristic of infections with *Capillaria philippinensis*. Intestinal capillariasis as a result of autoinfection and hyperinfection causes malabsorption, protein-losing enteropathy, electrolyte imbalance, weight loss, wasting, and death. Thousands of *C philippinensis* organisms in all stages are present in the small intestine.[558] The parasite does not become disseminated but remains in the small intestine. The electrolyte imbalance and other physiological changes are responsible for pathological damage in other organs.

Anisakid nematode larvae, upon entering the human gastrointestinal tract, attempt to penetrate the mucosa and cause an eosinophilic granuloma. In addition, protease secretions from the worms can cause tunnels in the gastric mucosa. The larval worms are also known to enter the peritoneal cavity and other organs. Symptoms of an acute abdomen are produced by anisakid infections. In some species, the larvae remain in the throat and cause a condition termed "tickle throat."

Angiostrongylus cantonensis larvae in humans reach the CNS and cause an eosinophilic meningitis or eosinophilic meningoencephalitis. Dead worms rather than living ones are thought to cause disease. Eosinophilic pleocytosis is common. The larvae may also enter eyes and cause blindness. *Angiostrongylus costaricensis* larvae are responsible for abdominal angiostrongyliasis. The larvae enter the mesenteric blood vessels, causing a granulomatous inflammation in the intestinal wall and obstruction.

Dracunculus larvae migrate throughout the tissue, and in approximately 1 year adult females provoke the formation of a vesicle in the skin. Allergic manifestations result from toxic secretions from the worm and a painful, burning sensation occurs. When an infected area is immersed in water, the vesicle breaks and larvae emerge from the uterus of the female worm and escape into the water. Secondary bacterial infections can also occur.

Cestodes

Cestodes that inhabit the intestinal tract usually cause little pathology. Taenid scolices may cause some inflammation at sites of attachment in the mucosa, but the parasites have little other effect except competing with the host for food. *Diphyllobo*th *rium latum*, on the other hand, competes with the host for vitamin $B_{12,}$ which may result in megaloblastic anemia. Spargana of diphyllobothrids that infect a variety of mammals, especially of dogs and cats (*Spirometra* species), may invade tissues of humans who ingest copepods, eat infected intermediate hosts, or use animal poultices. The spargana migrate, causing larval migrans and disease to the invaded organs. Spargana have been found in transient erythematous swellings in many parts of the body and in eyes of Asians who used incised frog abdomens as a poultice. Infections caused by *Taenia saginata*, *H nana*, or *H diminuta* usually cause little pathology.

Cysticercosis occurs in humans who ingested eggs of *T solium*. The egg hatches in the intestine and the hexacanth embryo migrates to tissues and develops into a cysticercus. Brain, heart, muscle, and skin are preferred locations. Palpable nodules can be found in the skin, and in such cases there is usually CNS involvement. Cysticercosis involving the CNS will provoke symptoms of epilepsy. The cysticercus may degenerate, causing granulomas, calcification, and neurologic symptoms in the CNS.

Trematodes

Trematode infections are acquired with the ingestion of plant or animal life harboring the infective stage (metacercaria) of the parasite. There is usually little pathology associated with infections, except when a large number of worms are involved.

Opisthochid species, such as *O viverrini, O felineus*, and *Clonorchis sinensis,* are acquired by eating raw freshwater fish. After being released from the fish muscle following digestion, the larvae migrate up the bile duct and may cause jaundice, epigastric pain, diarrhea, and eosinophilia. Long-term infection causes chronic cholanigitis, liver damage,

and gallstones. In endemic areas, the parasitosis is considered carcinogenic and is responsible for a high frequency of cholangiocarcinoma. Increased endogenous production of *N*-nitrosodimethylamine and *N*-nitrosodiisopropanolamine or hepatic activation of dietary carcinogens, plus chronic hyperplasia of the bile duct epithelium, may enhance susceptibility to cancer.[559]

There are several trematodes that inhabit the hepatobiliary system. The sheep liver fluke (*Fasciola hepatica*) damages the liver parenchyma while migrating through liver tissue to the bile ducts and causing hepatomegaly, necrosis, and hemorrhage along the migratory tracts. Adult worms in the bile ducts cause dilatation, inflammation, thickening of the walls, and obstruction. Extensive fibrotic changes in the bile ducts seem to be mostly caused by the large amount of proline produced by the adult worms.[560]

The normal habitat of the Asian lung fluke, *Paragonimus westermani,* is the lung, where cystic and inflammatory lesions develop. Lung infections are often misdiagnosed as tuberculosis because of hemoptysis and other pulmonary symptoms (eg, cough, bronchiectasis). Other organs, such as the brain and abdominal cavity, are occasionally invaded by the parasite. *Paragonimus* infections may cause symptoms of fever, cough, dyspnea, chest pain, and hemoptysis. Cerebral paragonimiasis simulates brain tumors, Jacksonian-like seizures, epilepsy, or meningitis.

Intestinal flukes such as *Fasciolopsis buski* are large and may cause intestinal obstruction and toxemia resulting in fascial paralysis and periorbital edema. Death is rare but does occur. Heterophyids, such as *Metagonimus* species and *Heterophyes* species, are small flukes that are also relatively short-lived. They live attached to the wall of the small intestine and cause disease by releasing tiny eggs that are picked up by the lymphatics and are carried to ectopic locations such as the brain, spinal cord, and heart. Large numbers of adults may cause diarrhea, nausea, and vague abdominal complaints. There are many other species of tiny flukes that inhabit the intestines of those who eat raw or undercooked vegetables, fish, and meat, particularly in Asia; these usually cause little disease, however. Echinostome infections are common throughout Asia, but they are short lasting and cause little disease.

Diagnostic Approaches

Most intestinal parasitic helminthiasis can be diagnosed under field conditions provided that standard field laboratory conditions, equipment, and supplies (eg, microscope, slides, cover glasses, laboratory reagents) are available. Tissue helminthic infections diagnosed by biopsy or serologic methods require more sophisticated conditions, however. Direct and concentration methods can also be used if the equipment and supplies are available. Rapid dipstick enzyme-linked immunosorbent assay tests are under development that will have field applicability.

Intestinal parasitic infection may be diagnosed by examining the feces for eggs, larvae, or adult stages of the parasites. New techniques for detecting antigens and DNA by polymerase chain reaction may be used in the future. The definitive diagnosis, however, is by detecting the parasite or its products. Manuals on the laboratory diagnosis of parasitic diseases are available.[561,562] The parasitologic diagnosis is made by gross examination of the fecal specimen for large worms or the microscopic examination for eggs, larvae, and adults. Since some parasites produce eggs cyclically, eggs may not be present all the time. Therefore, multiple stools (seven stools over 10 days) should be examined if parasites are suspected. A small sample of stool may be placed onto a slide, a drop of saline or iodine solution added, and the mixture covered with a cover-glass and examined under a microscope. Stools can also be examined after concentration by sedimentation, formalin-ethyl-acetate, or zinc sulfate flotations. Microscopic examination is satisfactory for ascariasis, hookworm infections, trichuriasis, strongyloidiasis, intestinal capillariasis, and cestode and trematode infections. Culture methods such as the Harada-Mori filter paper-tube technique may be used to recover larvae of hookworm and *S stercoralis*. Placing stool into agar and observing larval tracts may also be used to isolate larvae of *S stercoralis*. Biopsied tissue can be examined histologically or pressed between two microscope slides and examined microscopically for evidence of trichinosis, cysticercosis, or sparganosis. Diagnosis of other tissue parasitoses can be presumptive, based on symptoms, or by serologic methods for angio-strongyliasis, gnathostomiasis, trichinosis, cysticercosis, sparganosis, disseminated strongyloidiasis, paragonimiasis, and liver fluke infections.

Recommendations for Therapy and Control

Therapy

Helminthic infections are commonly asymptomatic and simply require specific anthelmintic treatments. Some infections require antidiarrheal drugs and fluid replacement (eg, intestinal capillariasis), and some specific infections require symptomatic

treatment with immunosuppressants (eg, steroids for trichinosis). Hookworm diseases may require blood transfusions and ferrous sulfate followed by an anthelmintic. Antipyretics are recommended where fever is encountered (eg, paragonimiasis) and analgesics when pain is involved (eg, dracunculiasis). Vitamin B_{12} and folic acid may be given after the expulsion of *Diphyllobo*th *rium latum.*

A number of anthelmintics are available to treat intestinal nematode infections.[563] Mebendazole (100 mg twice a day for 3 days or 500 mg once) or albendazole (400 mg once) are effective against ascariasis, trichuriasis, and hookworm; pyrantel pamoate (11 mg/kg once) is effective against ascariasis and hookworm. Thiabendazole (50 mg/kg per day in divided doses for 2 days), ivermectin (an investigational drug in the United States, 200 μg/kg per day for 1 to 2 days) or albendazole (200 mg twice a day for 3 days) are effective against strongyloidiasis. Gnathostome infections can be treated surgically or by the use of albendazole (400 mg once or twice daily for 21 days).[564] Mebendazole (200 mg twice a day for 20 days) or albendazole (200 mg twice a day for 10 days) is recommended for intestinal capillariasis. Anisakid nematodes are removed surgically or by endoscopy. Angiostrongyliasis has been treated in children with mebendazole (100 mg twice a day for 5 days) or thiabendazole (75 mg/kg per day in 3 doses for 3 days). Some authorities, however, do not recommend using anthelmintics for angiostrongyliasis because the disease is self-limiting and killing massive numbers of worms at one time may cause more pathology than if worms die off gradually. Dracunculiasis may be treated with metronidazole (250 mg three times a day for 10 days).

Most cases of trematodiasis respond to praziquantel (60-75 mg/kg per day in 3 doses for 1 to 2 days). The only drug presently available that is effective against fascioliasis, however, is triclabendazole (10 mg once).[560] Bithionol, once used for the treatment of fascioliasis, is no longer available. Praziquantel (5-10 mg/kg once) may be used to treat intestinal pork and beef tapeworms, as well as the fish tapeworm (ie, *Diphyllobo*th *rium latum*). Cysticercosis has been known to respond to praziquantel (50 mg/kg per day in 3 doses for 15 days) or albendazole (400 mg twice a day for 8 to 30 days). Sparganosis is usually treated surgically or with praziquantel (60-75 mg/kg for 2 days).

Control

Helminthic infection prevalences are highest in areas where indiscriminate defecation and poor sanitation practices persist. When populations dispose of feces under sanitary conditions, most intestinal parasitic infections decrease and eventually disappear. South Korea, once highly endemic for intestinal helminthiasis, has nearly eradicated the worms through mass treatments, sanitary disposal of feces, and education.[565] Investigations into environmental sources of infection should be conducted. Military personnel under field conditions in endemic countries should avoid areas where human and animal feces have contaminated the soil. Sanitary latrines should be constructed for the military and even civilians where toilet facilities are absent. Fresh vegetables and fruits should be avoided if they have been fertilized with human feces (night soil) unless the produce has been cooked thoroughly and the fruits have been washed with safe water and peeled. Fecally contaminated water may contain helminth eggs and should not be consumed unless boiled or filtered; chemical purification has little effect on helminth eggs. Some species of hookworm larvae may be acquired in water, and copepods in water may be infected with *Dracunculus* or tapeworm larvae. Those living next to bodies of water should not use the water as latrines. Fresh sewage should not be dumped into the water unless treated first to destroy parasites and other pathogens. Parasites and vectors can be eliminated from water by boiling or passing water through fine-mesh filters, especially to remove copepods. Wearing shoes will protect the feet from skin-penetrating hookworm and *S stercoralis* larvae.

An abundance of helminthic infections are acquired from food. These diseases can be controlled by thoroughly cooking all meats. Pork should always be cooked well to prevent trichinosis; pork, beef, and fish should be cooked completely to prevent tapeworm infections. Dry cereals often contain beetles that serve as intermediate hosts for hymenolepid tapeworm infections; the cereal should not be eaten uncooked, if at all. There are many exotic parasitoses acquired from wild animals, which should never be eaten raw, especially fish, snails, other aquatic animal life, and carnivores. Domestic and wild animal pets should be examined and periodically treated for helminthic infections. Pet feces, especially from dogs, cats, and even raccoons and skunks, should be buried or burned and not permitted to lie on the ground. Eggs from *Toxocara* species (from dogs and cats) and *Baylisascaris procyonis* (from raccoons), when eaten by humans, can cause visceral larva migrans. Aquatic plants and nuts should also be eaten well cooked. Irradiation has been shown to be an excellent tool that sterilizes infected foods, but obtaining public support for the use of this potential disease prevention tech-

nique has been a problem.[566] At present this technology is not applicable to the field.

Indigenous populations and deployed military personnel should be educated to the dangers of helminthic parasites endemic to the area. Paragonimiasis and fasciolopsiasis have been nearly eradicated from Taiwan because children were taught in school not to eat crabs and water plants raw.[567] When children are educated about parasitic diseases in school, they often return home and tell their parents, who in turn become aware of the problems. Using television, radio, and other public relations avenues is a valuable means to educate populations.

[John H. Cross]

SCHISTOSOMIASIS

Introduction and Military Relevance

Schistosomiasis (also known as bilharziasis, snail fever, and Katayama fever) is a parasitic disease in tropical and semitropical regions. It requires amphibious or freshwater snails as intermediate hosts for development of the larval forms that can infect humans. It is a disease complex, with multiple ecological agents, that has mission-aborting potential. A basic understanding of its epidemiology, pathogenesis, clinical presentation, diagnosis, treatment, prevention, and control is crucial to military medicine.

Schistosomiasis has been implicated as a factor in military operations since biblical times.[568] In World War II, the US Army hospitalized 2,088 patients with schistosomiasis. The average number of days lost per admission was 159, resulting in 124,192 days lost to commanders.[569] During the reinvasion of Leyte alone, 1,500 cases were reported in US troops.[570]

In late 1949, a massive outbreak of acute schistosomiasis in soldiers from the People's Republic of China, who were training for an amphibious invasion of Taiwan in early 1950, resulted in an estimated 30,000 to 50,000 medical casualties. The impact of those casualties delayed the planned invasion of Taiwan for 6 critical months,[571] long enough for the US 7th Fleet to establish a Taiwan Defense Command and provide routine naval patrols through the Strait of Formosa.

The impact of schistosomiasis on a military operation comes from its acute syndrome, which can occur as early as 2 to 4 weeks after exposure. If left untreated, infected service members can be noneffective for weeks to months, depending on the species of schistosome involved and the intensity of the infection.

Description of the Pathogen

Microbiology

Schistosomes are parasitic flatworms found in the blood vessels of vertebrates. They are unique among the trematodes for having separate sexes. More than 15 species have been reported in humans; however, the major agents of human infections are *Schistosoma mansoni*, *S haematobium*, and *S japonicum*.[572] Three other species (*S intercalatum*, *S mekongi*, and *S malayensis*) are responsible for human disease in geographically limited areas of Africa and Asia.[573] Other schistosomes

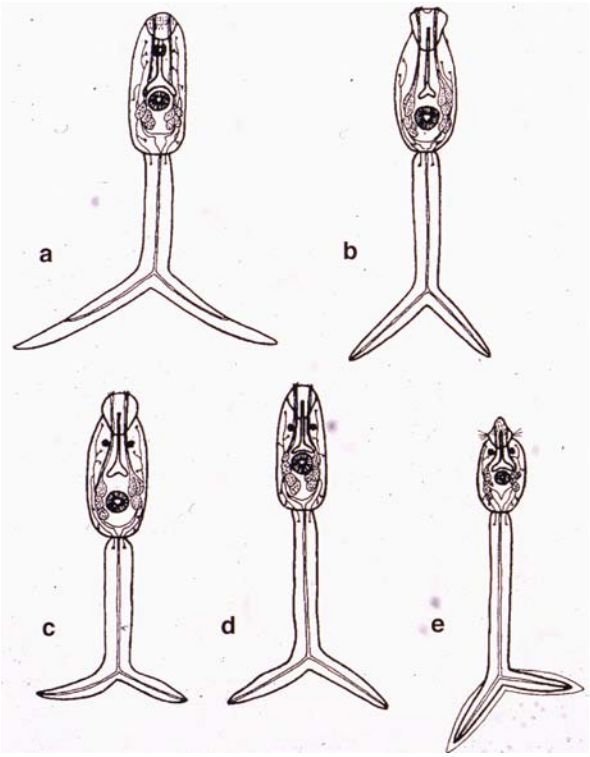

Fig. 37-6. Some fork-tailed (furcocercous) cercariae found in freshwater and amphibious mollusks: (**a**) strigeid cercaria, (**b**) human-infecting schistosome cercaria, (**c**) cercaria of *Schistosomatium douthitti*, (**d**) cercaria of a bird schistosome, and (**e**) cercaria of spirorchid trematode from turtles.
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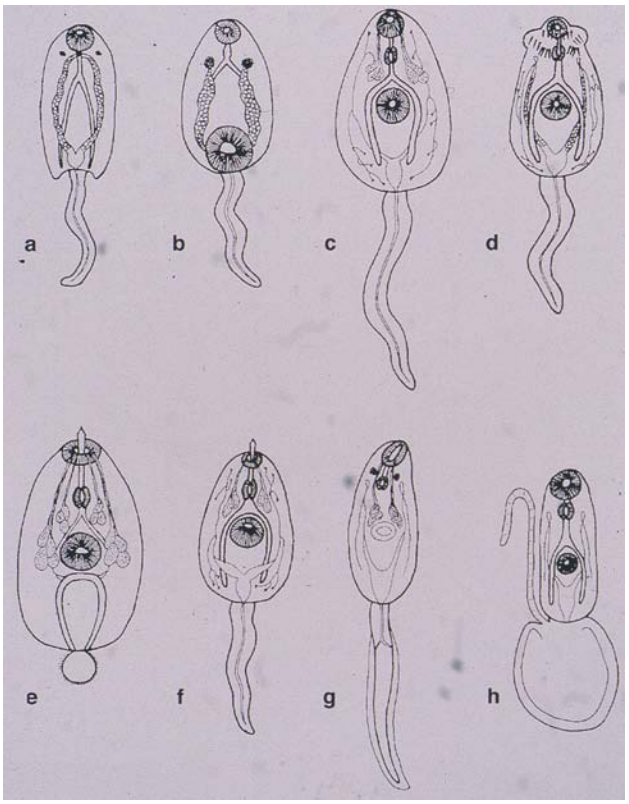

Fig. 37-7. Common types of cercariae found in freshwater and amphibious mollusks that should be distinguished from fucocercous cercariae: (**a**) gymnophallid, (**b**) monstome, (**c**) amphistome, (**d**) echinostome, (**e**) pleurolophocercous, (**f**) xiphidiocercaria, (**g**) microcercous, and (**h**) gasterotome.
Reprinted with permission from: World Health Organization. *Snail Control in the Prevention of Bilharziasis*. Geneva: WHO; 1965: 193.

found in humans are zoophilic, and humans are incidental hosts. *Human Schistosomiasis*,[574] published in 1993, is the most recent comprehensive source of information on this disease complex.

The cercariae, or larval forms, of the schistosomes that infect humans have a fork-tail, a characteristic that distinguishes them from most cercariae (Figure 37-6). In addition, schistosome cercariae lack other common surface features of many other types of cercariae (Figure 37-7), such as a stylet (see Figure 37-7e,f) or rings of spines (see Figure 37-7d) in the oral sucker region. Schistosome cercariae can be distinguished from other fork-tail cercariae by two characteristics: a lack of eye spots in the anterior half of the body and a ratio of the length of the forks of the tail to the total tail length of approximately 1:2.[575]

Life Cycle

Schistosomiasis is acquired from free-swimming cercariae, which are released from snails (Figure 37-8). The cercariae seek out and penetrate human skin, metamorphose to the schistosomula stage, and penetrate into veins; they are then carried passively to the lungs. In the lungs, they elongate into slender organisms that can negotiate the capillaries leading to the systemic circulatory system. Larval schistosomes must enter the mesenteric arteries, their capillaries, and then the hepatic portal veins to reach the liver, where they mature into adults and mate. The male then transports the female to a branch of the superior mesenteric veins of the intestine or to the veins associated with the urinary bladder, where egg laying commences. Pairs of schistosomes produce hundreds to thousands of eggs per day, depending on the species. Adults of *S mansoni*, *S japonicum*, *S mekongi*, and *S intercalatum* usually migrate to the superior mesenteric veins. *S haematobium* adults usually migrate into the vascu-

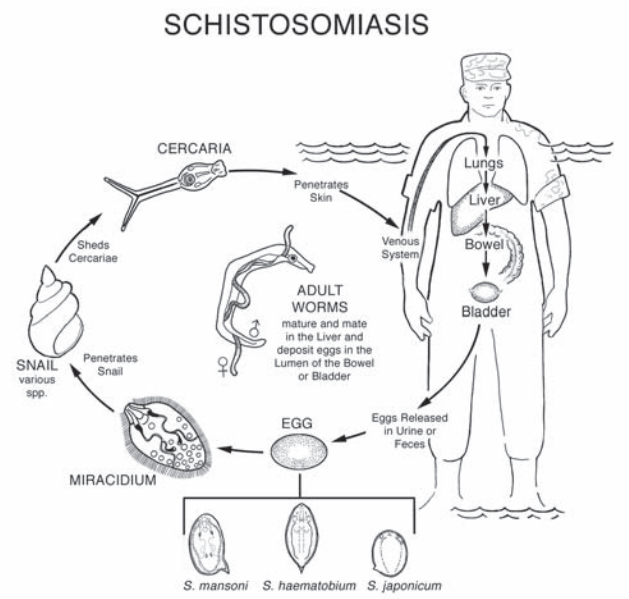

Fig. 37-8. Adult worms mature and mate in the liver. Males carry females to veins and capillaries of the bowel or bladder where eggs are deposited. Less than 50% of eggs deposited in capillaries reach the lumen of the intestine or bladder and are viable when passed in feces. Most are encapsulated by the host reactions, die, and contribute to pathology associated with chronic disease in either liver and intestine or urinary systems.
Drawing by Annabelle Wright, Walter Reed Army Institute of Research; research by Amelia Pousson.

lature surrounding the urinary bladder. In either location, eggs are released in small venules. Some eggs escape into the lumen of the intestine or urinary bladder and are voided in feces or urine. Those that do not escape (usually more than 50%) are trapped in tissues and become the focus of the host's immunological responses; this accounts for much of the pathology associated with chronic schistosomiasis.

The first free-living stage, the miracidium, hatches from the egg in a freshwater environment, then seeks out and penetrates a snail. In the snail, it undergoes a series of asexual (sporocyst) generations. Each miracidium that establishes a patent infection in a snail produces thousands of cercariae. The cercariae are the second free-living stage; more importantly, they are the infective stage for humans.

Epidemiology

Transmission

Transmission requires three factors: freshwater, infected snails, and susceptible mammalian hosts. The most limiting of these factors is the distribution of the snail that serves as the intermediate host. *S haematobium* is principally transmitted through aquatic *Bulinus* species (Figure 37-9), *S mansoni* through aquatic *Biomphalaria* species (Figure 37-10), and *S japonicum* through amphibious *Oncomelania* species (Figure 37-11). *Neotricula aperta* is the intermediate host of *S mekongi, S malayensis* is transmitted through *Robertsiella* species,[576] and *S intercalatum* is transmitted through *Bulinus* species.[573] In Asia, where schistosomiasis is a true zoonosis, infections in other mammalian hosts and the vector snails maintain significant transmission potential even in the absence of human populations. Sources of malacological expertise are identified in *Snail Hosts of Schistosomiasis and Other Snail-transmitted Diseases in Tropical America: A Manual*[577] and *Medical and Economic Malacology*.[575]

All military personnel who enter freshwater habitats in an endemic area are at risk of contracting schistosomiasis. The transmission potential of an area is directly related to the density of the molluscan host population and the infection rate in that population. In endemic areas, a 2% infection rate in the molluscan host population can maintain a more than 50% infection rate in the indigenous human population. The transmission potential of an area can be assessed by sampling suspected molluscan hosts and examining them for the cercarial stage using either photo-stimulation or crushing techniques.[575,577] When handling snails, forceps and rubber or latex gloves should be used, and 70% alcohol should be available to immediately disinfect any accidentally exposed skin.

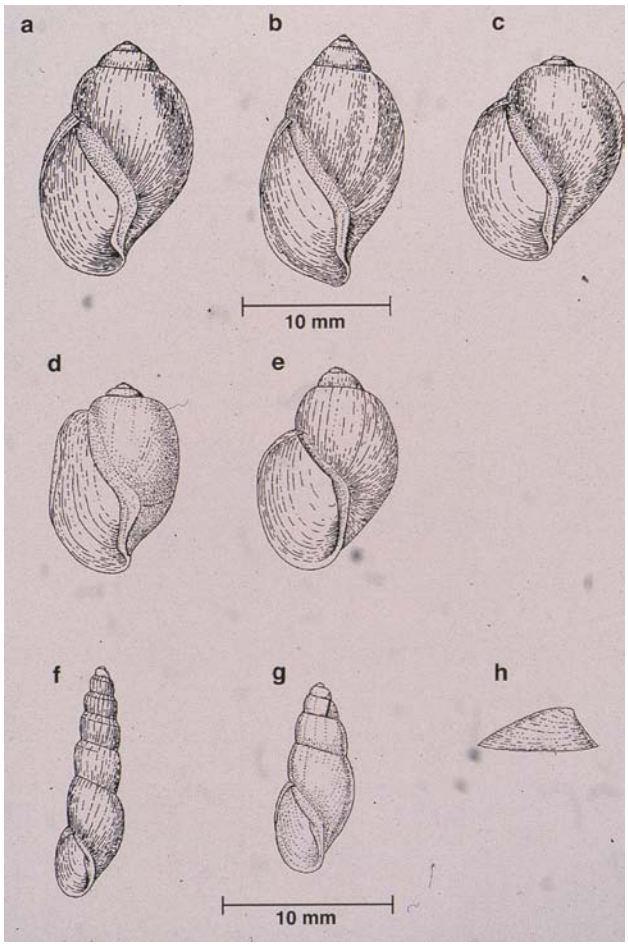

Fig. 37-9. Illustrations of shells of the intermediate hosts of *Schistosoma*: (***a***) *Bulinus (Physopsis) africanus* from Kenya, (***b***) *B* (*Phys*) *nasutus* from Tanganyika, (***c***) *B* (*Phys*) *globosus* from Angola, (***d***) *B* (*Phys*) *abyssinicus* from Somalia, (***e***) *B* (*Bulinus*) *truncatus* from Egypt, (***f***) *B* (*B*) *forskalii* from Sudan, (***g***) *B* (*B*) *senegalensis* from Gambia, and (***h***) *Ferrissia tenuis* from India.
Reprinted with permission from: World Health Organization. *Snail Control in the Prevention of Bilharziasis.* Geneva: WHO; 1965: 19.

Outbreaks of "swimmer's itch" or "clam digger's itch" are due to avian or mammalian schistosomes that are transmitted through local freshwater, amphibious, or estuarine snails. These zoophilic schistosomes are able to penetrate human skin but are unable to develop to maturity. Transmission is usually seasonal along the shores of freshwater lakes and estuarine waterways in temperate climates with peaks in the spring or early summer, but in tropical regions transmission can occur throughout the year. Sources of expertise identified in references 8 and

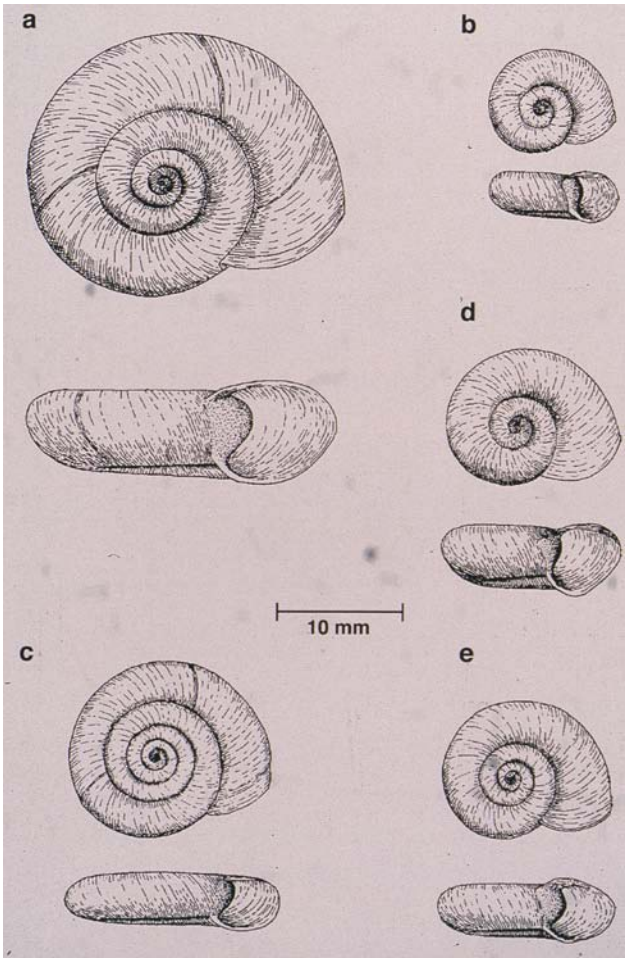

Fig. 37-10. Illustrations of shells of the intermediate hosts of *Schistosoma mansoni*: (***a***) *Biomphalaria glabratus* from Brazil, (***b***) *B straminea* from Brazil, (***c***) *B sudanica* from Uganda, (***d***) *B pfeifferi* from Rhodesia (now Zimbabwe), and (***e***) *B alexandria* from Egypt.
Reprinted with permission from: World Health Organization. *Snail Control in the Prevention of Bilharziasis.* Geneva: WHO; 1965: 18.

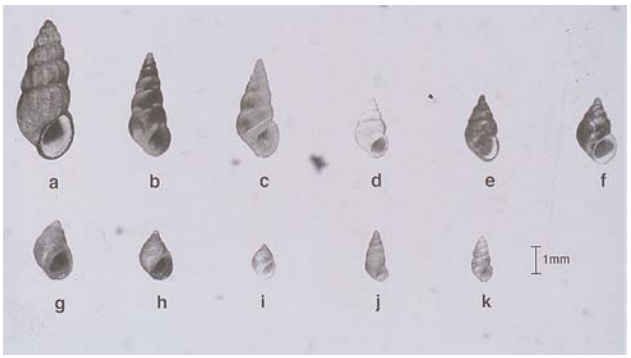

Fig. 37-11. Shells of snail hosts of oriental schistosomes: (**a**) *Oncomelania hupensis* from China, (**b**) *O nosophora* from Japan, (**c**) *O fortrwsana* from Taiwan, (**d**) *O hupensis chiui* from Taiwan, (**e**) *O quadrasi* from the Philippines, (**f**) *O lindoensis* from Indonesia, (**g**) *Neotricula aperta* alpha race from Thailand, (**h**) *N aperta* beta race from Thailand, (**i**) *N aperta* gamma race from Thailand, (**j**) *Tricula bollingi* from Thailand, and (**k**) *Robertsiella kaporensis* from Malaysia.
Reprinted with permission from: Sobhon P, Upatham ES. *Snail Hosts, Life Cycle, and Tegumental Structure of Oriental Schistosomes.* Geneva: United Nations Development Programme/World Bank/World Health Organization, Special Programme for Research and Training in Tropical Diseases; 1990: 20.

10 will be helpful in determining the identity of both animal schistosomes and their molluscan hosts.

Geographic Distribution

Schistosomiasis is endemic in 74 countries and territories[573] (Figures 37-12 and 37-13). *S haematobium* is found in 54 countries in Africa, the islands off the west coast of Africa, and the eastern Mediterranean region; *S mansoni* occurs in 52 countries and territories in South America, the Caribbean islands, Africa, Madagascar, and the eastern Mediterranean region; *S intercalatum* is present in at least five countries in western and central Africa (Cameroon, Equatorial Guinea, Gabon, Sao Tome and Principe, and Zaire); and *S japonicum* has been reported from Japan, Taiwan, China, the Philippines, Indonesia, and Thailand. (However, *S japonicum* is no longer considered endemic in Japan, the strain of *S japonicum* in Taiwan is zoophilic,[578] and the strain originally reported from peninsular Thailand[579] is now considered to be *S mekongi*.[576]) *S mekongi* has been reported from the Mekong River delta in Cambodia, Laos, and Thailand, and the distribution of *S malayensis* is limited to peninsular Malaysia.[573]

Prevalence

The most comprehensive summary of distribution and prevalence of schistosomiasis, based on data collected in the mid-1980s, is found in the *Atlas of the Global Distribution of Schistosomiasis*.[572] The World Health Organization[573] estimates that 600 million persons are exposed and 200 million persons are infected with schistosomiasis, but rates of infection vary considerably in any endemic area. Most cases have few symptoms, while a small, heavily infected cohort demonstrates severe disease. Where programs emphasizing morbidity control have been

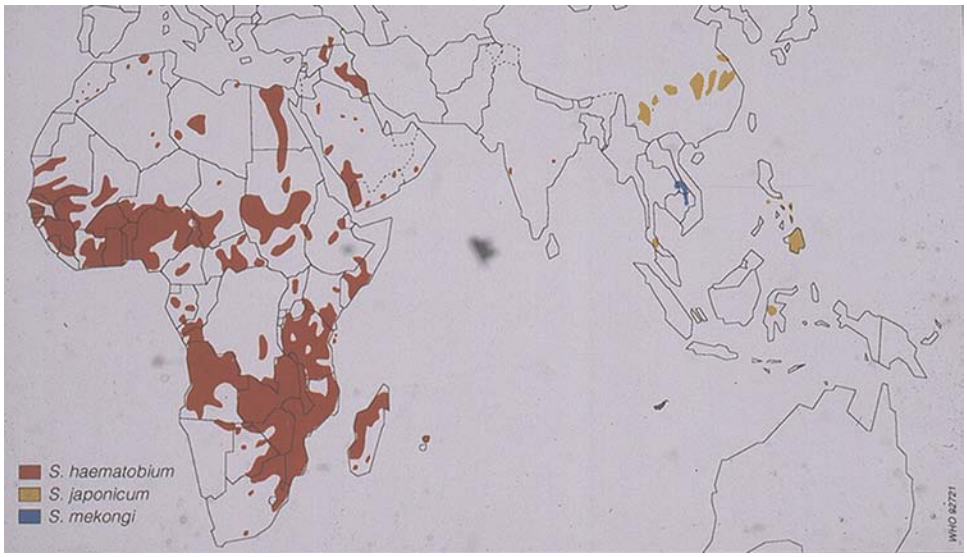

Fig. 37-12. Global distribution of schistosomiasis caused by *Schistosoma haematobium*, *S japonicum*, and *S mekongi*. Reprinted with permission from: World Health Organization Expert Committee. *The Control of Schistosomiasis*. Geneva: WHO; 1993: 16. WHO Technical Report Series 830.

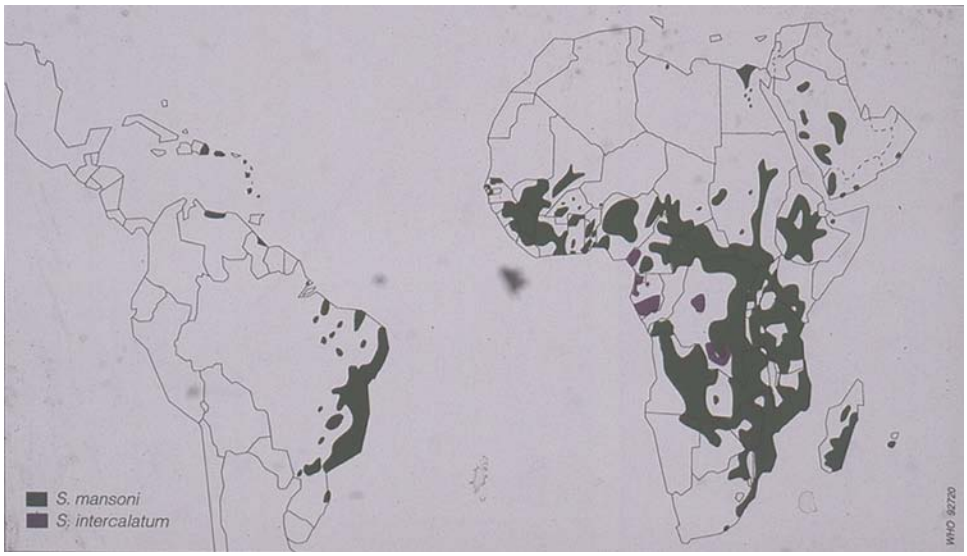

Fig. 37-13. Global distribution of schistosomiasis caused by *Schistosoma mansoni* and *S intercalatum*.
Reprinted with permission from: World Health Organization Expert Committee. *The Control of Schistosomiasis*: Geneva: WHO; 1993: 17. WHO Technical Report Series 830.

initiated and sustained, prevalence rates and, more importantly, the morbidity associated with worm burdens have been greatly reduced.

Pathogenesis and Clinical Findings

Cercarial Dermatitis

The initial exposure to cercariae of a schistosome that infects humans produces a transient dermatitis, particularly in nonindigenous populations, that is difficult to distinguish from other forms of dermatitis. However, a recent history of water contact, itching between 12 and 24 hours after exposure, and distribution of papular or blistering lesions only on parts of the body that were immersed in water should suggest schistosome dermatitis in an endemic region.[580,581] Dermatitis (Figure 37-14) is more commonly seen after exposure to *S haematobium* and *S mansoni* than after exposure to *S japonicum*.[582]

The dermal reactions to zoophilic species of schistosomes are similar to those of the anthropophilic species but are usually more severe and are especially severe in individuals sensitized by previous exposures. Itching at the site of entry is common and is followed by a short-lived macular rash. Within 24 hours, pruritic, urticarial, or papular eruptions appear that can last a week or longer.[583,584]

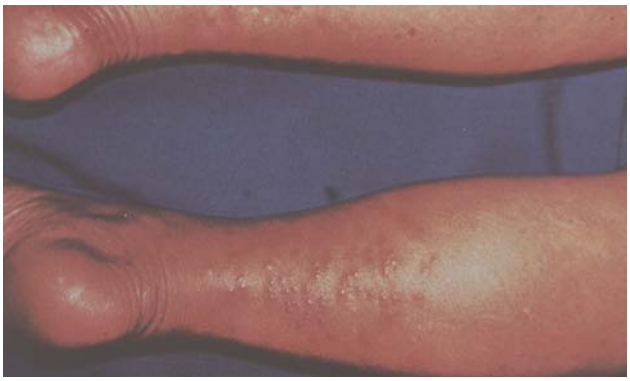

Fig. 37-14. Cercarial dermatitis. Note the typical distribution of lesions around the ankle, which was exposed to schistosome cercariae.
Photograph: Courtesy of Colonel Llewellyn J. Legters, Medical Corps, US Army (ret).

Acute Disease

Acute schistosomiasis is the result initially of immune responses to antigens of developing worms and subsequently of the formation of immune complexes to eggs released by sexually mature females.[581,585] The syndrome is usually reported after an initial heavy infection with any of the major anthropophilic species.[582] Although symptoms are similar regardless of the species of schistosome infecting humans, the intensity of the syndrome varies in proportion to the number of pairs of worms present and to the number of eggs produced. Females of *S japonicum* produce one egg per minute, of *S mansoni* one egg every 5 minutes, and of *S haematobium* one egg every 10 minutes.[586] Thus, it is not surprising that the acute syndrome is most severe in cases of *S japonicum* infection and least severe in cases of *S haematobium* infection.

Central nervous system manifestations are frequently reported in acute cases caused by *S japonicum*; they also occur, however, in acute cases caused by *S haematobium* and *S mansoni*. Most cases of acute cerebral schistosomiasis are caused by *S japonicum*, and most cases of schistosomal transverse myelitis are caused by *S mansoni*.[578,587,588] There were two case reports in 1992 of acute schistosomiasis caused by *S haematobium* involving the central nervous system in two Peace Corps volunteers: a 30-year-old exposed while swimming in Lake Malawi approximately 3 months before evaluation at a US medical center was diagnosed with acute cerebral schistosomiasis and a 26-year-old who had snorkeled in Lake Malawi a month before onset of symptoms was diagnosed with acute (transverse) myelitis.[589]

Acute schistosomiasis resembles serum sickness or an allergic syndrome, which is initially mediated by immediate and delayed-type hypersenstivity to cercarial and larval antigens. There is an abrupt onset of fever (usually late in the evening or at night), chills, abdominal pain followed by coughing, sweating, diarrhea, vomiting, headache, urticaria, hepatosplenomegaly, lymphadenopathy, and often marked elevations of IgE and IgG levels and eosinophil counts.[578,582,590,591] The more severe manifestations occur when egg production starts and large numbers of schistosome eggs are released.[581] This usually occurs 4 to 6 weeks after exposure in *S haematobium* infections,[590] 2 to 12 weeks after exposure in *S japonicum* infections,[578] and 3 to 9 weeks after exposure in *S mansoni* infections.[586] Gastrointestinal disturbances and recurrent diarrhea with mucoid and bloody stools are common features in the late stage of acute disease in its intestinal forms,[578,591] while hematuria is a common feature in the late stage of acute urinary schistosomiasis.[582,590]

In Chinese hospitals, before praziquantel (the current treatment of choice) was available, the mortality related to acute schistosomiasis varied from 2% to 20%. In the Orient, acute schistosomiasis (Katayama fever) has been observed in chronically infected persons and persons with documented cures after they have been exposed to many cercariae in a brief period.[578] In Egypt, acute schistosomiasis caused by *S haematobium* or *S mansoni* is not commonly diagnosed in rural populations of endemic areas, but it is frequently diagnosed in urban children visiting relatives in rural areas for the first time.[590,591] In contrast, acute oriental schistosomiasis is frequently observed in rural inhabitants after their first exposure, as well as in urban residents visiting relatives in rural areas.[578]

Chronic Disease

Chronic schistosomiasis develops gradually as a result of immunological responses to schistosome eggs deposited in tissues. The degree of disease is directly related to the number of eggs deposited in host tissue and the host reaction to them. In turn, egg deposition is a function of the number of worm pairs and duration of an infection.[581,583] Symptoms in heavily infected individuals, such as bleeding, ulceration, or polyposis, are due to the initial granulomatous response. In intestinal schistosomiasis (caused by *S japonicum* and *S mansoni*), ulceration and polyp formation occur in the bowel; in urinary

schistosomiasis (*S haematobium*), those symptoms occur in the mucosa of the ureter and bladder.[581] In endemic regions, bleeding, ulceration, and polyposis are more common in teenagers than adults. The classical symptoms of intestinal schistosomiasis (ie, liver "pipestem" fibrosis and portal hypertension) and urinary schistosomiasis (ie, hydronephrosis, hydroureter, and bladder calcification) develop in adults who have been repeatedly infected over a long time. Pulmonary symptoms occur in all forms but are most common in cases caused by *S haematobium*. Central nervous system involvement is most common in *S japonicum* infections and least common in *S haematobium* infections.[592–594] Since eggs of *S japonicum* are relatively small and round and have a minute spine (Figure 37-15c), their size and shape may be responsible for their more frequent deposition in ectopic locations such as the central nervous system. Chronic disease sequelae can be prevented by prompt treatment of suspected and confirmed cases.

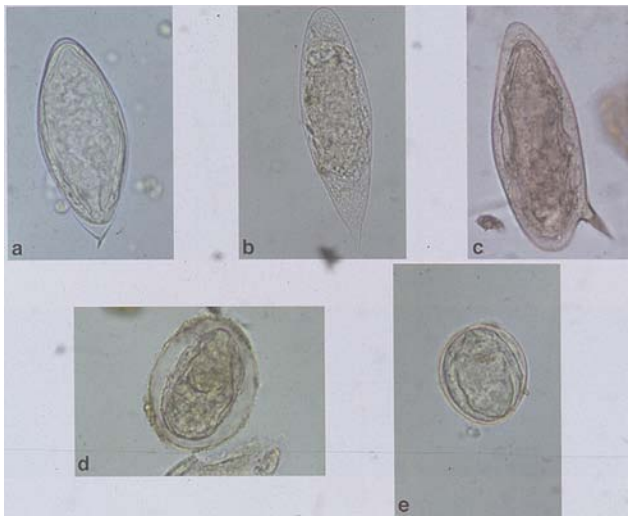

Fig. 37-15. Eggs of schistosomes commonly infecting humans are relatively large and nonoperculate with a transparent shell and either a lateral or terminal spine. (**a**) *S haematobium* (110-70 x 40-70 μ) and (**b**) *S intercalatum* (140-240 x 40-70 μ) eggs possess a distinct terminal spine. Eggs of *S intercalatum* are usually found in feces whereas eggs of *S haematobium* are usually found in urine. (**c**) *Schistosoma mansoni* eggs (115-175 x 45-70 μ) possess a distinct lateral spine and are usually recovered from feces. (**d**) Eggs of *S japonicum* (70-10 x 55-65 μ) and (**e**) *S mekongi* (51-78 x 39-66 μ) are round with a short, dull spines. Note that a short, dull spine is clearly visible on the *S mekongi* egg shell, whereas a short, dull spine on the shell of the *S japonicum* egg could easily be obscured by debris or orientation.
Photomicrographs: Courtesy of Dr. Lawrence R. Ash, Department of Epidemiology, School of Public Health, University of California, Los Angeles.

Diagnostic Approaches

Signs and symptoms of cercarial dermatitis and acute schistosomiasis must be considered in a differential diagnosis under field conditions, as it takes weeks for a patent infection to be diagnosed by stool, urine, or serological methods. History of freshwater contact, dermatitis on regions of the body that were submersed, and itching within the past few days should suggest schistosomiasis. In the following weeks, malaise, fever, urticaria, and vague intestinal complaints associated with transient toxic and allergic manifestations are common in light-to-moderate exposures. If an individual is initially exposed to many cercariae, there is an abrupt onset of fever with chills, abdominal pain, diarrhea, nausea, vomiting, cough, headache, urticaria, hepatosplenomegaly, frequently high eosinophilia counts (> 50), and elevated IgG and IgE levels. These acute symptoms, which can last for several days or weeks, are most common upon exposure to *S japonicum* cercariae and least common upon exposure to *S haematobium* cercariae.[593]

Definitive diagnosis has depended on the demonstration of eggs either in stool or urine specimens or in intestinal or bladder biopsy specimens from suspected cases.[595] Stool and urine examinations can be made with minimum laboratory support. Eggs of schistosomes are relatively large, are distinct in shape, and contain a fully developed embryo (miracidum) (Figure 37-15). Eggs of *S haematobium* and *S intercalatum* possess a distinct terminal spine (Figure 37-15a,b). The latter eggs are usually found in feces, are larger, and frequently have an equatorial bulge. *S mansoni* eggs possess a distinctive lateral spine (Figure 37-15c), whereas those of *S japonicum* and *S mekongi* are round with a short, dull spine (Figure 37-15d,e). Concentration methods and multiple stool or urine examinations are recommended.[595,596] Clinical dipsticks for hematuria are efficient and effective screens for patent infections with *S haematobium* because hematuria is usually indicative of urinary schistosomiasis in areas where individuals are continually exposed.[596] However, hematuria is not a common sign of urinary schistosomiasis in light infections.

Even though current serological assays are unable to distinguish past infection from current ones, they are valuable in establishing a diagnosis of schistosomiasis in US military personnel, because most US

forces have not been exposed to anthropophilic schistosomes or even to related helminths. The Centers for Disease Control and Prevention's Division of Parasitic Diseases has developed very sensitive and specific antibody assays for both *S haematobium* and *S mansoni*.[597] Serological assays are particularly useful for the diagnosis of acute schistosomiasis cases, as most cases are symptomatic before eggs can be detected in fecal or urine specimens.[581] Antigen detection assays for *S mansoni* and *S haematobium*, which can be used with either urine or serum samples, are as reliable as the Kato-Katz stool and urine filtration examinations, and antigen levels correlate well with egg counts for quantification of parasitemia.[598] Reagents for circulating cathodic antigen and circulating anodic antigen detection in urine and sera are available through the Laboratory of Parasitology, Medical Faculty, University of Leiden, Netherlands. If a suspected infection cannot be determined by stool or urine examination, sera should be tested for schistosome antigen or antibodies to schistosome antigens or both. If a suspected case demonstrates neurological symptoms in the absence of eggs in fecal or urine specimens, antibody or antigen assays may be the only means of establishing a diagnosis.

Recommendations for Therapy and Control

Therapy

Currently three anhelminthic drugs are used to treat schistosomiasis: praziquantel, oxamniquine, and metrifonate. Praziquantel is the drug of choice for treatment of all acute and patent cases of schistosomiasis.[573,563] Oxamniquine is an alternative treatment for both acute and patent cases of *S mansoni* infection, and metrifonate is an alternative treatment for cases of *S haematobium* infection.[573] All cases of schistosomiasis, whether or not they are symptomatic, and all suspected cases chould be treated to prevent potential pathological sequelae.

Praziquantel is exceptionally well tolerated. Side effects, such as abdominal discomfort, bloody diarrhea, nausea, vomiting, headache, dizziness, and drowsiness, are usually associated with heavy worm burdens. Praziquantel is better tolerated if given with meals, and side effects are fewer if it is given in divided doses. The World Health Organization[573] recommends 40 mk/kg of praziquantel as a single dose for infections with all species of schistosomes. *The Medical Letter*[563] recommends 60 mg/kg of praziquantel, divided in three equal doses over 1 day for *S japonicum* and *S mekongi* infections, and 40 mg/kg in three equal doses over 1 day for *S haematobium* and *S mansoni* infections. Praziquantel is the only drug now recommended to treat infections with *S japonicum*, *S intercalatum*, and *S mekongi* because these parasites are unresponsive to oxamniquine. All patent cases, whether or not they are symptomatic, and all suspected cases should be treated to prevent potential pathological sequelae of chronic infections.

Effective doses of oxamniquine for *S mansoni* infections range between 15 and 60 mg/kg and should be given over 2 or 3 days.[573] *The Medical Letter*'s generic recommendations for treatment of *S mansoni* infections with oxamniquine are 15 mg/kg once for adults and 20 mg/kg divided into two doses for children; however, in East Africa they recommend that the dose be increased to 30 mg/kg, and in Egypt and South Africa to 30 mg/kg per day for 2 days.[563] Shekhar[599] recommends 40-60 mg/kg of oxamniquine over 2 to 3 days to treat *S mansoni* infections throughout Africa. In north Senegal, where *S mansoni* responds poorly to standard praziquantel therapy (36% cure rate), oxaminquine is highly recommended.[600]

Cercarial Dermatitis. If the dermatitis needs treatment, palliative topical agents such as corticosteroid creams should be used. In more severe cases, oral or parenteral antihistamines can be administered.[582] Usually, however, species of schistosomes that readily infect humans are well adapted to humans, and the dermatitis elicited is mild in comparison to that elicited by cercariae of zoophilic schistosomes.

Acute Disease. The combined use of steroids and praziquantel to treatment of acute schistosomiasis syndrome is based on clinical and experimental evidence that steroids act synergistically with schistosomicides. This combination augments cure and speeds recovery, even though there is an occasional worsening of clinical status and praziquantel is less effective against immature worms.[573,581,583,591,601] Prompt treatment with praziquantel and concurrent use of nonsteroid anti-inflammatory agents is recommended for persons with mild symptoms; corticosteroids should be used only for persons who appear extremely toxic or whose symptoms fail to respond to or worsen with treatment.[583] Farid[591] recommends 75 mg/kg of praziquantel, divided into 3 equal doses over 1 day, for treatment of acute *S mansoni* infections in Egypt.

Exposed Personnel. There are no clinical reports of the efficacy of any Food and Drug Administration–approved schistosomicidal drug against the schistosomal stage or immature schistosomes, but derivatives of artemisinin have been reported to suppress development of immature schistosomes.[602]

Two studies[603,604] in regions of rural China where *S japonicum* is endemic have demonstrated the efficacy of artemether in the reduction of acute schistosomiasis, both in the infection and reinfection rates and in the intensity of infections. In the two field trials, no cases of acute schistosomiasis were seen in groups treated with artemether, whereas in 4% and 9% of the control groups, acute schistosomiasis was diagnosed. While subsequent infection rates in the control groups were 13.6% and 15%, they were 5.5% and 4.2%, respectively, in the artemether groups. Similarly, the intensity of infection, as measured by eggs per gram using the Kato-Katz method, was reduced more than 5-fold in one field trial and 1.5-fold in the other. In neither field trial were adverse side effects observed. These results are encouraging and suggest that artemether, and probably other artemisinin derivatives, may provide a means of safely reducing the number of acute schistosomiasis cases and the rate and intensity of patent infections in persons who cannot avoid exposure.

An experimental study[605] in mice suggested that the efficacy curve of praziquantel is bimodal. Worm reduction rates ranged from 80% to 50% in the first 2 weeks, varied between 0% and 20% in the third and fourth week, and climbed back to 95% to 100% by the sixth week after exposure. Since praziquantel is well tolerated and its known side effects are related to worm burden,[573] its preemptive use should be seriously considered in personnel who have been exposed in order to prevent or lessen the impact of the acute state of this disease.

Prevention and Control

From a military perspective, control is prevention. Cases are a direct consequence of contact with or use of snail-infested freshwater contaminated with feces or urine containing schistosome eggs. The basic preventive options fall into four categories: limiting water contact, treating water, controlling snails, and educating personnel.

Limiting Water Contact

Since the intensity of the acute disease is directly related to the number of egg-depositing female schistosomes present, any protective barrier is better than none at all. Thus, clothing; gloves of rubber, latex, or vinyl; rubber boots; or anything that prevents a cercaria from contacting skin will reduce the chance of transmission.[606] For example, uniform trousers will provide some protection for legs if they are tucked into the top of combat boots with enough slack to form a cuff over the boot top, but the protective effect diminishes as the exposure lengthens.[607] If feasible, skin that contacts suspect water should be vigorously toweled dry as soon as possible, and 70% alcohol should be applied to the skin immediately.

No topical repellent is presently available that provides long-term protection against cercarial penetration. Field trials of 1% niclosamide as a topical antipenetrant demonstrate approximately 20% reduction in reinfections from *S mansoni*[608] but no significant reduction in reinfection rates from *S haematobium*[609] among Egyptian farmers. Pellegrino[606] summarizes numerous studies, conducted in the 1940s and 1950s, demonstrating that many compounds could provide relatively effective protection for limited periods of time. Repellents containing dibutylphthalate and benzylbenoate as principal agents in a turpentine base have been used with success in China.[610] Most oily substances that are hydrophobic offer some degree of protection for short periods, and a limited degree of protection is offered by topical insect repellents.[568,606]

A recent report[611] suggests that DEET, probably one of the most widely used insect repellents in the world, at concentrations of 7.5% or higher was 100% effective in immobilizing and killing cercariae of *S mansoni* in vitro, and cutaneous application of DEET in an isopropanol vehicle or as a commercial insect repellent preparation (Off with 7.5% DEET) was more than 99% effective in preventing entry of *S mansoni* cercariae into mouse tail skin. DEET may not only be a safe prophylactic agent in the control of human schistosomiasis, but it may also be potentially useful in the control of cercarial dermatitis associated with exposure to schistosomes of birds and mammals. A follow-up study[612] reported that DEET incorporated into liposomes (LIPODEET) appears to prolong the activity of DEET for more than 48 hours after a single application. In addition, LIPODEET was found to be minimally absorbed through the skin and loss from washing off was limited, suggesting that LIPODEET may be a safe, long-acting formulation of DEET that is effective in preventing successful penetration of schistosome cercariae.

The time of day can be a factor. Cercarial emergence from the snail is circadian, but the periodicity varies depending on the species involved. Cercariae of *S mansoni, S haematobium*, and *S japonicum* are usually shed in the mid to late morning. However, snails infected with *S mansoni* in the Caribbean region or with *S japonicum* in the Philippines and Indonesia usually shed cercariae in the late afternoon or early evening when rodents that are important reservoir hosts of schistosomiasis are active.[613,614] Risk can be minimized by restricting water contact during and for a few hours after this peak transmission period.

Treating Water

Before surface water is used for drinking, bathing, and washing clothes, it must be treated to remove or inactivate cercariae. If available, subsurface water should be used for these purposes. Surface water can be held in tanks that do not contain any infected snails for 24 hours before use,[615] boiled, or heated to either 50°C for 5 minutes or 80°C for 30 seconds to inactivate cercariae.[568] Drinking water treated with iodine is safe. Cercariae are killed within 30 minutes by 1 ppm chlorine residual in a pH range of 7.5 to 8.9, by 0.3 ppm at pH 5, and by 5 ppm at pH 10.[615] Sand grains smaller than 0.35 mm and diatomaceous earth filters remove cercariae.[616] US Army mobile water purification units employing either diatomite filters or a reverse-osmosis system are effective in removing cercariae.[568]

Controlling Snails

Niclosamide (Bayluscide [Bayer AG], Mollutox in the Middle East and North Africa) is the only highly effective synthetic molluscicide. In addition, nicolsamide is toxic to cercariae and will have a rapid and focal impact on transmission when applied.[615] A classic reference for snail control, *Snail Control in the Prevention of Bilharziasis*,[617] has chapters on both chemical and environmental methods of control. A more recent text, *Molluscicides in Schistosomiasis Control*,[618] is an excellent review of the use of chemicals to control molluscan hosts of schistosomes.

There are a number of environmental and biological measures that can be used to control snail populations. One example comes from Asia: habitats of amphibious oncomelanid snails can simply be buried or flooded to drastically reduce snail populations. In regions where aquatic snails are involved, a well-designed irrigation system allows snail habitats to be dried out, and ditches drained and cleaned on a regular schedule. Although these measures may not be practical in a traditional military operation, they may be very useful in nontraditional military operations, such as humanitarian assistance and peacekeeping missions, in endemic areas.

Educating Personnel

Personnel must be alerted to hazards of freshwater contact (eg, swimming, bathing, washing clothes) before deployment to an endemic area. Any activity or intervention that reduces the frequency or duration of exposure to snail-infested waters will reduce the chance of infections. Military personnel should be taught that the first symptom of an exposure is a dermatitis affecting areas exposed to surface water within 6 to 48 hours of exposure. If exposed, they should seek medical attention.

[W. Patrick Carney]

COCCIDIOIDOMYCOSIS

Introduction and Military Relevance

Coccidioidomycosis was first recognized in 1892 in an Argentinean soldier who died of a disseminated case of this fungal infection. Pivotal to understanding the epidemiology and clinical course of this mycosis is surveillance work using the coccidioidin skin test and serologies done in the US Army air bases of the San Joaquin Valley in California during World War II. Smith[619,620] found that this inhalationally acquired infection from soil caused high morbidity among the military in endemic areas, although the majority of those infected had mild symptoms. Many soldiers were symptomatic, requiring 4 to 6 weeks of hospitalization for respiratory illness. A small percentage of those infected had serious, often fatal, infection, and persons of color were predisposed to having this severe course. Those who had reactive skin tests seemed immune to reinfection. It was also found that there were seasonal differences in infection rates and that dust control could significantly decrease the incidence of primary infection.

In the military, outbreaks have been associated with maneuvers of nonimmune units. For example, in 1992 a Tennessee-based US Marine Corps Reserve unit experienced an outbreak after training in San Luis Obispo County, Calif.[621] Other reports include an outbreak associated with moving earth to provide foundations for a housing project at Edwards Air Force Base, Calif.,[622] coccidioidomycosis as a sequela of a dust storm at Lemoore Naval Air Station, Calif.,[623] infection among German air defense artillery trainees in El Paso, Tex.,[624] and cases in those deployed to the Desert Training Center in Fort Irwin, Calif.[625]

Description of the Pathogen

Coccidioides immitis is a dimorphic fungus found in soil. In nature and in laboratory culture, it exists as a mycelial-arthrospore form. Animal studies suggest inhalation of as few as 7 to 12 arthroconidia

suffice to cause infection.[626] In the host, the arthroconidia develop into spherules—spheres 20 to 60 μm in diameter—with small endospores inside.

Coccidioides is a hardy organism and has remained viable in dry soil and beach sand for more than 10 years.[627] It can be sterilized by soaking in hypochlorite, phenols, iodophors, or formaldehyde for at least 15 minutes.

Epidemiology

Transmission

Coccidioidomycosis is transmitted by inhalation of arthrospores from dust or soil in endemic areas. Reactivation can occur, principally in immunosuppressed hosts, such as organ transplantees and those with chemotherapy-induced lymphopenia and human immunodeficiency virus (HIV) infection. Infection has been reported to have been caused by fomites such as cotton, dirt moved from an endemic area, packing material around archaeological artifacts, fruit, and dust on cars driven through an endemic region. Infections in laboratory workers have usually been inhalationally acquired, but some have been primary inoculations leading to skin lesions. Inoculation from barbed wire and splinters has also been reported.[628] Person-to-person transmission has occurred—in a cast covering a draining sinus, the spherule form had converted to the mycelial phase. The organism aerosolized when the cast was opened, exposing many health care workers.[629]

Transmission seems to be most intense from August to November, especially if there is prolonged drought followed by heavy spring rains.[620] California had a marked increased incidence of primary *Coccidioides* infection due to this pattern in 1991 and 1992; incidence also increased later because of the disruption and construction related to the 1994 earthquake.[630] Large dust storms facilitate the transmission of coccidioidomycosis.

Geographic Distribution

The endemic zone for *Coccidioides* is restricted to the Western hemisphere between 40° north (California) and 40° south (Argentina) latitude (Figure 37-16). *Coccidioides* is usually found in arid climates of low rainfall, hot summers, few winter freezes, and alkaline soil. In the United States, this includes the deserts of Arizona, west Texas, and the central valleys of California; some areas of southern New Mexico; Las Vegas, Nev.; and southwest Utah. Outside the United States, endemic areas are found in Mexico, Guatemala, El Salvador, Honduras, Colombia, Argentina, Brazil, Venezuela, and Paraguay.[631] It should be emphasized that areas of endemicity are focal within this distribution.

Incidence

Estimates suggest that 100,000 persons in the United States are infected each year.[632] In endemic areas of the Southwest, 30% to 50% of long-term residents are *Coccidioides* skin-test positive. Studies in Tucson, Ariz., suggest an annual infection risk of 2% to 4% per year.[633] There are several factors associated with a higher risk of dissemination once coccidioidomycosis is acquired. These include race and

Fig. 37-16. Areas in which coccidiomycosis is endemic. Reprinted with permission from: Pappagianis D. *Coccidioidomycosis: A Text*. New York: Plenum Publishing; 1980.

ethnic origin (especially black and Filipino), HIV infection with CD4 counts of less than 250, having received an organ transplant, having Hodgkins disease or uremia, taking steroids for collagen vascular disease, and being in the second or third trimester of pregnancy.

The US military's experience in World War II suggests that immunity develops to exogenous reinfection.[619] In the San Joaquin Army air fields, active infection occurred only in those patients who had negative skin tests or were untested.

Occupational risk groups for the acquisition of coccidioidomycosis include agricultural laborers; archaeologists; geologists; paleontologists; construction, highway, pipeline, and oil-well drilling workers; laboratory technicians; and military personnel. Coccidioidomycosis is recognized as an occupational illness under the California worker's compensation law.

Pathogenesis and Clinical Findings

The arthroconidia are inhaled and establish infection in the small bronchi. The initial host response is neutrophilic, but the spherules are not killed by polymorphonuclear leukocytes. Cell-mediated immunity is essential to kill the fungus. Dissemination has been related to hematogenous spread of the fungus from suppurating lymph nodes in the hilae and mediastinum.

The majority (60%) of cases are asymptomatic or have symptoms similar to an upper respiratory tract infection.[619] Forty percent are symptomatic, mainly with an acute febrile illness lasting 7 to 28 days that often includes cough (usually nonproductive), malaise, pleuritic chest pain, night sweats, fatigue, occasional dyspnea, headache, pharyngitis, arthralgia, and, infrequently, hemoptysis. About 10% of symptomatic patients (especially females) may have a syndrome known as desert rheumatism or valley fever, which includes erythema nodosum (painful erythematous nodules often over the pretibial area, Figure 37-17) with or without symmetrical nonmigratory arthralgias and occasionally arthritis. Another skin manifestation of an early immune response to *C immitis* is toxic erythema, which can be scarlatiniform, morbilliform, or urticarial. Erythema multiforme can also occur, usually in the upper half of the body, and is sometimes accompanied by palmar desquamation. Valley fever is self limited, is associated with very large reactions to spherulin skin testing, and generally has a good prognosis. In these acute cases, spherulin skin test reagent should be diluted to 1:1,000 or 1:10,000 to avoid large local reactions.

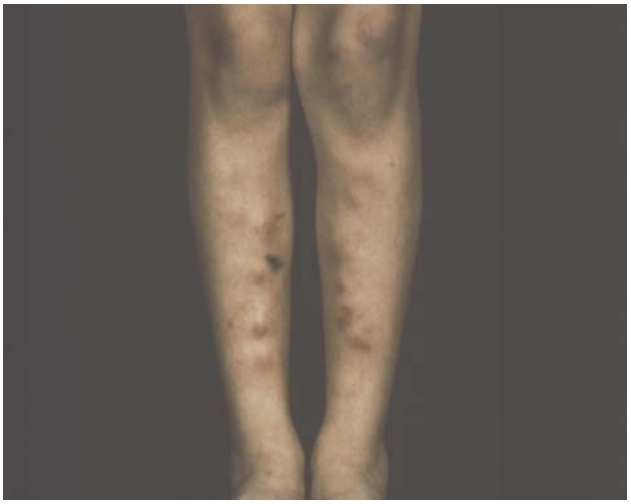

Fig. 37-17. Erythema nodosum is associated with acute coccidioidal infection. An immunologic phenomenon, it portends a benign course of infection.
Photograph: Courtesy of William Beaumont Army Medical Center, El Paso, Tex.

Disseminated extrapulmonary coccidioidomycosis occurs in 1% of symptomatic white persons and 10% of symptomatic black persons.[619] This is often a severe, relapsing, potentially life-threatening complication. Disseminated infection usually develops within a year of initial infection. The most common sites are skin, bone, joint, and meninges; other sites include the genitouritary tract, peritoneum, thyroid, lymph nodes, and spleen. It often manifests in a miliary pattern. The skin is frequently involved in disseminated coccidioidomycosis and may be the manifestation that a deployed military health care provider is most likely to see. Most commonly, the lesion is verrucous; it can also be a chronic ulcer (Figure 37-18), draining sinus tract, plaque, nodule, subcutaneous abscess, or sporotrichoid lesion with regional lymphadenitis.

Findings on chest radiograph include infiltrates (which can be single or multiple), hilar adenopathy, and occasionally ipsilateral pleural effusion or cavitary lesions. Five percent have chronic radiograph findings, which include nodules and thin-walled cystic lesions. Diffuse reticulonodular infiltrates suggest disseminated disease and are more frequently seen in immunocompromised hosts.

Laboratory clues are an elevated erythrocyte sedimentation rate and a fairly normal total white blood cell count. More than 25% will have an eosinophilia count of greater than 5%.

Fig. 37-18. Photograph (**a**) shows Verrucous cutaneous coccidioidomycosis. Photograph (**b**) shows the ulcerative form of cutaneous coccidioidomycosis above the lip. This lesion represents disseminated infection. Photographs: Courtesy of William Beaumont Army Medical Center, El Paso, Tex.

Diagnostic Approaches

In the field, coccidioidomycosis should be considered in cases of respiratory illness occurring approximately 1 to 3 weeks after exposure in endemic areas. Spherulin skin testing (1:100) designates those who have been infected; however, like the tuberculin skin test, it is better to have baseline data so as to detect conversion. A significant reaction is an induration of greater than or equal to 5 mm at either 24 or 48 hours. For febrile patients, a chest radiograph is recommended, as those at highest risk for dissemination may have an anergic result on the spherulin skin test. A positive coccidioidin skin test can be seen 2 to 21 days after exposure in 99% of those infected.[634] Causes of false-positive tests include the merthiolate preservative used in the skin test, histoplasmosis, paracoccidioidomycosis, and, possibly, recurrent recent (within 2 months) skin testing.[635] Causes described for false-negative skin tests include dissemination, placement too early, and methodologic problems with skin test placement such as subdermal injection or inaccurate measurement of the induration.

In garrison, several additional diagnostic aids may be employed. Coccidioidal serology can be very helpful. IgM antibodies can be seen in 7 to 10 days and measured by several assays (eg, tube precipitins, latex particle agglutination, immunodiffusion). Serum IgG antibodies occur later (50% by 4 weeks) and persist for a long time. Complement fixation IgG titers of greater than 1:16 to 1:32 are of concern because they are associated with a higher risk of dissemination, particularly if the test is standardized to the antigen of Smith.[636]

The spherules are rarely seen in sputum, pus, sinus tract drainage, or other body fluids. In tissue sections, the spherules may be seen with hematoxylin, hematoxylineosin, and Gomori's methenamine silver stain. *Coccidioides* can also autofluoresce.

The organism grows well on artificial media in 3 to 5 days. The mycelial form that is generated is highly infectious, so the laboratory should be warned that *C immitis* is suspected so safety measures will be carefully maintained.

Recommendations for Therapy and Control

Those with severe primary infection and those at risk for disseminated illness should be treated. This includes persons who are immunocompromised and those who have had a large inoculum exposure, have had symptoms for longer than 6 weeks, have an anergic reaction to the spherulin skin test, have an increased complement fixation titer, or are in the second or third trimester of pregnancy. All patients with extrapulmonary coccidioidomycosis should receive therapy. For patients who do not receive specific therapy, a repeat encounter at 1 to 2 years to document resolution or identify complications is suggested.

The current guidelines for treatment are in flux, with the availability since the early 1990s of the oral triazoles.[637] For severe illness, intravenous amphotericin B (1.5 to 3 g total dose, 0.5-0.7 mg/kg per day) is given; intrathecal amphotericin B (0.01-1.5 mg) must be given as well for meningeal coccidioidomycosis. During pregnancy, amphotericin B is the treatment of choice. For mild-to-moderate nonmeningeal coccidioidomycosis, itraconazole 200 mg orally twice a day or fluconazole 400 to 800 mg per day may be used; the regimen must be contin-

ued for at least 6 months after the disease becomes inactive. For meningeal coccidioidomycosis, fluconazole 600 to 800 mg per day is considered first-line therapy; in limited experience it is effective and less toxic than intrathecal amphotericin.[638] Some would initiate therapy for meningitis with amphotericin B intrathecally as well, trying for a more rapid treatment response. Therapy should be continued lifelong.

Overall, response rates of less than 75% are the norm in the treatment of coccidioidomycosis, and all patients with disseminated infection should be considered at risk for relapse.[639]

Data gathered at the San Joaquin Valley Army air bases support the utility of dust control in decreasing the incidence of infection in susceptible persons.[620] Lawns and trees should be aggressively planted, roads and airfields paved, and athletic fields oiled (optimal dosage is 1 qt of highly refined oil per square yard of dry field[619]). Temporary benefit has been observed with soil fumigation using 1-chloro-2-nitropropene.[640] Local authorities should be consulted about the legality of this measure. For optimal control, ground maneuvers in focal areas known to be highly endemic, especially in the late summer and fall, should be curtailed or limited to those persons known to have positive spherulin skin tests (although heavy reexposure may overwhelm this immunity). For those involved with earth-moving equipment, use of vehicles with air conditioned cabs is recommended. Buildings in endemic areas should have filtered air or air conditioning. Vehicles covered with dust from endemic areas should be thoroughly cleaned before departure. The use of personal respirators or masks for potentially heavy but limited exposure may be in theory useful but in practice very uncomfortable, given the hot, dry environment where *Coccidioides* is endemic.

In the clinical setting, dressings or casts over active coccidioidomycosis infections (eg, draining skin lesions) should be completely wetted before removal and the dressing treated with phenol or sodium hypochlorite solution to decrease any subsequent transmission.

Laboratory personnel should maintain *Coccidioides* isolates in sealed containers and handle culture samples with appropriate biosafety equipment for a class 3 biologic agent. For the first 3 to 5 days of growth, though, the sample is not particularly infectious.

There is as yet no successful vaccine for the prevention of coccidioidomycosis. While azole prophylaxis in high-risk patients (eg, those with HIV or transplanted organs) has been considered, it has not yet been adequately studied. Of note, in three reported cases in immunosuppressed hosts, disseminated coccidioidomycosis developed while the patients were receiving ketoconazole.[641]

Control in military units from a nonendemic region training in or deployed to endemic, nonimproved areas of the US Southwest should include a surveillance and education program. Optimally, this would include spherulin skin testing before training and 1 to 2 months after training, surveillance for clustering of febrile respiratory illness within a month of potential exposure, and observation for cases of erythema nodosum. Military personnel should be educated about the significance of symptoms consistent with disseminated infection. Dissemination will often occur once service members have redeployed to a nonendemic region where health care providers may not readily consider coccidioidomycosis in the differential diagnosis.

Coccidioidomycosis is a reportable medical condition in the US military and several southwestern states.

[Naomi E. Aronson]

HISTOPLASMOSIS

Introduction and Military Relevance

Histoplasmosis, caused by the fungal pathogen *Histoplasma capsulatum* var. *capsulatum*, is an infection of worldwide distribution. Usually an asymptomatic infection, histoplasmosis can be a severe and sometimes fatal disease. Outbreaks of acute histoplasmosis have been associated with military operations in the past. These epidemics have most frequently been associated with cleaning and clearing contaminated debris from structures such as infrequently used bunkers. Some of the earliest epidemics were reported in soldiers in Camp Gruber, Okla, and Camp Crowder, Mo, in the 1940s.[642] More recent outbreaks include those described in 1977 and 1982 associated with troop activity in Panama.[643,644] Histoplasmosis has the potential to affect the readiness and effectiveness of service members in situations where contaminated structures are cleaned or cleared for use.

First described by Samuel Darling in 1906, histoplasmosis was initially thought to be a parasitic infection.[645] Describing an autopsy performed while working in the Panama Canal Zone, Darling re-

ported finding organisms in histiocytes that resembled plasmodia and appeared to have a capsule. Because of these observations, he recommended naming the new parasite *Histoplasma capsulata*. De Monbreun established that the causative agent, *H capsulatum*, was a dimorphic fungus.[646] He described the cultural characteristics of both the yeast and mycelial phases and fulfilled Koch's postulates by producing disease in animals with the isolate.

From its discovery and up until the late 1940s, histoplasmosis was considered to be widespread in distribution but rare and fatal. That a nonfatal infection could also occur was not elucidated until the introduction of histoplasmin skin testing. In the early 1940s, it was noted that military recruits from Kentucky and many south-central states had a higher than usual rate of calcifications on chest roentgenogram, changes suspicious of healed tuberculosis. Many people in those areas with abnormal chest roentgenograms had negative tuberculin skin tests. In the mid-1940s, studies by Palmer[647,648] and Christie[649] showed that reaction to the new skin test for histoplasmosis was widespread in the midwestern United States and correlated with asymptomatic pulmonary calcification in subjects with negative tuberculin tests. These studies, along with other epidemiologic work, firmly established histoplasmosis as a predominantly self-limiting infection of humans and animals.

Description of the Pathogen

H capsulatum var. *capsulatum* is a temperature-dependent, dimorphic, fungal pathogen.[650,651] In its natural habitat (soil) and in culture at room temperature, *H capsulatum* forms a mycelium of septate hyphae, which can produce both microconidia (2-5 μm) and tuberculate macroconidia (8-16 μm). It is this form of the fungus (and especially aerosolized microconidia) that is the infectious inoculum. In its pathogenic form or in culture at 37°C, *H capsulatum* var. *capsulatum* is a small yeast (2-5 μm). Conversion of the mycellial form, grown from clinical isolates, to a yeast at 37°C can be used in the identification of this organism. The mycelial form of *H capsulatum* grows well in soils with high nitrogen content and is found in soil contaminated by guano and debris of birds and bats. The most common niche of the fungus is in soil contaminated with the droppings of starlings, bats, or chickens. In addition to causing infection in humans, histoplasmosis is common in both wild and domesticated mammals. *H capsulatum* consists of three varieties: *capsulatum*, *duboisii*, and *farciminosum*. Most cases of histoplasmosis are caused by *H capsulatum* var. *capsulatum*. *H capsulatum* var. *duboisii* (*H duboisii*, African histoplasmosis) is a second variety of the fungus, which is found principally in Africa and causes disease usually limited to bone and skin. *H capsulatum* var. *farciminosum* is a pathogen that has thus far been limited to horses and mules.

Epidemiology

Transmission and Geographic Distribution

Inhalation of aerosolized conidia is the route of transmission. Histoplasmosis has been reported throughout the world, with greatest prevalence from 45° north latitude to 30° south latitude.[652] The distribution of this disease is concentrated in and around the Mississippi and Ohio River valleys in the United States.

Incidence

Clinically apparent disease is more common in males (4:1 ratio), although skin testing does not support a difference in exposure or infection between the sexes.[653] In the less-commonly seen forms of histoplasmosis, including disseminated disease, immunocompromised patients (eg, those who have a hematologic malignancy, have acquired immunodeficiency syndrome [AIDS], or have taken steroid or immunosuppressive therapies) and the very young are at higher risk.

The world's highest concentration of skin-test–positive individuals exists in the Mississippi and Ohio River valleys, with 80% to 90% of residents there testing positive. In the more highly endemic areas of this region, 80% to 90% of the population is skin-test–positive by age 20.[654] Large-scale skin testing of Navy recruits has enhanced the understanding of the epidemiology of histoplasmosis in the United States (Figure 37-19).[655] The annual incidence of histoplasmosis is thought to be approximately 250,000 in the United States.[656] In addition to endemic disease, about 200 small epidemics of histoplasmosis have also been described. Epidemics of histoplasmosis usually present with acute pulmonary disease in subjects exposed to large inoculum loads, although at least one outbreak presented as undifferentiated febrile syndrome without pulmonary signs or symptoms.[644] The source and causation of these epidemics is usually the disruption of debris, soil, or guano through cleaning or removing structures that are heavily contaminated by starlings, bats, or chickens. Examples include outbreaks associated

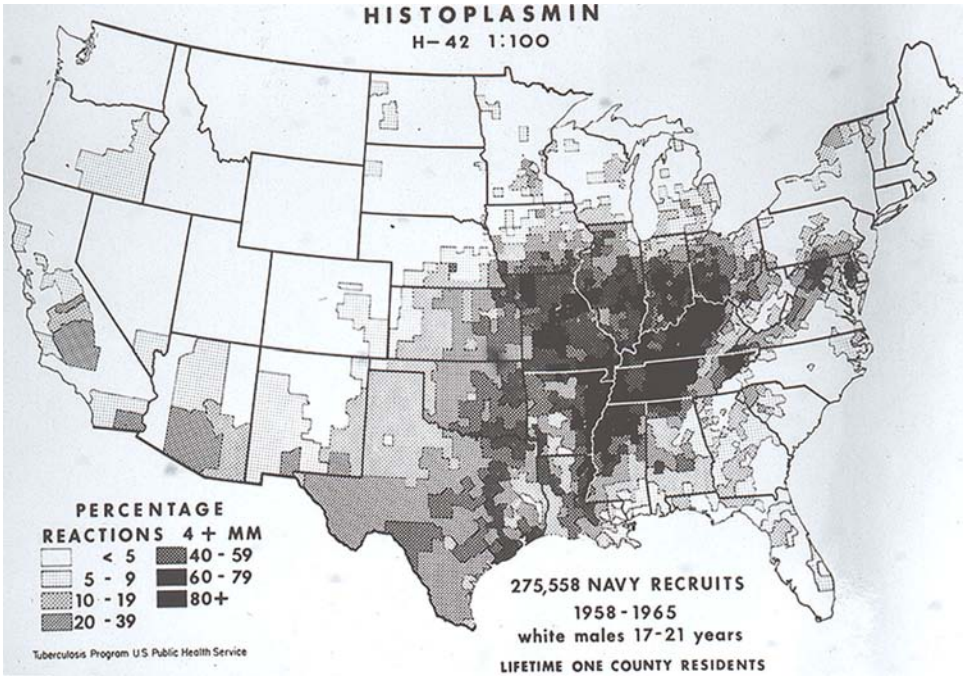

Fig. 37-19. Prevalence of histoplasmin skin test reactivity in the continental United States.
Reprinted with permission from: Edwards LB, Acquaviva FA, Livesay VT, Cross FW, Palmer CE. An atlas of sensitivity to tuberculin, PPD-B, and histoplasmin in the United States. *Am Rev Respir Dis*. 1969;99(Suppl):1–132.

with cleaning buildings, bunkers, caves, silos, and areas of bird roosts; excavation of soil; and removal of dead trees. Attack rates of 90% to 100% have been reported in such outbreaks.[642] Disease caused by such high-inoculum exposure is often severe and incapacitating, requiring intensive care acutely and long periods of convalescence.

Pathogenesis and Clinical Findings

Histoplasmosis in humans can be manifested in many forms, from acute to chronic and localized or disseminated.[657,658] *H capsulatum* is not present in humans as normal flora or colonies and is not spread person-to-person. Infection most commonly occurs after inhalation of conidia of the fungus from the sources previously mentioned. Infection of normal, healthy adults usually results in mild, self-limiting pulmonary disease. The pathogenesis of these infections is complex and not completely understood. It is estimated by skin testing and chest roentgenogram findings that approximately 95% of infections are asymptomatic.[650,651] Symptomatic illness most commonly presents 10 days after a heavy exposure as an influenza-like illness with pulmonary infiltrates and development of mediastinal lymphadenopathy. Although the lungs are the most commonly affected site in acute symptomatic disease, nonspecific febrile illness without pulmonary signs or symptoms has been reported in at least one US Army outbreak.[644] The prevalence of this atypical form of histoplasmosis is not known.

Acute pulmonary histoplasmosis is the most common form of histoplasmosis, presenting as an acute respiratory illness. Most of these infections do not come to medical attention and resolve spontaneously. Symptoms develop 3 to 21 days following exposure, often occurring sooner in patents exposed to large amounts of inoculum or developing infection following reexposure. Symptoms and disease severity are believed to be correlated with host immunity and inoculum size. In symptomatic cases, signs and symptoms most commonly seen can be difficult to distinguish from influenza or "atypical" community-acquired pneumonias. These include fever, chest pain, cough, headache, malaise, chills, abdominal pain, and myalgias. Chest roentgenogram findings include hilar or mediastinal lymphadenopathy with or without patchy, often bilateral infiltrates. Hilar and splenic calcifications are common radiographic findings in patients who have previously had acute pulmonary disease. Mild anemia and transient increases in alkaline phosphatase can be noted. Rheumatologic signs and symptoms may be present in up to 5% of patients. More commonly presenting in white females, these include arthralgias, arthritis, erythema multiforme, and erythema nodosum. In severe cases, adult respiratory distress syndrome with diffuse reticulonodular infiltrates can occur.

Isolated mediastinitis or pericarditis may occur in persons with clinically inapparent infection. Me-

diastinitis due to histoplasmosis can present with a wide spectrum of disease. It can range from acute pulmonary disease presenting as only mediastinal adenopathy and pain that quickly resolves to a progressively destructive fibrosis that obstructs or destroys the mediastinal structures. Mediastinal granulomatosis is a description given to histoplasmosis that causes the coalescence and enlargement of mediastinal and hilar lymph nodes. Depending on the severity of this disease, patients may develop symptoms of esophageal or superior vena caval compression. Appearing as a central mass lesion on radiologic studies, this process may resolve spontaneously. Mediastinal fibrosis is a localized, progressive scarring reaction secondary to previous histoplasmosis. This process may cause obstruction and compression as described previously for granuloma formation and may ultimately lead to obliteration of mediastinal structures. Symptoms can include cough, dyspnea, hemoptysis, chest pain, and wheezing, plus those of superior vena cava syndrome. With mediastinal fibrosis, chest roentgenograms may reveal only mild mediastinal widening.

Chronic pulmonary histoplasmosis is a disease that most often affects middle-aged, white, male smokers with underlying emphysema. This form of histoplasmosis occurs in patients with underlying lung disease; it presents and progresses in a fashion similar to tuberculosis. Chronic pulmonary histoplasmosis usually causes upper lobe disease, often with progression to cavitation and fibrosis. Patients usually present with persistent or worsening cough, weight loss, malaise, and low-grade fever. Because of this, it is difficult to distinguish this disorder from exacerbation of chronic bronchitis, tuberculosis, and malignancy. Chest roentgenogram may show bullae, calcified granulomas or mediastinal nodes, pleural thickening with upper lobe infiltrates, or cavitation. Hilar adenopathy is rare. Disease may spontaneously resolve with linear scarring with or without cavity formation. Patients who develop thick-walled cavities usually do not have spontaneous resolution.

Acute, progressive, disseminated histoplasmosis is usually a primary infection, which can occur in normal, healthy adults but is much more common in immunocompromised persons and those at the extremes of age. It is very common in endemic areas in persons with AIDS, with attack rates possibly as high as 27%.[659] Patients with Hodgkin's lymphoma and lymphocytic leukemia are also at high risk. In acute disease, *H capsulatum* is found throughout the reticuloendothelial system, including bone marrow, blood, liver, spleen, and lymph nodes. Untreated, acute disseminated histoplasmosis is usually a fatal disease. In small children and infants, fever, malaise, weight loss, hepatosplenomegaly, and cervical adenopathy is common. Chest roentgenograms may show a miliary infiltrate or hilar adenopathy. Laboratory changes, including anemia, leukopenia, thrombocytopenia, and elevated alanine transaminase and alkaline phosphatase levels, are frequently noted. In adults with AIDS, acute disease usually results in fever, weight loss, malaise, cough, and dyspnea. Subacute and chronic forms of disseminated histoplasmosis can also occur, particularly in the elderly. These have common features, which include weight loss, malaise, fatiguability, and low-grade fever. Ulcers of the gums, tongue, tonsillar areas, and larynx can occur in up to one third of those affected with the chronic form. Chronic disease is often localized to specific organs, producing clinical disease associated with that particular site. The adrenal glands, gastrointestinal tract, central nervous system, and heart valves are the more frequently involved sites.

Diagnostic Approaches

As the majority of cases of histoplasmosis are asymptomatic, diagnosis is often retrospective and epidemiologic in nature, using histoplasmin skin testing or observation of calcified granuloma on chest roentgenogram. Diagnosis of symptomatic histoplasmosis may be difficult. Histoplasmosis should be included in the differential diagnosis of clusters of acute febrile disease, especially respiratory disease, in groups of personnel who have been performing duties that expose them to organic debris contaminated with bird or bat guano. Direct visualization on biopsy or smears and growth of the organism in culture are the most accurate means of diagnosis. Serological tests are of limited value. Detection of *H capsulatum* antigen in urine or blood is a newer method that has been shown to be most useful in acute, progressive, disseminated disease.[660]

Histopathological diagnosis is possible when infected tissue is available. Finding small budding yeasts in a granulomatous infection strongly suggests the diagnosis. These yeasts are difficult to see on routine staining but become readily apparent on Gomori methenamine silver staining. *H capsulatum* occasionally may be seen in peripheral blood smears of patients with acute disseminated disease. Calcofluor white preparations are useful in detecting *H capsulatum* in bronchoalveolar lavage.

Culture of sputum, blood, and bone marrow for *H capsulatum* is usually done on brain-heart infusion agar or diphasic medium at room temperature. Growth usually takes 4 to 6 weeks. Use of lysis centrifugation with blood samples may increase the recovery and decrease the time to grow the organism. Identification of *H capsulatum* from culture is made by either DNA probe, conversion of the mycelial phase to the yeast phase at 37°C, or, less commonly, by exoantigen testing.

Two available serologic tests for histoplasmosis are complement fixation (CF) and immunodiffusion (ID). These tests may be used in the retrospective confirmation of infections: CF by documentation of a 2-fold rise in titer, ID by the appearance of M or H identity bands. CF develops faster than ID but is less sensitive. Because of this, ID is often considered the confirmatory test. CF antibodies can be detected in most presentations of histoplasmosis but may take 4 to 6 weeks to develop.

Diagnosis by radioimmunoassay testing for antigen in blood and urine has become commercially available. Although this test has been shown to be very sensitive in patients who develop disseminated disease (especially in those who have AIDS[661]), less than 20% of patients with acute, self-limited, pulmonary infection have been shown to have a positive test.[660] The sensitivity of this test is highest when used with urine samples. It is currently only available at one site in the United States and the its full usefulness is not known.

The role of skin testing in histoplasmosis is limited and may be counterproductive. Skin-test positivity from endemic exposure is common, especially in the midwestern United States. Up to two thirds of those with active disease may have negative skin tests. Exposure to skin testing has also been shown to cause seroconversion in uninfected subjects, leading to false-positive complement fixation and immunodiffusion testing.

Recommendations for Therapy and Control

Asymptomatic and mild symptomatic cases of histoplasmosis do not require specific antifungal therapy. In general, antifungal therapy consists of intravenous amphotericin B (AMB) in life-threatening infections and oral itraconazole in less severe disease.[653,658] Moderate-to-severe acute pulmonary disease may be treated with itraconazole (400 mg/day for 3 to 6 weeks), ketoconazole (400 mg/day for 3 to 6 weeks), or AMB (0.5 mg/kg per day intravenously for 2 to 3 weeks). Overwhelming disease, including that with adult respiratory distress syndrome, should always be treated with AMB. Chronic pulmonary disease may be treated with itraconazole (400 mg/day for 6 to 12 months). Acute disseminated histoplasmosis is usually treated with AMB, given as 0.5 mg/kg per day to a total dose of 35 mg/kg or 2.5 g. Itraconazole (200 mg orally three times a day for 3 days, then 200 mg orally two times a day for 6 to 12 months) has been shown to be effective therapy in milder cases.[662] Patients with subacute or chronic disseminated histoplasmosis may be treated with AMB as in acute disease or with long courses of azole (6 to 12 months of ketoconazole or itraconazole). Treatment of the other forms of histoplasmosis is generally based on clinical disease activity.

As exposure to soil and guano with high concentrations of the organism is the major source of infections, avoidance of areas that are most likely to be contaminated is the key to prevention and control measures (Figure 37-20). These areas include chicken houses, bird roosts, caves with bats, and

Fig. 37-20. An area in the vicinity of Fort Campbell, Ky, posted to warn potential visitors of the risk of histoplasmosis. The area had a heavy accumulation of starling guano contaminated with *Histoplasma capsulatum*.
Reprinted with permission from: Rippon JW. Histoplasmosis (*Histoplasmosis capsulati*). In: *Medical Mycology: The Pathogenic Fungi and the Pathogenic Actinomycetes*. 3rd ed. Philadelphia, Penn: WB Saunders; 1988: 386.

any structure with deposits of bird droppings. Presence of *H capsulatum* in these droppings or debris is most prevalent where deposits of guano are deep or longstanding. Disturbing these areas in any manner that leads to the production of dusts and aerosols is more likely to lead to infections. It makes sense to avoid placing helicopter landing zones in the vicinity of these areas and to use care in the clean up or destruction of structures contaminated by bird or bat guano. When these areas or structures need to be entered, use of water or oil spraying to decrease dust and aerosols during clean up should lower the risk of infection. Sweeping or shoveling of dry material should be avoided. Material removed should not be left uncovered and can be buried without posing a health risk. Use of personal protective (nuclear-biological-chemical) masks or HEPA (high efficiency particulate air) filter masks should adequately protect individuals. The United States Army Center for Health Promotion and Preventive Medicine (USACHPPM, formerly the United States Army Environmental Hygiene Agency) suggests avoidance in preference to decontamination for histoplasmosis-contaminated sites.[663] USACHPPM recommends use of full-face respirators with HEPA filters or supplied air. They also recommend wearing disposable garments, hats, boots, and gloves (using duct tape to seal at wrists and ankles), using low velocity water mist spraying, double bagging of removed droppings (in 3 mil or thicker plastic bags), disposing of wastes in landfills, removing and disposing of contaminated clothing properly (ie, as infectious waste), and showering before putting on clean clothing. Masks and nondisposable items should be decontaminated in a bag. Three percent formalin has been used in the past to decontaminate sites. However, such a strategy should be limited or avoided and only employed after consultation with appropriate local and federal authorities because of the possible detrimental impact of this action on individuals and the environment.

[Duane R. Hospenthal]

MELIOIDOSIS

Introduction and Military Relevance

Melioidosis is a tropical disease found in regions that within 20° north and south of the equator, which includes Southeast Asia and northern Australia. Melioidosis can occur in humans and a wide variety of animals such as goats, pigs, monkeys, dogs, birds, and reptiles. The disease may be contracted through soil contamination of skin abrasions, by inhalation of soil particles, or by aspiration of contaminated water. The disease is caused by a gram-negative bacterium, *Burkholderia pseudomallei* (previously known as *Pseudomonas pseudomallei*). The range of clinical presentations include inapparent infections, asymptomatic pulmonary infiltration to acute pulmonary infection, acute septicemic infections or chronic suppurative infections, and localized abscesses in those who acquired the infection through skin abrasions. Fatality rates in severe infections may approach 40%.[644,645]

Melioidosis was diagnosed among French soldiers involved in armed conflicts in Indochina from 1948 to 1954.[646] In the 1970s, cases were reported in US service members fighting in Vietnam.[547,648] Cases continued to manifest in US military personnel many years after their exposure to the bacteria during the war. Meliodosis has been referred to as the "time-bomb disease."[649]

Description of the Pathogen

This organism, previously placed in the genus *Pseudomonas,* has been placed in the genus *Burkholderia* based on phylogenetic analysis of 16S rRNA sequences.[650] *B pseudomallei*, a motile, gram-negative, rod-shaped organism, appears as wrinkled colonies with a yeasty odor when cultured on agar (Figure 37-21**).** A closely related species, *B mallei*, is a nonmotile organism that causes glanders in horses. Although genetically indistinguishable, it is recognized as a separate species because of zoonotic and epidemiologic considerations. Both *B pseudomallei* and *B mallei* are known to cause disease in many animal species, but the only direct evidence of zoonotic disease transferable to humans is glanders. *B pseudomallei* is thought to be a ubiquitous environmental contaminant and only an accidental or opportunistic pathogen. A closely related avirulent environmental strain of *B pseudomallei* has been isolated in Thailand, and the name *B thailandensis* has been proposed for it.[651,652]

The bacteria survive optimally between 24°C and 32°C in vitro [653] and can usually be found at a soil depth of between 25 cm and 45 cm.[654] The bacteria survive best under laboratory conditions when the pH is kept between 5.0 and 8.0. *B pseudomallei* is more easily killed by ultraviolet light than other soil bacteria.[653]

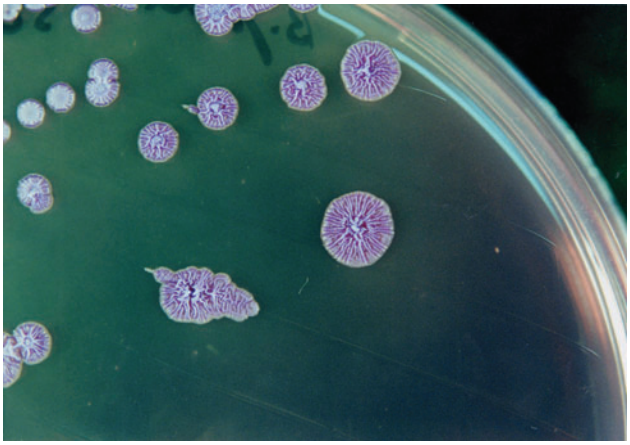

Fig. 37-21. Wrinkled colonies of *B pseudomallei* on modified Ashdown's medium agar.
Photograph: Courtesy of J.T.W. Thong and E.H. Yap, Department of Microbiology, National University of Singapore.

Epidemiology

Transmission

Humans are usually infected by inhalation or ingestion of contaminated soil and water or through the contamination of wounds. Most of the infections of US military personnel during the Vietnam War were attributed to inhalation of the organisms in dust raised by helicopter rotors.[655]

Geographic Distribution

B pseudomallei is widely distributed in soil and water in the tropics but is mainly found between the 20° north and 20° south (Figure 37-22). *B pseudomallei* has been frequently isolated from wet rice fields and cleared cultivated areas; the organisms have even been isolated from sport fields in the more urban environment of Singapore.[656] Human cases of melioidosis have been reported in the Caribbean islands of Guadeloupe and Puerto Rico.[657,658]

Incidence

Because of the failure to diagnose this infection in many topical countries besides northern Australia and Southeast Asian countries such as Thailand, Malaysia, and Singapore, little is known of the epidemiology of the disease. In Thailand, 2,000 to 3,000 cases of clinical melioidosis occur each year. The incidence rate in highly endemic areas is 3.5 to 5.5 cases per 100,000 population and is seasonal, with more cases occurring during the rainy season.[659] In Malaysia, antibodies to *B pseudomallei* have been detected in 6% of diabetics, 5% of pyrexics, 8% of pregnant women, and 3% of farmers.[660] Among 420 military personnel recruited by Malaysian Military serving in Sabah and Sarawak, 65.7% were found to have antibodies to the whole cell antigens of *B pseudomallei*.[661] Antibodies to *B pseudomallei* were also found in 18 of 905 British Commonwealth soldiers serving in West Malaysia.[662]

Fig. 37-22. World Distribution of *B pseudomallei* and *B pseudomallei*-like organisms from clinical and environmental isolates. The shaded areas show the main endemic areas; the hatched areas and asterisks show areas from which sporadic isolates have been gathered.
Reprinted with permission from: Dance DAB, Melioidosis: The Tip of the Iceberg? *Clin Microbiol Rev*. 1991, 4:52-60.

In Singapore between 1987 and 1994, 23 cases of melioidosis were diagnosed in persons serving in the Singapore Armed Forces.[663] During the period of 1989 to 1996, 372 cases of melioidosis with 147 deaths were reported in Singapore, giving a mean annual incidence rate of 1.7 per 100,000 population.[664]

Eight cases of melioidosis were diagnosed on Hainan Island in China from October 1995 to October 1996.[665] From 1989 to 1998, 206 cases of melioidosis were confirmed in the northern part of the Northern Territory of Australia, giving an incidence of 16.5 per 100,000 population.[666]

During the 1950s, cases of melioidosis were reported in French troops returning from Indochina after their military operations in the region. The US Army faced similar cases in troops returning from Vietnam.[667] A serological survey of US military personnel who served on active duty in Vietnam for at least two months showed that 20.7% had positive titers, as opposed to 5.7% in the control group.[655]

Pathogenesis and Clinical Findings

The incubation period for the infection can be as short as 2 days, or the infection can remain latent for more than 25 years. The clinical spectrum of melioidosis is protean, including acute fulminant septicemia, subacute illness, chronic infections, and subclinical disease. When latently infected patients manifest the disease after many years, usually it is in association with an immunocompromising illness such as diabetes mellitus, renal failure, systemic lupus, cirrhosis, alcoholism, or severe traumatic injury such as burns.[668] The infection can mimic various acute or chronic infections (eg, typhoid fever, malaria, tuberculosis, coccidiodomycosis, histoplasmosis). Correct clinical diagnosis at initial presentation is usually very difficult. Obtaining a compatible travel history should lead to inclusion of melioidosis in the differential diagnosis of any patient who is febrile and has an underlying disease or injury that could compromise host defenses.

The clinical presentation of septicemic melioidosis varies from an ill-defined febrile illness to fulminant septicemia. A history or clinical evidence of diabetes or uremia might suggest the diagnosis. In northern Thailand, melioidosis usually presents as acute septicemia, often resulting in metastatic abscesses in lungs, liver, and spleen and a rapid deterioration to shock and death.[669]

Subacute melioidosis can result from a primary infection that remains subacute or a reactivation of a previous infection. Most cases of melioidosis seen in nonendemic areas belong to this group. Patients may be asymptomatic or have symptoms indistinguishable from the common presentation of pulmonary tuberculosis. Recrudescent disease often involves the lungs, resembling reactivation tuberculosis with cavity formation in upper lobes.[668]

Chronic melioidosis may take the form of suppurative abscesses involving numerous anatomic sites. Patients can have infections lasting for years without symptoms. Chest radiographs usually show apical cavitary disease resembling tuberculosis; occasionally, patients may present with fever of unknown origin.

Subclinical melioidosis results in a chronic carrier state. The immune system probably suppresses the infection so no clinical disease develops. Once the host is immunocompromised, however, clinical disease can occur.

Diagnostic Approaches

Prompt diagnosis of melioidosis is important for initiation of treatment with the right combination of antibiotics. Definitive diagnosis of melioidosis is by culturing *B pseudomallei* from blood, sputum, pus, or urine during acute or subacute infections from any affected body fluid or source. The bacterium has been cultured from every body fluid except stool. It can be cultured on most routine laboratory media, and this is the main method of identification. The colonies appear rough and wrinkled, with a characteristic yeasty odor after 3 to 4 days' incubation. The use of selective media, such as the Ashdown's selective-differential agar medium, significantly increases the recovery of *B pseudomallei* from specimens with extensive normal flora (eg, sputum, specimens from the throat, rectum, and wounds).[669,670]

Serological methods such as the enzyme-linked immunosorbent assay, latex agglutination, and indirect hemagglutination assay can also be used to diagnose melioidosis. Indirect hemagglutination is commonly used for diagnosis; it detects antibodies that can agglutinate the *B pseudomallei* crude antigens coated onto the surface of erythrocytes. Use of the assay as a diagnostic tool in endemic regions is limited because of the background antibodies in a large portion of the healthy population living in endemic regions. In nonendemic regions, the assay is more sensitive and the cut-off titer of the assay is lower.[671]

Polymerase chain method has been developed for the detection of bacterial DNA in clinical samples. The method is rapid and sensitive, and it eliminates the need to propagate the pathogen.[672,673] Rapid immu-

noassays that work in 10 minutes have been developed for the detection of melioidosis. The assays have a sensitivity of 100% for the IgG tests and 93% for the IgM tests, while specificity is 95% for both.[674]

Recommendations for Therapy and Control

B pseudomallei has been shown to be susceptible in vitro to ceftazidime, tetracyclines, sulfonamides, chlorophenicol, kanamycin, and novobiocin.[668] Combinations of two or more antibiotics are usually used for treatment of melioidosis.[675] The use of high-dose intravenous ceftazidime, with or without trimethoprim-sulfamethoxazole (TMP-SMX), is the choice of treatment for severe melioidosis. Other suitable antibiotic regimens include imipenem with amoxycillin/clavulanate and cefoperazone/sulbactam with TMP-SMX. Potentially contaminated wounds should be well cleaned as soon as possible.

Exposure to *B pseudomallei* in the environment can be minimized by taking precautions when in contact with soil and water. This includes wearing boots and gloves, especially for those at high risk because of traumatic wounds or a debilitating illness. Person-to-person and zoonotic spread is virtually nonexistent, and quarantine of patients is unnecessary. Laboratory-acquired acute melioidosis, probably from the inhalation of an infectious aerosol, has been reported.[676] This underscores the need to take standard biosafety precautions when handling respiratory and sinus drainage and the wastes and body fluids of infected persons and animals.

[May-Ann Lee; Eric P. H. Yap]

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