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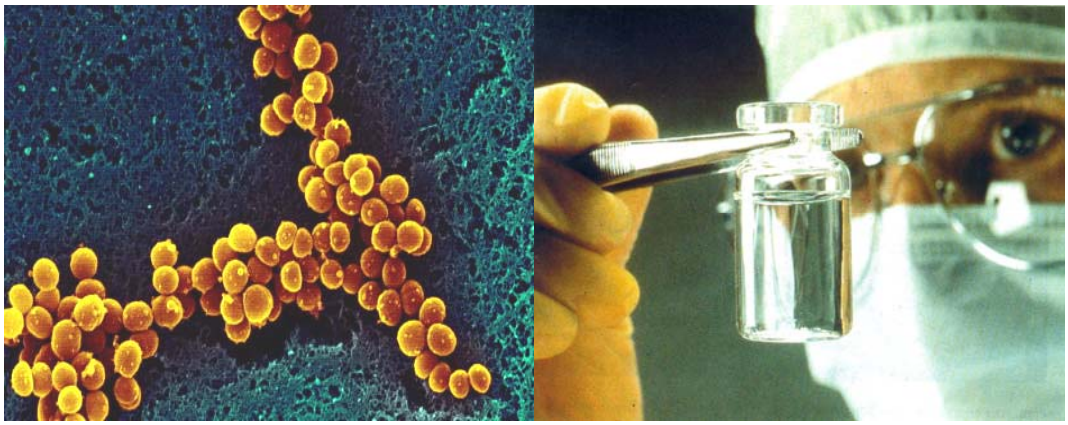
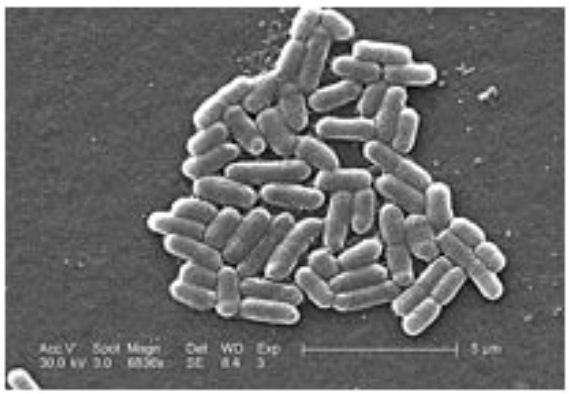


ACUTE INTESTINAL INFECTIONS



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МИНИСТЕРСТВО ЗДРАВООХРАНЕНИЯ УКРАИНЫ
ХАРЬКОВСКИЙ ГОСУДАРСТВЕННЫЙ
МЕДИЦИНСКИЙ УНИВЕРСИТЕТ

ACUTE INTESTINAL INFECTIONS

Textbook for V course medical student

ОСТРЫЕ КИШЕЧНЫЕ ИНФЕКЦИИ

Учебник для студентов V курса
медицинских ВУЗов

Утверждено
ученым советом ХГМУ.
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The material contained in the textbook reviews to the fundamental questions of acute intestinal infections (etiology, epidemiology, pathogenesis, clinical manifestations, differential diagnosis and treatment). It would be helpful to medical students and interns.

Материал представленный в учебнике посвящен фундаментальным вопросам острых кишечных инфекций (этиологии, эпидемиологии, патогенеза, клиники, лечения). Учебник рекомендованый для студентов медицинских ВУЗов и интернов.

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INTRODUCTION

Despite reductions in mortality worldwide, diarrhea still accounts for more than 2 million deaths annually1 and is associated with impaired physical and cognitive development in resource-limited countries. In US, an estimated 211 million to 375 million episodes of acute diarrhea occur each year (1.4 episodes per person per year); such episodes are responsible for more than 900,000 hospitalizations and 6000 deaths annually. Diarrheal diseases are extremely common in all parts of the world. Diarrheal disease is the largest single cause of death in the developing nations. In these countries, a child has a 50% chance of dying before the age of 7 years, primarily from a diarrheal disease.

The wide range of clinical manifestations of acute diarrheal disease is matched by the wide variety of infectious agents involved, including viruses, bacteria, and parasitic pathogens. The Foodborne Diseases Active Surveillance Network (FoodNet) of the Centers for Disease Control and Prevention (CDC) collects data on the incidence of diarrhea attributable to nine enteropathogens in 13 percent of the U.S. population (37.4 million people) living in nine states. Of these, the pathogens responsible for the most cases of diarrhea in 2002 were salmonella (16.1 cases per 100,000 population), campylobacter (13.4 cases per 100,000 population), shigella (10.3 cases per 100,000 population), Escherichia coli O157:H7 (1.7 cases per 100,000 population), and cryptosporidium (1.4 cases per 100,000 population); vibrio, yersinia, listeria, and cyclospora were reported in fewer than 1 person per 100,000. Other enteropathogens for which diagnostic testing is readily available include Clostridium difficile, giardia, rotavirus, and Entamoeba histolytica. Additional agents of infectious diarrhea for which clinical diagnostic testing is not routinely available include enterotoxigenic, enteropathogenic, enteroaggregative, and enteroinvasive strains of E. coli, toxin-producing Clostridium perfringens, Staphylococcus aureus, Bacillus cereus, and noroviruses. Thorough clinical evaluation of a patient who presents with acute diarrhea is essential in order to guide a cost-effective, evidence-based approach to initial diagnostic testing and therapy. In six studies conducted between 1980 and 1997, the diagnostic yield of stool cultures ranged from 1.5 to 5.6 percent. The estimated cost of $952 to $1,200 per positive culture can be reduced through improved selection and testing of the specimens submitted. As is indicated in Figure 1, the initial clinical evaluation of the patient with acute diarrhea should focus on the assessment of the severity of the illness, the need for rehydration, and the identification of likely causes on the basis of the history and clinical findings.

Microorganisms, which are course of diarrheal infections, have distinct epidemiologic and clinical features that aid in diagnosis. Diarrhea exists in several epidemiologic forms. Epidemic diarrhea occurs during disasters, in association with contaminated food, and in outbreaks in hospital nurseries. Diarrhea often is a result of a breakdown in sanitation mechanisms which can be elucidated by careful study. Other diarrheal illness occurs without clear-cut evidence of breakdown of hygienic

standards. Basically, all diarrheal disease is the result of oral contamination with material from other humans or from animals.

The transmission of diarrheal disease is primarily by the fecal-oral route. In most cases, this involves the ingestion of water or food contaminated with the feces of a carrier or of an active case. Occasionally, transmission of gastrointestinal infections may be via insect vectors such as flies or roaches that serve to transfer the infecting organism from feces to food. Major determinants in environmental exposure to enteric pathogens are personal hygiene, sanitary facilities, and the source of water. The type, severity, and frequency of diarrheal disease is determined by the geographical location of the person who is exposed to diarrheal pathogens and the season.

FOOD POISONING

DEFENITION *acute short-term infectious disease caused by miscellaneous bacteria developing exotoxins in food and characterizes by symptoms of disturbance in upper part of gastrointestinal tract (gastritis and gastroenteritis).*

Food-borne illnesses are diverse in etiology, and they can follow ingestion of infectious organisms or noninfectious substances. Food-borne diseases encompass classic toxin-mediated food poisoning, such as botulism, gastroenteritis that follows ingestion of preformed Staphylococcus aureus toxin, ingestion of chemicals in foods, and bacterial, parasitic, and viral infections. Many food-borne diseases are zoonoses, which means that the infectious agent has a primary animal reservoir and humans are affected incidentally.

ETIOLOGY

Different bacteriae are causative agents of food poisoning. Many enterobacteria, spore-formed cocci, anaerobe bacteria may produce exotoxins in period of multiplication. Some strains enterobacteria synthesize enterotoxin (termostabile and termolabile), which provokes watery diarrhea due to increased secretion of water and electrolytes in gastrointestinal tract. A cytotoxin destroys epithelium cover of intestine.

The most frequent causative agents of food poisoning are *Staphylococcus aureus*, *B. cereus, Proteus, E. coli, Klebsiella, Enterobacter, Citrobacter, Cl. perfringes, Serratia, V. parahemolyticus, Aeromonas etc*. (table 1).

Table 1. Bacterial Food Poisoning

Organisms	Symptoms	Common Food Sources
1 TO 6 h INCUBATION		
Staphylococcus aureus, Serraia	Nausea, vomiting, diarrhea	Ham, poultry, potato or egg salad, mayonnaise, cream pastries
Bacillus cereus	Nausea, vomiting, diarrhea	Fried rice
8 TO 16 h INCUBATION		
Clostridium perfringens	Abdominal cramps, diarrhea (vomiting rare)	Beef, poultry, legumes, gravies
B. cereus, Klebsiella, Citrobacter,	Abdominal cramps, diarrhea (vomiting rare)	Meats, vegetables, dried beans, cereals, milk product
>16 h INCUBATION		
Enterotoxigenic *Escherichia coli Enterobacter, Proteus, Aeromonas*	Watery diarrhea	Salads, cheese, meats, water, mollusks, crustaceans
Salmonella spp.	Inflammatory diarrhea	Beef, poultry, eggs, dairy products
Vibrio parahaemolyticus	Dysentery	Mollusks, crustaceans

EPIDEMIOLOGY

Causative agents of food born infection are spreaded in the world and can be distribute in human and animal feces, soil, polluted water, air, and on different objects. In many cases source of infection is unknown. But in some cases of outbreaks connecting with particular food product source of infection is a person working in food industry and suffering from purulent lesion of skin, sore throat, pneumonia, and laryngitis. In case of zoonotic causative agents the source of infection is animals and birds. The most important epidemiologic risk factor in outbreaks of this disease is the ingestion of food that has been left at room temperature for prolonged periods, thereby allowing toxin production to occur before consumption. Contaminated preparation equipment and poor personal hygiene of food handlers are frequently implicated as well.

The main way of transmission is contaminated by bacteria food. Different meat products such as sausage, liverwurst, jellied meat, headcheese, eggs and fish product, are very common among factor of transmission. Staphylococci can multiply at a wide range of temperatures thus, if food is left to cool slowly and remains at room temperature after cooking, the organisms will have the opportunity to form enterotoxin. Liquid food dishes (potato salad, mayonnaise, and cream pastries, soups, beer, beverages, milk products, ice-cream, kefir, sour cream) can be as a nutrient

medium for bacteria and therefore may be factor of infection. Staphilococcus intoxication in many cases connect with a confectionery (egg-white and butter creams). Proteus and clostridium highly multiply in meat products. B. cereus is undemanding to nutrient medium and so it can grows in vegetable salads, soups, kissel and pudding.

Susceptibility to food born infection is very high and depending to toxin dosage. Quite often 90-100% people who try infected food, became ill. From epidemiological side, food born infections have not only group characteristic of morbidity and explosive rate of outbreak development.

PATHOGENESIS

Enteric pathogens have developed a variety of tactics to overcome host defenses. Understanding the virulence factors employed by these organisms is important in the diagnosis and treatment of clinical disease.

Toxin production is the main pathogenic mechanism in food born infection. The production of one or more exotoxins is important in the pathogenesis of numerous enteric organisms. Such toxins include *enterotoxins*, which cause watery diarrhea by acting directly on secretory mechanisms in the intestinal mucosa; *cytotoxins*, which cause destruction of mucosal cells and associated inflammatory diarrhea; and *neurotoxins*, which act directly on the central or peripheral nervous system. The prototypical enterotoxin is cholera toxin, a heterodimeric protein composed of one A and five B subunits. The A subunit contains the enzymatic activity of the toxin, while the B subunit pentamer binds holotoxin to the enterocyte surface receptor, the ganglioside GM_1. After the binding of holotoxin, a fragment of the A subunit is translocated across the eukaryotic cell membrane into the cytoplasm, where it catalyzes the ADP-ribosylation of a GTP-binding protein and causes persistent activation of adenylate cyclase. The end result is an increase of cyclic AMP in the intestinal mucosa, which increases Cl^- secretion and decreases Na^+ absorption, leading to loss of fluid and the production of diarrhea. Enterotoxigenic strains of *E. coli* and some strains of Klebsiella, Proteus, Enterobacter may produce a protein called *heat-labile enterotoxin* (LT) that is similar to cholera toxin and causes secretory diarrhea by the same mechanism. Alternatively, enterotoxigenic strains of *E. coli* may produce *heat-stable enterotoxin* (ST), one form of which causes diarrhea by activation of guanylate cyclase and elevation of intracellular cyclic GMP. Some enterotoxigenic strains produce both LT and ST.

Bacterial cytotoxins, in contrast, destroy intestinal mucosal cells and produce the syndrome of dysentery, with bloody stools containing inflammatory cells. Enteric pathogens that produce such cytotoxins include *S. dysenteriae*, *Vibrio parahaemolyticus*, and *Clostridium difficile*. Enterohemorrhagic strains of *E. coli*, most commonly serotype O157:H7 in the United States, also produce potent

cytotoxins that are highly related to Shiga toxin from *S. dysenteriae* and have been termed *Shiga-like toxins*. Such strains of *E. coli* have been associated with outbreaks of hemorrhagic colitis and hemolytic-uremic syndrome.

Neurotoxins usually are produced by the responsible organism outside the host and therefore cause symptoms soon after ingestion. Included are the staphylococcal and *Bacillus cereus* toxins, which act on the central nervous system to produce vomiting.

CLINICAL MANIFESTATIONS

Incubation period equals to 30 min – 24 h (average 2-6 h). Duration of incubation period depends of type and dosage of toxin. Clinic picture is similar which cased by different causative agent. Diseases has acute onset. The first symptoms are vomit, nausea, and cramps in upper part of abdomen. In many cases a patient has repeated and exacted vomiting. Quite simultaneously diarrhea occurs after vomit and nausea. The feces is abounded, watery and liquid. Commonly stool does not contain mucous and blood. There is fever in clinic of food born infection. Decreasing of temperature accompanies by chills and feeling of hot, fatigue, and moderate headache.

Table 2. Gastrointestinal Pathogens Causing Acute Diarrhea

Mechanism	Location	Illness	Stool Findings	Examples of Pathogens Involved
Noninflammatory (enterotoxin)	Proximal small bowel	Watery diarrhea	No fecal leukocytes	*Enterotoxigenic enterobacteria* *Escherichia coli (LT and/or ST)* *Clostridium perfringens* *Bacillus cereus* *Staphylococcus aureus* *Aeromonas hydrophila* *Plesiomonas shigelloides*
Inflammatory (invasion or cytotoxin)	Colon or distal small bowel	Dysentery or inflammatory diarrhea	Fecal polymorphonuclear leukocytes	*Shigella spp., Salmonella spp., Campylobacter jejuni* *Enterohemorrhagic E. coli* *Enteroinvasive E. coli* *Vibrio parahaemolyticus* *Aeromonas hydrophila* *Plesiomonas shigelloides*

The examination of patients for signs of dehydration provides essential information about the severity of the diarrheal illness and the need for rapid therapy. Mild dehydration is indicated by thirst, dry mouth, decreased axillary sweat, decreased urine output, and slight weight loss. Signs of moderate dehydration include an orthostatic fall in blood pressure, skin tenting, and sunken eyes (or, in infants, a sunken fontanelle). Signs of severe dehydration range from hypotension and tachycardia to confusion and frank shock.

Bacterial disease caused by an enterotoxin elaborated outside the host, such as that due to *Staphylococcus aureus* or *B. cereus*, has the shortest incubation period (1 to 6 h) and generally lasts less than 12 h. Most cases of staphylococcal food poisoning are caused by contamination from infected human carriers. Staphylococcal food poisoning begins abruptly with nausea, vomiting, crampy abdominal pain, and diarrhea. The majority of cases are self-limited and resolve between 8 and 24 h after onset. In severe cases, hypovolemia and hypotension can develop. Although most cases probably do not come to medical attention or are not diagnosed, staphylococcal intoxication is the second or third leading cause of diagnosed food poisoning in developed countries. Fever and rash are absent, and the patient is neurologically normal.

Diarrhea, nausea, vomiting, and abdominal cramping are common, while fever is less so. *B. cereus* can produce either a syndrome with a short incubation period – the *emetic* form, mediated by a staphylococcal type of enterotoxin – or one with a longer incubation period – the *diarrheal* form, caused by an *E. coli* LT type of enterotoxin, in which diarrhea and abdominal cramps are characteristic but vomiting is uncommon. Two types of illness, both mild and self-limited, are caused by this organism: an emetic form with a short incubation of 1 to 5 hours and characterized by vomiting and abdominal cramps and occasional diarrhea persisting for 8 to 10 hours; and a diarrheal form with an incubation period of 10 to 12 hours followed by watery diarrhea, abdominal cramps, and moderate nausea lasting about 12 hours. The emetic form of *B. cereus* food poisoning is associated with contaminated fried rice; the organism is common in uncooked rice, and its heat-resistant spores survive boiling. If cooked rice is not refrigerated, the spores can germinate and produce toxin. Frying before serving may not destroy the preformed, heat-stable toxin.

Food poisoning due to *Clostridium perfringens* results from the survival of heat-resistant spores in inadequately cooked meat, poultry, or legumes. After ingestion, toxin is produced in the intestinal tract, causing moderately severe abdominal cramps and diarrhea; vomiting is rare, as is fever. The illness is self-limited, rarely lasting for more than 24 h.

In contrast to Staphylococcal and salmonella gastroenteritis, C. *perfringens* food poisoning most frequently occurs in the fall and winter months. The incubation period is 8 to 24 hours and is followed by the onset of repeated bouts of abdominal cramps and watery diarrhea which persist for 24 hours.

The foods involved are usually meat stews, poultry dishes, (most commonly turkey), or gravies that are precooked in large amounts, cooled, and subsequently reheated for serving. The food is contaminated with spores of C. *perfringens* from the animal's intestinal tract or from soil. Because of the bulk of the food, the internal temperature reached during cooking is inadequate to kill the spores, but serves to reduce the redox potential to a level that permits the surviving spores to germinate

during the prolonged cooling stage, releasing the enterotoxin. The enterotoxin is a heat-stable protein component of the spore coat formed during sporulation. It exerts its maximal activity in the ileum where it inhibits glucose transport, damages the intestinal epithelium, and causes a loss of protein into the intestinal lumen.

The specific diagnosis is made by demonstrating large numbers of C. *perfringens* in the incriminated food.

The answers to questions with high discriminating value can quickly narrow the range of potential causes of diarrhea and help determine whether treatment is needed. Since few food-borne illnesses present with their own pathognomonic clinical picture, and since laboratory tests are not of value in acute situations, a systematic interrogation of patients and their families is the best way to deduce the etiology. Immediately following initiation of supportive treatment, the practitioner should obtain a history in the areas described below. This allows the list of possible agents to be narrowed, which helps dictate treatment and laboratory investigation.

Food poisoning is cased by enterobacteriae such as Klebsiella, Proteus, Enterobacter, Acinetobacter, characterizes by Gastroenteritis with the abrupt onset of nausea, vomiting, and diarrhea, occurring 8 to 48 hours after the ingestion of contaminated food. Low-grade fever for the first day or so is usual, accompanied by headache, and gripping abdominal pain.

Clinical criteria of diagnosis Food Poisoning

1. Short incubation period
2. Consumption of incriminated food
3. Group of patient with similar food history
4. Acute onset of diseases
5. In clinic symptoms of intoxication and gastroenteritis
6. Self-limited clinical course

DIAGNOSTIC APPROACH

If the history and the stool examination indicate a noninflammatory etiology of diarrhea and there is evidence of a common-source outbreak, questions concerning the ingestion of specific foods and the time of onset of the diarrhea after a meal can provide clues to the bacterial cause of the illness.

After the severity of illness is assessed, the most important distinction that the clinician must make is between *inflammatory* and *noninflammatory* disease. Using the history and epidemiologic features of the case as guides in making this distinction, the clinician can rapidly evaluate the need for further efforts to define a specific etiology and for therapeutic intervention. Examination of a stool sample is an important supplement to the narrative history. Grossly bloody or mucoid stool suggests an inflammatory process, but all stools should be examined for fecal leukocytes; the latter task is accomplished by the preparation of a thin smear of the

stool on a glass slide, the addition of a drop of methylene blue, and examination of the wet mount. Causes of acute infectious diarrhea, categorized as inflammatory and noninflammatory.

The organisms that cause traveler's diarrhea vary considerably with location. In all areas, enterotoxigenic *E. coli* is the most common isolate from persons with the classic secretory traveler's diarrhea syndrome; the proportion of cases accounted for by this organism ranges from a high of approximately 50 percent in Latin America, Africa to a low of 15 percent in Asia. *Shigella*, *Salmonella*, and *Campylobacter* spp. are classically considered to cause more invasive dysenteric disease than enterotoxigenic *E. coli*, but clinical differentiation of infections attributable to these organisms can be difficult. *Shigella*, *Salmonella*, and *Campylobacter* are isolated in 1 to 15 percent of cases, with different organisms being more common in different locations. Less common bacteria are *Aeromonas hydrophila* and *Plesiomonas shigelloides*, which have been isolated from travelers to Thailand. Parasitic causes of traveler's diarrhea include *Entamoeba histolytica*, which is responsible for up to 5 percent of cases in Mexico and Thailand, and *G. lamblia*, which has been associated with contaminated freshwater supplies in many areas of the world. *Giardia* is found in association with zoonotic reservoirs in the northern United States and poses a risk to hikers and campers who drink from freshwater streams. A striking association of *Giardia* with contaminated water supplies has likewise been noted in St. Petersburg in the former Soviet Union. *Cryptosporidium* has been recognized as a problem in travelers to the Commonwealth of Independent States, Mexico, and Africa and has caused large-scale urban outbreaks of infection in the United States. Viruses such as rotavirus and Norwalk-like viruses have been isolated from up to 12 percent of visitors to Latin America, Asia, and Africa.

Day-care centers are sites of particularly high attack rates of enteric infections. Rotavirus is most common among children less than 2 years old, with attack rates of 75 to 100 percent among those exposed. *G. lamblia* is more common among older children, with somewhat lower attack rates. Other common organisms, often spread by fecal-oral contact, are *Shigella*, *Campylobacter jejuni*, and *Cryptosporidium*. A characteristic feature of infection in day-care centers is the high rate of secondary cases among family members.

Similarly, hospitals are sites for concentrations of enteric infections. In medical intensive-care units and pediatric wards, diarrhea is among the most common nosocomial infections. *C. difficile* and *Salmonella* species are predominant causes of nosocomial diarrhea in the United States; viral pathogens, especially rotavirus, can spread rapidly in pediatric wards. Enteropathogenic *E. coli* has been associated with outbreaks of diarrhea in newborn nurseries. One-third of elderly patients in chronic-care institutions develop a significant diarrheal illness each year. Surveillance stool cultures suggest that 25 percent of the residents of these institutions harbor cytotoxin-

producing *C. difficile*, which causes more than half of all cases of diarrhea in this population. Antimicrobial therapy can predispose to pseudomembranous colitis by altering the normal colonic flora and allowing the multiplication of *C. difficile*.

Most of the morbidity and mortality from enteric pathogens involves children less than 5 years of age. Breast-fed infants are protected from contaminated food and water and derive some protection from maternal antibodies, but their risk of infection rises dramatically when they begin to eat solid foods. Infants and younger children are more likely than adults to develop rotaviral disease, while older children and adults are more commonly infected with Norwalk-like viruses. Other organisms with higher attack rates among children than among adults include enterotoxigenic and enteropathogenic *E. coli*, *C. jejuni*, and *G. lamblia*. In children, the incidence of *Salmonella* infections is highest among infants under 1 year of age, while the attack rate for *Shigella* infections is greatest among children aged 6 months to 4 years.

LABORATORY INVESTIGETION

Many cases of noninflammatory diarrhea are self-limited or can be treated empirically, and in these instances the clinician may not need to determine a specific etiology. Potentially pathogenic *E. coli* cannot be distinguished from normal fecal flora by routine culture. Special tests to detect LT and ST are not available in most clinical laboratories. In situations in which cholera is a concern, stool should be cultured on thiosulfate citrate bile salts sucrose (TCBS) agar. A latex agglutination test has made the rapid detection of rotavirus in stool practical for many laboratories, but electron microscopy or measurement of serologic response with a radioimmunoassay is still necessary for the identification of Norwalk-like viruses. At least three stool specimens should be examined for *Giardia* cysts or stained for *Cryptosporidium* if the level of clinical suspicion regarding the involvement of these organisms is high.

All patients with fever and evidence of inflammatory disease should have stool cultured for *Salmonella*, *Shigella*, and *Campylobacter*. *Salmonella* and *Shigella* can be selected on MacConkey's agar as non-lactose-fermenting (colorless) colonies or can be grown on *Salmonella-Shigella* agar or in selenite enrichment broth, both of which inhibit most organisms except these pathogens. Isolation of *C. jejuni* requires inoculation of fresh stool onto selective growth medium and incubation at 42^{o}C in a microaerophilic atmosphere. Enterohemorrhagic *E. coli* strains of serotype O157:H7 can be identified in specialized laboratories by serotyping but also can be identified presumptively as lactose-fermenting, indole-positive colonies of non-sorbitol fermenters (white colonies) on sorbitol MacConkey plates. Fresh stools should be examined for amebic cysts and trophozoites. Pathogenic strains of *C. difficile* generally produce two toxins, A and B. Toxin B can be detected with a cytotoxin assay; if the toxin is present, a monolayer culture of fibroblasts will show cytopathic

effects within 6 to 24 h. Rapid enzyme immunoassays and latex agglutination tests for both toxin A and toxin B have recently been developed.

TREATMENT

In many cases, a specific diagnosis is not necessary or not available to guide treatment. The clinician can proceed with the information obtained from the history, by stool examination, and by evaluation of the severity of dehydration. The first aid is gastric and intestinal lavage.

The mainstay of treatment is adequate rehydration. Tthe efficacy of oral rehydration depends on the fact that glucose-facilitated absorption of sodium and water in the small intestine remains intact in the presence enterotoxin. The use of oral rehydration solutions has reduced mortality due to diarrheal infections. The World Health Organization recommends a solution containing 3.5 g of sodium chloride, 2.5 g of sodium bicarbonate, 1.5 g of potassium chloride, and 20 g of glucose (or 40 g of sucrose) per liter of water. Patients who are severely dehydrated or in whom vomiting precludes the use of oral therapy should receive intravenous solutions such as Ringer's lactate.

Although most secretory forms of food poisoning with diarrhea usually due to enterotoxigenic *E. coli or* other enterobacteriae can be treated effectively with rehydration, bismuth subsalicylate, or antiperistaltic agents, antimicrobial agents can shorten the duration of illness from 3 to 4 days to 24 to 36 h.

TYPHOID AND PARATYPHOID FEVERS

DEFINITION: *Typhoid and paratyphoid fevers is an acute infectious disease with similar clinical features and characterizes by lesion of Peyer's patches, bacteriemi, severe intoxication, enlarged lever and spleen and rosella.*

Typhoid fevers are disease whose name means, "smoke" in Greek. The smoke refers to the mental clouding that characterizes severe cases of disease. The term enteric fever is a convenient collective term for the small group of sallmonellosis lacking an animal reservoir and they all involve Peyr's patches in intestines, and known as typhoid and paratyphoid fevers.

Typhoid fever is a systemic infection with the bacterium *Salmonella enterica* serotype typhi. This highly adapted, human-specific pathogen has evolved remarkable mechanisms for persistence in its host that help to ensure its survival and transmission. Typhoid fever was an important cause of illness and death in the overcrowded and unsanitary urban conditions of the United States and Europe in the 19th century. The provision of clean water and good sewage systems led to a dramatic decrease in the incidence of typhoid in these regions. Today most of the

burden of the disease occurs in the developing world, where sanitary conditions remain poor. Reliable data from which to estimate the burden of disease in these areas are difficult to obtain, since many hospitals lack facilities for blood culture and up to 90 percent of patients with typhoid are treated as outpatients.

Community-based studies have consistently shown higher levels of typhoid than public health figures suggest. Annual incidence rates of 198 per 100,000 in the Mekong Delta region of Vietnam and 980 per 100,000 in Delhi, India, have recently been reported. According to the best global estimates, there are at least 16 million new cases of typhoid fever each year, with 600,000 deaths. The introduction of chloramphenicol for the treatment of typhoid fever in 1948 transformed a severe, debilitating, and often fatal disease into a readily treatable condition. The emergence of resistance to chloramphenicol and other antimicrobial agents has been a major setback. We now face the very real prospect that untreatable typhoid fever will reemerge.

Typhoid is usually contracted by ingestion of food or water contaminated by fecal or urinary carriers excreting *S. enterica* serotype typhi. It is a sporadic disease in developed countries that occurs mainly in returning travelers, with occasional point-source epidemics. In endemic areas, identified risk factors for disease include eating food prepared outside the home, such as ice cream or flavored iced drinks from street vendors, drinking contaminated water, having a close contact or relative with recent typhoid fever**,** poor housing with inadequate facilities for personal hygiene, and recent use of antimicrobial drugs.

Typhoid fever (latin. *Typhus abdominalis*) is an acute systemic bacterial infection with prolonged course and frequent complications. Typhoid fever and paratyphoid fevers (latin. Paratyphoid abdominalis A et B) have similar clinical features, and there fore these diseases are united in one group, which called as typho-paratyphoid diseases.

Clinic of typhoid and paratyphoid fevers characterize intoxication, bacteriaemia, Peyer's patches lission, hepatosplenomegaly and rose spots on the skin.

ETIOLOGY

The agent of typhoid, stricly, Salmonella enterica subsp enterica, serotype Typhi, popularly this microorganism is known as S. typhi. Clinically similar syndromes (paratyphoid fever) are caused by S. paratyphi A and S. paratyphi B, known as. S. schottmuelleri. All agent caused typhoid and paratyphoid fevers are Gram-negative bacillus. S. typhi and paratyphi infect only man (but sometimes the accasional fruit-bat). S. paratyphoid multiplies in animals. The reservoir of paratyphoid fever B is a live-stock. Salmonellae don't have capsulla and spora. Salmonellae are Gram-negative, facultative aerobes.

S. enterica serotype typhi is a member of the family Enterobacteriaciae. The Vi capsular antigen is largely restricted to *S. enterica* serotype typhi, although it is shared by some strains of *S. enterica* serotypes hirschfeldii (paratyphi C) and dublin, and *Citrobacter freundii*. A unique flagella type, Hj, is present in some *S. enterica* serotype typhi isolates from Indonesia. Phage typing, pulse-field gel electrophoresis, and ribotyping have shown that areas of endemic disease usually have many strains in circulation but that outbreaks are usually due to a restricted number of strains. The genus Salmonella is divided into serogroup based upon their somatic O antigen. The polysaceharile envelope is O antigen. The bacterium is serologically positive for lipopolysaccharide antigens O_9 and O_{12}, protein flagellar antigen Hd, and polysaccharide capsular antigen Vi. Vi-antigen has no instrinsic virulence but appears to confer virulence by masking the oligosaccharide somatic O-antigen from immunological attack. The microrganism possesses flagella thet contain the protein flagella or H-antigen. There is the third K-antigen, which conected with microrganism envelope. Typhoid fever is caused by different phagotypes of S. typhi. Strains of salmonella are capable of survival in hostile enveronments such as ice, dust, clothes and water. Typhoid bacteria are very resistance to high and low temperature. Favourable environment for salmonella is food (milk, sour scream, curds, minced, meat etc.) in which it can survive but and multiply. S. typhi can acguire R-plasmids, which endow it with resistance to chloramphenical, amoxycillin, and Co-trimoxazole. The studies of S. typhi in resent years have indentified a variety of genes (pho P/pho Q, omp R, env Z) that enable the organism to adapt to changes in the environment, such as shift of pH, osmolality and calcium concentrations and to withstand the effects of microbicidal proteins (defensins) present in the phogosomes of phogocytic cells.

Salmonellae have biochemical activity. Carbohydrates are enzimed by the salmonella to acid and gas. Typhoid and paratyphoid bacteria good multiply on simple culture but better – which contents the bile.

EPIDEMIOLOGY

Typhoid is a typical intestinal infection. This group of infection has the faecal-oral route of transmission, the entrance gut and the system of organs, which are offected by disease. Typhoid is transmitted mainly by the feacal-ora route. The course of typhoid fever are patient with acute disease or carriers of organism. The reservoir of paratyphi B is the live stoke. The carrier state can Sollow clinical or inapparent infection and may persist for long periods of time, especially in middle aged women with chronic cholecystitis.

The transmission of typhoid and paratyphoid A fevers is primarily by food or water contaminated by fingers of a carrier or inderectly by flies or the feces or urine of infected persons. Shellfish taken from waters polluted by sowage.

Typhoid has bee described throughout the globe. In poorer countries, typhoid is associated particularly with bad sunitation, powerty, crowdiny and war. The epidemiological feature is on of continuous transmission with a tindency to peak in hot periods and sometimes, at onset of rains. The areas of high incidence, estimated to have 100 to 1000 cases 100.000 population per year include Chile, Nepal, South Atrica, Indonesia and India. In these regions the case-fotality rates in patient admitted to hospital are about 10 per cent. Case- fatality rates in potient promptly treated by antidioties estimates 1 per cent. Group of people in age 15-45 years is the most frequent suffer from typhoid fever. After typhoid fever patients have steady immunnitet but some man, very rare, can have repeated disease.

PATHOGENESIS

Sensibility to typhoid fever is different and dependtds from different factors. Major-histocompatibility-complex class II and class III alleles have been shown to be associated with typhoid fever in Vietnam. HLA-DRB10301/6/8, HLA-DQB10201-3, and TNFA2(–308) were found to be associated with susceptibility to typhoid fever, whereas HLA-DRB104, HLA-DQB10401/2, and TNFA1(–308) were associated with disease resistance.

The evidence for an association between typhoid and infection with the human immunodeficiency virus (HIV) is conflicting, whereas there is a large increase in the incidence of non-typhi salmonella bacteremia in HIV infection.

Following ingestion of S. typhi appears to the stomach, where some of microorganisms survive. The infective dose for health voluntteers varies between 1000 and 1 million organisms.

Survival through the low pH of the stomach is facilitated by the buffering action of foods. Achlorhydria as a result of aging, previous gastrectomy, or treatment with histamine H_2-receptor antagonists, proton-pump inhibitors, or large amounts of antacids lowers the infective dose. The infective dose is smoller with more virulent strains. Vi-negative strains of *S. enterica* serotype typhi are less infectious and less virulent than Vi-positive strains. In the small intestine, the bacteria adhere to mucosal cells and then invade the mucosa. The M-cells, specialized epithelial cells overlying Peyer's patches, are probably the site of the internalization of *S. enterica* serotype typhi and its transport to the underlying lymphoid tissue. This phase of phatogenesis is ***the phase penetration*** (**Table 3**) of infections agent. *S. typhi* reaches to lymphoid tissue, they are ingested by mononuclear cells of intestinal lymph follieles (Peyer's patches). Through the stomach infections agent reaches to the proximal part of small intestine. After penetration, the invading microorganisms translocate to the intestinal lymphoid follicles and the draining mesenteric lymph nodes, and some pass on to the reticuloendothelial cells of the liver and spleen.

Table 3. Pathogenesis of typhoid fever

Stage	Patophysiological processes in patient's organism	Morphological features	Period of illness
The stage of infection	Ingestion of Salmonella typhi. The infective dose is equal to 10^7 organisms. This dose is enough for beginning of typhoid fever.		1-3 weak incubation period
The stage of the firstly regional infection	The microorganisms penetrate the mucosal epithelium and are ingested by mononuclear cells of intestinal lymph follicles (Peyer's patches). In this place salmonella multiplyes. Some microorganisms come to nusenterical lymph nodes.	Cerebri form swelling (last week of incubation period). Lympoid tissue in the intestin is enlaged. Peyer's putches is marked hypertrophy.	1-3 weak incubation period
The stage of bacteremia and toxinemia.	Through the thorocic duct salmonella disseminates to bloodstream. The microorganisms are break down by complement system of serum, that leads to the appearent of toxinemia. This bacteremia persists for about 3 weak with seeding of the liver, lien, kidney, gall bladder.	Cerebriform swelling.	Stadium incrementis the first weak of clinical course
The stage of parenchimol dissemination.	Salmonella cyrculates in the bloodstream that is cause of its dissemination in organs. The organs, which have reticuloendo the liad fissue, are effected by salmonella. These organs are the liver, lien. Dissemination of infections agends leads to disturbance of blood microcyrculation, that causes distrofia process in tissues.	Toxical damage of marrow. Apperance of rose rash. Damage of internal organs.	Stadium acme the second-third weak of clinical course.

Table 3 continued

Stage	Patophysiological processes in patient's organism	Morphological features	Period of illness
The secretorial allergical stage.	Massive secretion survival microorganism through the kidney, gallbladder ways, and intestinal etypts take place in patient's organism. There are many trombs in microcyrculation. In this stage immunological processes have maximal effort. There are local allergical reaction.	Stages formation ulcers, and dear ulcers.	Stadium acme the second-third weak of clinical course.
The stage of immunal development and recovering	The patient immune system produces high level of antibodies. The microorganisms disappears from bloodstream and patient begins to feel better. Antibody production is increasing day to day. Microcyrculation and damages in internal organs is restored.	Stage healing of ulcers.	Stadium decrementis the forth weak of clinical course. Stadium reconvolescent the fifth-sixth weak.

Bacteria penetrate the enterocytes and without causing damage, they multiply in the lamina propria. This phase – ***phase of firstly regional infection***. These phase, which were mentioned, is according to incubation period in the clinic picture. The incubation period is usually 7 to 14 days. The Salmonella are able to survive and multiply within the mononuclear cells and are carried by the cells from the mesenteric lymph nodes to the thoracic duct and eventually to the blood stream. At a critical point that is probably determined by the number of bacteria, their virulence, and the host response, bacteria are released from this sequestered intracellular habitat into the bloodstream (**Table 3**).

Bactericide proteins of blood serum break down microorganisms in transient primary bacteremia. Salmonella is destroyed by mononuclear cells. In the ***bacteremic phase***, the organism is widely disseminated. These actions lead to release of endotoxine, which affects to different organs and systems of organism. This period of disease can be defined as a phase of bacteriemia and toxinemia. In the stage endotoxine acts as a neurotropie posion, which mainly affects on CNS and CVS. Endotoxin is a lipo – oligo saccharide components of the bacterial cell wall. The pathogenesis of typhoid is attributed to a cytokine cas code induced by host immune responses, together with inflammatory damage mediated by neutrophil proteases, free oxigen radicals and arachidonic acid metabolites.

The sustained bacteremia persists for about 3 weeks, with seeding patient's organism.

Fever increases during this with patients becoming acutely ill. The infection disseminates widely to the liver, gallbladder, spleen, bone marrow and kedney. This period is the phase of parenchimal dissemination. In this stage, salmonella appear in urine, saliva, sweat, milk ete. In the gallbladder the microorganisms multiply in the bile, reinfecting the infestine.

In the intestine, the Peyer's patches become inflamed and ulcerated and salmonella appear in the feces. This stage is defined as the **secretory - allegical phase**. In damaged Peyer's patcches necrotic processes quicly develope that leads to appearence of hyper ergical inflammation.

The main morphological changes in patients with typhoid is observed in limphoid tissue of intestine. The regularity and following development of these changes is the reason of distingnishing five morphological period:

1. Cerebriform swelling of Peyer's patches;
2. Necrosis;
3. Ulceration of Peyer's patches;
4. Stage of clear ulcers;
5. Healing of ulcers.

The histopatological examination of infected tissue shows an initial influx of polymorphs, followed by the development of "typhoid nodules", clusters of

lymphocytes and macrophoges with ingested bacteria, erythrocytes, and other debris concentrated in principal organs of reticuloendotelial system but also to be found in cites such as the kidney, testis, and parotid glands. Observation of this process in Peyer's patches shows an initial marked hypertrophy that makes the lymphoid tissue stand out prominently from the surrounding mucous. The tissue then becomes ischaemic and necrotic forming a dark slough. Perforation and hemorrhage are potential consequences of these damages.

In the ***stage of immunal development and recovering,*** patient's condition is getting better. Bacteremia and intoxication decreases due to development of immune responce. Titer of specific antibody increases. This period lasts from two three weeks.

Typhoid induces systemic and local humoral and cellular immune responses, but these confer incomplete protection against relapse and reinfection. The interaction of host immunologic mediators and bacterial factors in infected tissue may contribute to the necrosis of Peyer's patches in severe disease.

CLINICAL MANIFISTATION

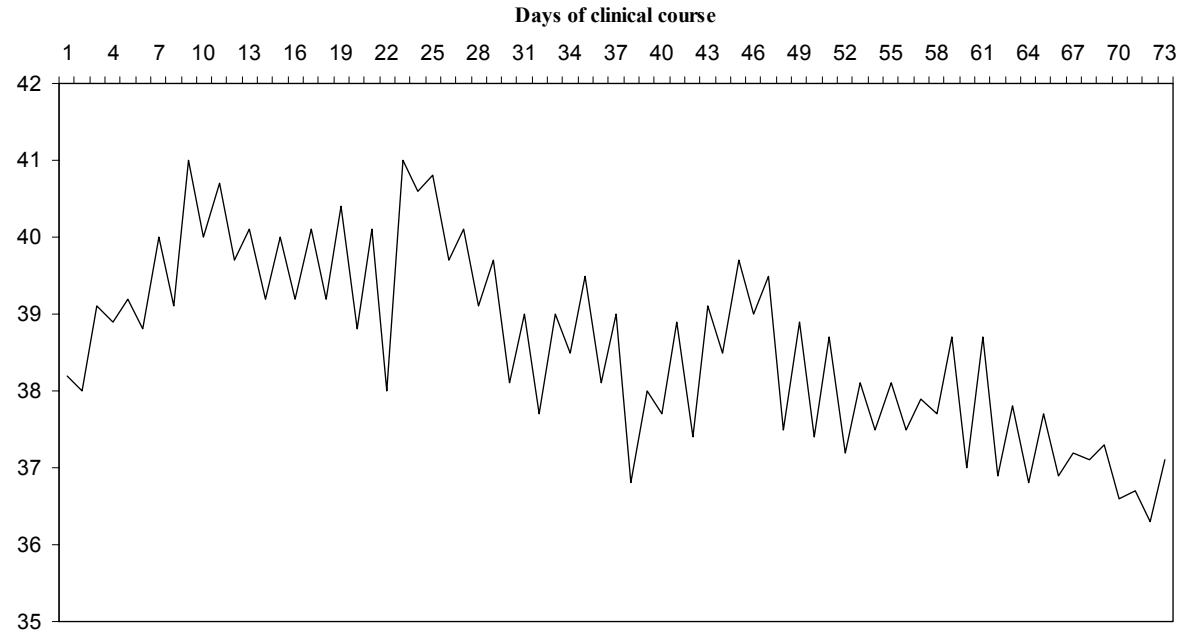
The incubation is dictated by the peculiarities of infecting strain, the infected dose, and condition of host organism.

The average incubation period of typhoid fever is 12 - 21 days, for paratyphoid A fever – 12-14 days, and paratyphoid B fever – 7-12 days. The extremes of the range are 3 to 60 days.

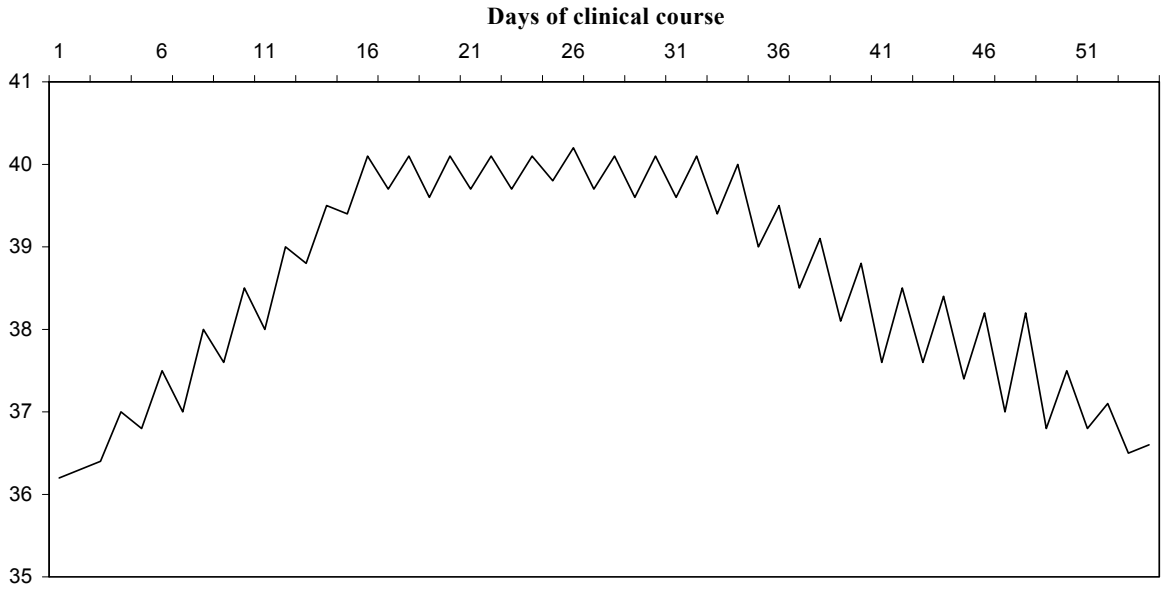
Fever is the main symptom of typhoid fever. In the past many patients have been made of stepwise contour of the temperature chart in cases observed during the first week of illness. There are some types of temperature charts.

The rigors are uncommon, and they can develope when the fever reaches a high figures (39-40°C). Headache is the most constant symptom of the fever in typhoid. Other non-specific symptoms, as are malaise, lassitude, myalgia, arthralgia, anorexia. These features of intoxication syndrome gradually develope. In many patient of typhoid fever constipation is a frequent early symptom, which caused by damage of lymphoid tissue. The onset is insidious with sustained nonproductive cough and bronchitis, diarrhea. Neurological examination of the patient finds out tremor of the outstretched hands, and possibly some degree of gait ataxia. If the patient's condition deteriorates, in clinic there are muttering delirium, twitching of the fingers and wrists, agitated plucking at the bedclothes, and a staring, stupor. There are is diffuse lower quadrant abdominal discomfort with tenderness and distention. Percution in this area a doctor can find out that sound becomes dull. This clinical feature is Padalka's symptom.

There are some different typical temperature curve (**Figure 1-2.**)

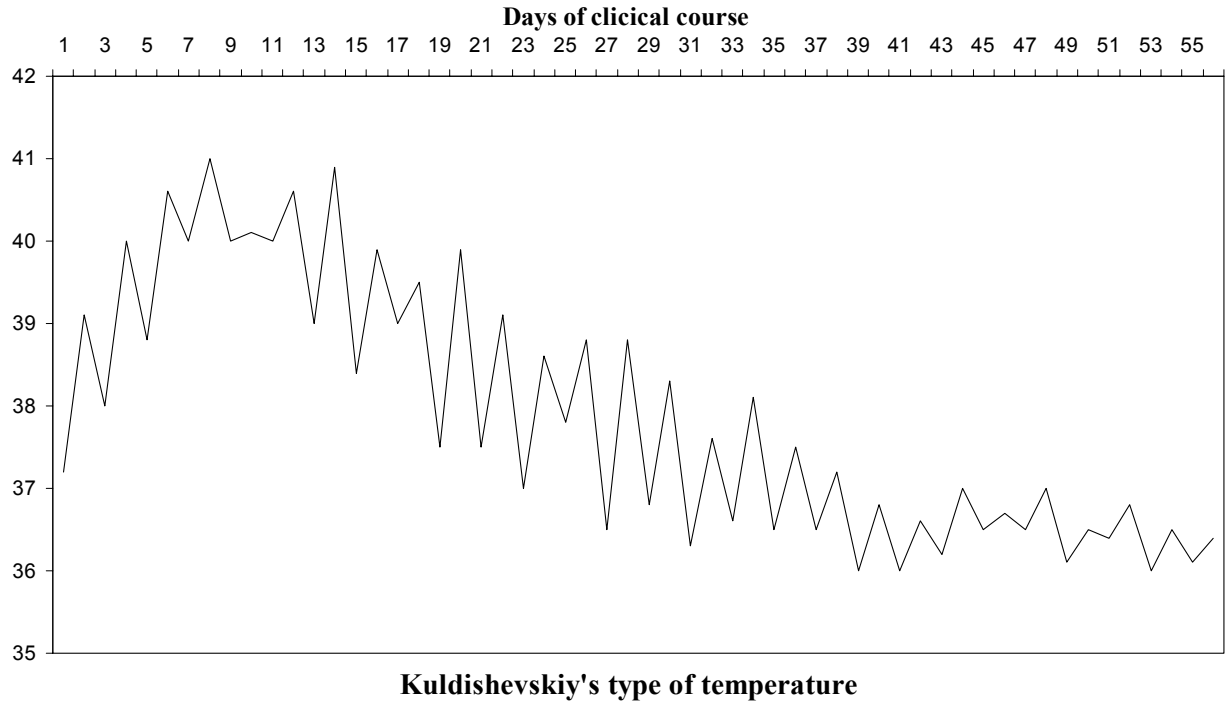


Botkin's type of tmperature.

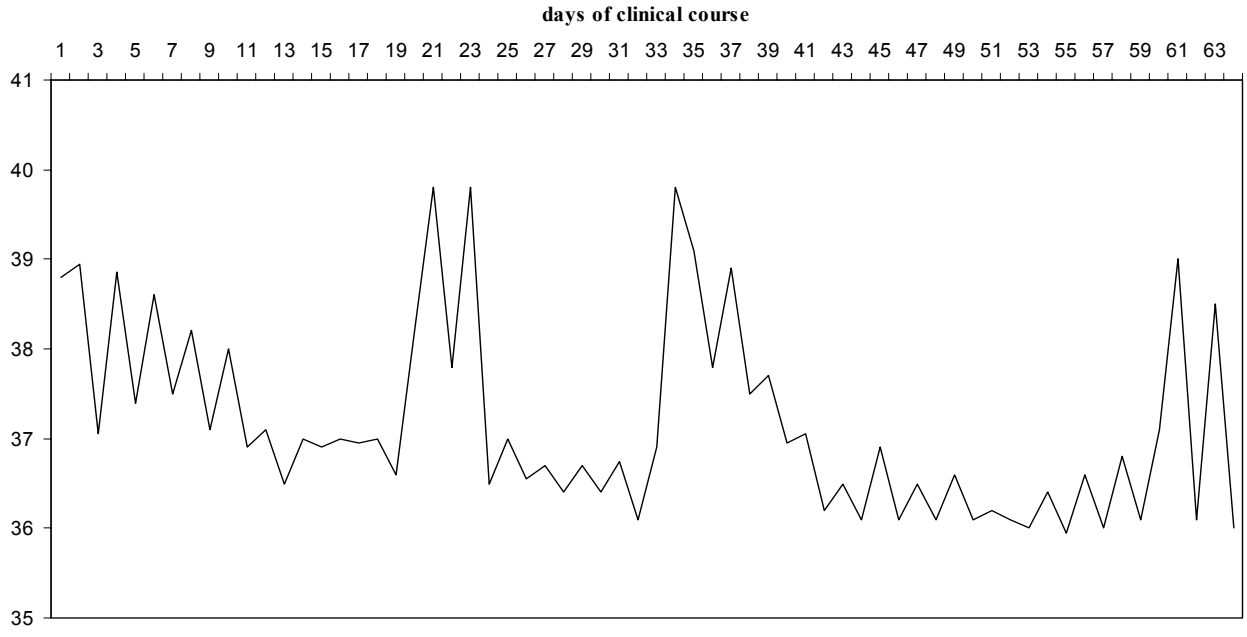


Wunderlicsh's type of temprature

Figure 1.



Kuldishevskiy's type of temperature



Clinical course of typhoid fever with three relapses

Figure 2.

The fever makes its gradual ascent in the first week, remains on a high plat can during the second and then makes a gently decreasing in the third and fourth. In untreated cases, the fever lasts 2-3 weak, other symptoms resolve in an additional week, but weakness persists for several weeks after normalization of the temperature. The most notable clinical developments in the later stages of typhoid is the alteration of patient's mental state so-called "*Status typhosus*". In this stage, in typically cases, the mental state manifests initially as mental apathy and progresses to an agitated delirium, frequency accompanied by tremor of the hands, tremulous speech, and gait ataxia. This stage develops in period when the temperature is the higher. The so-called pea-soup stools are not particularly common and in many cases is result by milk diet. After the first week, there are features of hepato- and spleenmegaly.

In the majority of typhoid patients, especially who has sever course, the liver and spleen can be palpated after 8-10 day of clinical onset. Careful and repeated examinations are required to catch the rash, which is special diagnostic feature of typhoid fever. The time of rash appearance is different in typhoid and paratyphoid fevers. In the end of the first week, the patient's skin is dry, pale and hot.

In the typical cases of typhoid fever, the rash appears by the end of the first week. It localizes on the front of the lateral surface of abdomen. Crops of periumbilical erythematous maculopapular roseolas, 2-to 4 mm in diameter, that blanch on pressure (rose spots) may be seen in 25-30% of the patients. Rose spots are transient and disappear within a day or so. New elements can be appeared when old do not disappear.

In the early period of typhoid fever, tachicardia is found, but in climax period of disease, the temperature, pulse-dissociation, so-called relative bradicardia, develops. The blood pressure must be recorded, as hypotension has important prognostic and therapeutic implications. The patient's tongue is dry and coated by grey fur, which localizates on the tongue back but the tip is free and has brightly red color. This vie of tongue in patient with typhoid fever is distinctive enough to merit the term "typhoid tongue".

In severe cases the patient with typhoid fever are accelerating weight loss. On of typically clinic feature is the facial expression, which is districting as the term "typhoid face". This face it thin, flushed, with bright eyes and dull, heavy, staring, apathetic expression there is the blue around eyes.

In the common laboratory findings include a mild normochromic anaemia, mild, trombocytopenia and an encreased erytrocyte sedimentation rate, these hacmotological features are seen in climax period of typhoid fever.

In the firstly days of disease transient leukocytosis can be found, and by the end of the first week, leucopenia with relative nentropenia and anesonophilia are presented in blood test: there is relative lymphocytosis in blood.

Biochemical futures include hypernatriemia, hypokalaemia, and little elevation of liver enzymes. The urine test often contains some protein and white cells.

Relapse usually is milder than the first episode of diseases. It occurs a week or two after the recovery from a first attack. The relapse is usually milder than the original attack, and the *S. enterica* serotype typhi isolate from a patient in relapse usually has the same antibiotic-susceptibility pattern as the isolate obtained from the patient during the original episode. Reinfection may also occur and can be distinguished from relapse by molecular typing.

Up to 10 % of convalescing patients with untreated typhoid excrete *S. typhi* in the feces for up to three months. In 1-4% cases become long-term carriers, excreting the organism for more than one year. Up to 25 % of long-term carriers have no history of typhoid. Chronic carriage is more common among women and the elderly and in patients with cholelithiasis. Most carriers are asymptomatic. Patients with an abnormal urinary tract, such as those who have schistosomiasis, may excrete the organism in the urine for long periods.

The main cause of death is complication. The case fatality rate in untreated cases is 10% but can be reduced to less that 1% with appropriate therapy. The complication of typhoid fever occur in the third week of the disease. Complications due to necrosis and ulceration of the typhoid tissue of the terminal part of thin intestine.

Among hospitalized patients, the case fatality rate varies from less than 2 percent in Pakistan and Vietnam to 30 to 50 percent in some areas of Papua New Guinea and Indonesia. The case fatality rates are highest among children under one year of age and among the elderly. However, the most important contributor to a poor outcome is probably a delay in instituting effective antibiotic treatment.

COMPLICATIONS

There are specific and nonspecific complications. The specific complications are mental confusion, shock, intestinal perforation, intestinal hemorrhage. Which are produced by specific pathomorphological processes.

Complications occur in 10 to 15 percent of patients and are particularly likely in patients who have been ill for more than two weeks. Many complications have been described (**Table 4**), of which gastrointestinal bleeding, intestinal perforation, and typhoid encephalopathy are the most important.

Gastrointestinal bleeding is the most common, occurring in up to 10 percent of patients. It results from erosion of a necrotic Peyer's patch through the wall of an enteric vessel. In the majority of cases, the bleeding is slight and resolves without the need for blood transfusion, but in 2 percent of cases, bleeding is clinically significant and can be rapidly fatal if a large vessel is involved. Intestinal (usually ileal) perforation is the most serious complication, occurring in 1 to 3 percent of

hospitalized patients. Perforation may be manifested by an acute abdomen or, more covertly, by simple worsening of abdominal pain, rising pulse, and falling blood pressure in an already sick patient. A reduced level of consciousness or encephalopathy, often accompanied by shock, is associated with high mortality. The patient is commonly apathetic although rousable. Patients can be severely agitated, delirious, or obtunded, but complete stupor or coma is infrequent. The incidence of these neuropsychiatric presentations varies among countries. It ranges from 10 to 40 percent among hospitalized patients with typhoid in Indonesia and Papua New Guinea but is less than 2 percent in Pakistan and Vietnam. This geographic variation is unexplained. Typhoid fever during pregnancy may be complicated by miscarriage, although antimicrobial treatment has made this outcome less common. Vertical intrauterine transmission from an infected mother may lead to neonatal typhoid, a rare but severe and life-threatening illness.

Table 4. Important complications of typhoid fever

Abdominal	Gastrointestinal perforation Gastrointestinal hemorrhage Hepatitis Cholecystitis (usually subclinic)
Cardiovascular	Asymptomatic ECG changes Myocarditis Shock
Neuropsychiatric	Encephalopathy Delirium Psychotic stages Meningitis Impairment of coordination
Respiratory	Bronchitis Pneumoniae
Hematologic	Anemia Disseminated intravascular coagulation (usually subclinic)
Other	Focal abscess Pharynitis Miscarriage Relapse Chronic carriage

The criteria for severe typhoid is marked mental confusion or shock defined as the systolic blood pressure of less than 90 mm Hg, with evidence of decreased skin, cerebral, or renal perfusion. Intestinal perforation is most serious complication. It occurs in less than 5% of patients Perforation is found in the terminal ileum. 75% of cases with perforation are observed about 20 days of disease.

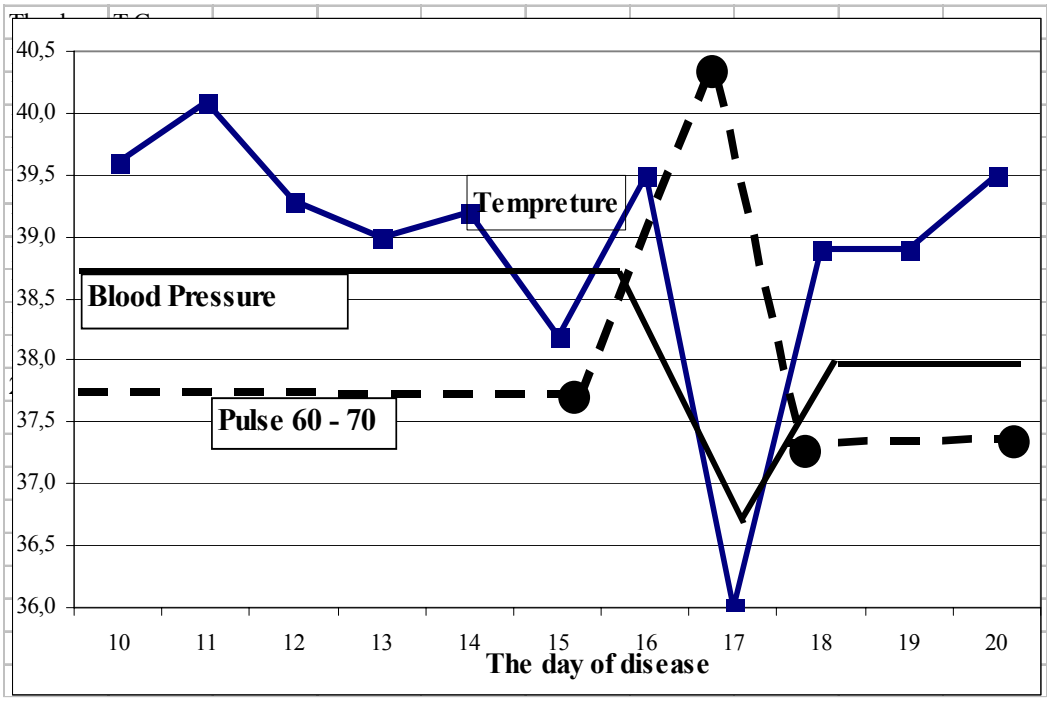


Figure 3.

Relapse occurs in 5 to 10 percent of patients, usually two to three weeks after the resolution of fever. The relapse is usually milder than the original attack, and the *S. enterica* serotype typhi isolate from a patient in relapse usually has the same antibiotic-susceptibility pattern as the isolate obtained from the patient during the original episode. Reinfection may also occur and can be distinguished from relapse by molecular typing. Up to 10 percent of convalescing patients with untreated typhoid excrete *S. enterica* serotype typhi in the feces for up to three months; 1 to 4 percent become long-term carriers, excreting the organism for more than one year. Up to 25 percent of long-term carriers have no history of typhoid. Chronic carriage is more common among women and the elderly and in patients with cholelithiasis. Most carriers are asymptomatic. Patients with an abnormal urinary tract, such as those who have schistosomiasis, may excrete the organism in the urine for long periods.

The clinical feature of intestinal perforation rarely abrupt. Most often there is a subtle transition from vague abdominal pain and tenderness to rather more definite pain and restlessness with rise in pulse rate and fall of blood pressure. Distension and guarding increase gradually. Rigidity, absent bowel sounds, and loss of resonance

over the liver results from pneumoperitoneum can take several hours to appear. A chest radiograph can confirm free gas under the diaphragm, and ultrasonography is useful for demonstrating and aspirating packets of facculent fluid in the peritoneal cavity. Silent bleeding can be defined by sudden collapse of a patients or a steadily falling haemotocrit and quantity of erytrocytes and haemoglobin (**Figure 3**). The rise in pulse rate and fall of temperature are observed in patient with intestinal hemorrhage. The most of episodes of this complication are self-limiting and only a few need transfusion. In exceptional cases, surgical intervention is required.

The average case fatality rate is less than 1 percent, but the rate varies considerably among different regions of the world. Among hospitalized patients, the case fatality rate varies from less than 2 percent in Pakistan and Vietnam to 30 to 50 percent in some areas of Papua New Guinea and Indonesia. The case fatality rates are highest among children under one year of age and among the elderly. However, the most important contributor to a poor outcome is probably a delay in instituting effective antibiotic treatment.

DIAGNOSIS

The absence of specific symptoms or signs makes the clinical diagnosis of typhoid difficult. In areas of endemic disease, a fever without evident cause that lasts more than one week should be considered typhoid until proved otherwise.

Blood cultures are the standard diagnostic method. About 80% is the yield of positive blood cultures. It is maximized by taking generous volumes (15 ml in adults), by repeat cultures, and by careful attention to providing the optimum ratio of blood to broth (1:10).

The liquid broth with bile is used for blood culture. The best method for confirming of diagnosis is bone marrow aspirates. Culture of bone marrow is more sensitive. The result is positive in 80 to 95 percent of patients with typhoid, even patients who have been taking antibiotics for several days, regardless of the duration of illness. This method that are often positive for some days after the start of antibiotic treatment.

In routine practice culture blood, urine faeces, and bile are used. These method will only exceptionally provide a positive culture when marrow culture is negative.

The blood culture is positive in whole period of fever. Urine, faeces and bile culture are informative in the third week of disease. Rose spots may give positive results in 30% of patient.

Rectal swabs are less satisfactory than faecal samples. The sensitivity of stool culture depends on the amount of feces cultured, and the positivity rate increases with the duration of the illness. Stool cultures are positive in 30 percent of patients with acute typhoid fever. For the detection of carriers, several samples should be examined because of the irregular nature of shedding.

The blood culture can be performed in period of temperature. It is more advantage in stage, when temperature higher then 37,5˚C.

The immune response begins after onset of typhoid fever. In this case cell-mediated response appears after the first week and high titres last around 16 weeks. After recovering from typhoid fever there are specific antibodies in the blood serum for up two years. The traditional method is tube Widal's test. It is demonstrated a rise of antibodies titre. There is passive haemagglutination reaction for serology diagnosis of typhoid fever. Serological inverstigation can be precribed at the first time after 7 day of illness, and repeated in 10 days. The diagnostic titre in Widal test and PHA is 1:200, or the rise of titre in four time.

The role of Widal's test is controversial, because the sensitivity, specificity, and predictive values of this widely used test vary considerably among geographic areas. The test detects agglutinating antibodies to the O and H antigens of *S. typhi*. Unfortunately, *S. typhi* shares these antigens with other salmonella serotypes and shares cross-reacting epitopes with other Enterobacteriaceae. Furthermore, patients with typhoid may mount no detectable antibody response or have no demonstrable rise in antibody titer. Despite this, some centers have found Widal's test helpful when it is used with locally determined cutoff points. A Vi agglutination reaction has been used to screen for *S. typhi* carriers. Its reported sensitivity is 70-80%, with a specificity of 80-95%.

There are many alternative methods for detection of antibodies to O, H and Vi antigenes (passive hacmagglutination (PHA), latex agglutination (LA), counterimmune electrophoresis, CIEF, radioimmunoassay (RIA), enzyme immunoassay (EIA), indirect fluorescent antibody test (IFAT), monoclonal antibodies, lgM capture, DNA probes (polymeroze chain reaction (PCR). LA, RIA, EIA, IFAT, PCR - these methods are more sensetive and specific then Widal test and PHA, but only a few of them are adopted for routine use.

Newer serologic tests are being developed but do not yet perform well enough to ensure their widespread adoption. DNA probes and PCR protocols have been developed to detect *S. enterica serotype typhi* directly in the blood. The methods are not yet widely used and are impractical in many areas where typhoid is common.

ANTIMICROBIAL RESISTANCE

In 1948 chloramphenicol became the standard antibiotic for treating typhoid. Although resistance emerged within two years after its introduction, it was not until 1972 that chloramphenicol-resistant typhoid fever became a major problem. Outbreaks occurred in Mexico, India, Vietnam, Thailand, Korea, and Peru. Chloramphenicol resistance was associated with high-molecular-weight, self-transferable, *Inc*HI plasmids. These *S. enterica* serotype typhi strains were also resistant to sulfonamides, tetracycline, and streptomycin, but initially amoxicillin and

trimethoprim–sulfamethoxazole remained effective alternative drugs. Toward the end of the 1980s and the 1990s, *S. enterica* serotype typhi developed resistance simultaneously to all the drugs that were then used as first-line treatment (chloramphenicol, trimethoprim, sulfamethoxazole, and ampicillin). Outbreaks of infections with these strains occurred in India, Pakistan, Bangladesh, Vietnam, the Middle East, and Africa. These multidrug-resistant strains also carried the 100,000-to-120,000-kD *Inc*HI plasmids that encoded the resistance genes. Spread results from the clonal dissemination of individual multidrug-resistant *S.enterica* serotype typhi strains or from transfer of the plasmid to multiple *S. enterica* serotype typhi strains. Resistance rarely emerges during the course of treatment. Multidrug-resistant *S. enterica* serotype typhi are still common in many areas of Asia, although in some areas strains that are fully susceptible to all first-line antibiotics have reemerged.

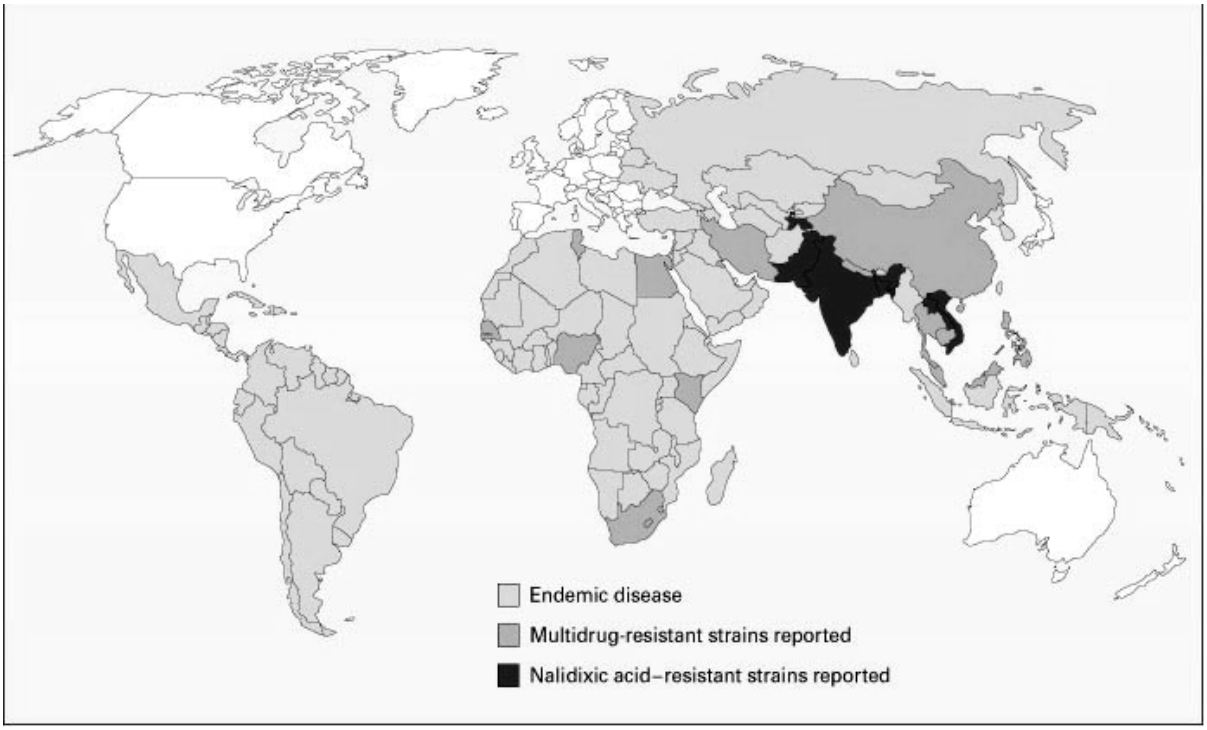


Figure 4

There have been sporadic reports of high-level resistance to ceftriaxone (minimal inhibitory concentration [MIC], 64 mg per liter) in *S. enterica* serotype typhi and *S. enterica* serotype paratyphi A, although these strains are very rare. *S. enterica* serotype typhi strains with reduced susceptibility to fluoroquinolones have become a major problem in Asia. An outbreak of typhoid with such strains in Tajikistan in 1997 sickened 8000 people in a six-month period and caused 150 deaths. Although they were reported to be susceptible to fluoroquinolones, by disk testing with the use of recommended break points, these organisms were resistant to nalidixic acid and the MIC of fluoroquinolones for these strains was 10 times that for fully

susceptible strains. This reduction in susceptibility results in a poor clinical response to treatment. Quinolone resistance is frequently mediated by single point mutations in the quinolone-resistance-determining region of the *gyr*A (DNA gyrase enzyme) gene.

Quinolones, such as nalidixic acid, are a group of synthetic compounds based on the 4-quinolone nucleus (**Figure 4** Global Distribution of Resistance to *Salmonella typhi*). The introduction of fluorine at position 6 of the nucleus creates the fluoroquinolone group of compounds, which have substantially greater antimicrobial activity. In other Enterobacteriaciae, higher levels of quinolone resistance have been associated with additional mutations in the *gyr*A gene, mutations in other topoisomerase genes, or alterations in fluoroquinolone uptake. No such mutations have been reported yet in *S. enterica* serotype typhi, although there are sporadic reports of fully fluoroquinolone-resistant isolates. Because the clinical response to fluoroquinolones in patients infected with nalidixic acid-resistant strains is greatly inferior to the response in those infected with nalidixic acid-susceptible strains, we believe that the break points for the classification of *S. enterica* serotype typhi strains according to their susceptibility to fluoroquinolones should be changed. A pragmatic solution would be to classify strains that are resistant to nalidixic acid but susceptible to fluoroquinolones according to current disk-testing criteria as resistant to quinolones or nonsusceptible to fluoroquinolones. All strains that have intermediate susceptibility or resistance to fluoroquinolones on disk testing (as defined by national guidelines) should be considered fluoroquinolone-resistant.

TREATMENT

Outcome of typhoid fever is influenced from diet, regiment, right care, antibiotic and pathogenic treatment. In areas of endemic disease, more than 60 to 90 percent of cases of typhoid fever are managed at home with antibiotics and bed rest. For hospitalized patients, effective antibiotics, good nursing care, adequate nutrition, careful attention to fluid and electrolyte balance, and prompt recognition and treatment of complications are necessary to avert death.

The patient must have rest, comfortable bad, and good gigeine care. Medical staff should care of mouth cavity and skin. The patient must stag in bad in 6-7 day after temperature normalization. After this period the patient can sit, and in 10-11 day of normal temperature he can walk. In feverish period the diet should have enough energy, but its mechanical and chemical properties must not effect on intestine wall.

Effective antibiotic therapy in typhoid shortens the duration of clinical course and reduces frequency off deaths and complication.

Chloramphenical is pretty effective, but wide usege of this antibiotic lead to appearence of multiresistant strains. They circulate in Mexico, Vietnam, Thailand, India, Pakistan and Bangladesh. Although in much of the world, chloramphenical remains a valuable drug for the management of typhoid. Dosage schedule of

chloramphenical 50-75 mg/kg (**Table 5**). Antibiotics do not influence on emergence of relapses and asymptomatic carriage.

Table 5. Essential antibacterial therapy for typhoid.

	Daily dose	Times in day	Route
Chloramphenicol	50 – 70 mg/kg	4	O / im / iv
Co-trimoxazole	6,5 – 10 mg/kg – trimethoprim 40mg/kg - sulphamethoxazole	2 - 3	O / im / iv
Amoxycillin	75 – 100 mg/kg	3	O / im / iv
Furozolidone	7,5 mg/kg	4	O
Cefoperozone	100 mg/kg	2	im
Cefriaxone	50 – 60 mg/kg	2	im
Ciprofloxacin	0,5 – 1g	2	O / iv
Cefixime	20 mg/kg	2	O
Norfloxacin Oflaxacin Pefloxacin	800 mg	2	O / iv
Enoxacin Flezoxacin	400 mg	2	O / iv

Co-trimoxazole, amoxycillin and furazolidone can be used for treatment of typhoid fever.

The data on the use of fluorinated quinolones (ciprofloxacin, fleroxacin, norfloxacin, pefloxacin, and ofloxacin) and cephalosporins (cefoperazone, cefixinme, and ceftrriaxone) suggest that these drugs are very effective against multidrug resistance *S.typhi* strains.

There is strong evidence that the fluoroquinolones are the most effective drugs for the treatment of typhoid fever. In randomized, controlled trials involving patients infected by quinolone-susceptible *S. enterica* serotype typhi, these drugs have proved safe in all age groups and are rapidly effective even with short courses of treatment (three to seven days). The average fever-clearance time is less than four days, and the cure rates exceed 96 percent. Less than 2 percent of treated patients have persistent fecal carriage or relapse. The published data also suggest that the fluoroquinolones are more rapidly effective and are associated with lower rates of stool carriage than the traditional first-line drugs (chloramphenicol and trimethoprim–sulfamethoxazole).

Concern has been expressed about three main issues regarding the use of fluoroquinolones in the treatment of typhoid fever: the potential for toxic effects in children, the cost, and the potential emergence of resistance. In preclinical testing, the fluoroquinolones damaged the articular cartilage of young beagles. There is now a considerable body of reassuring evidence from the long-term use of fluoroquinolones in children with cystic fibrosis and from the short-term use of fluoroquinolones to treat typhoid fever and of fluoroquinolones or nalidixic acid to treat bacillary

dysentery in children. There has been no evidence of bone or joint toxicity, tendon rupture, or, in long-term follow-up, impairment of growth. The production of generic fluoroquinolones in Asia has reduced the price considerably. However, the emergence of quinolone resistance in areas where these drugs are inexpensive and readily available is likely to be the greatest limitation on their use. Fortunately, full fluoroquinolone resistance is still rare.

SUSCEPTIBILITY	FIRST-LINE ORAL DRUG			SECOND-LINE ORAL DRUG		
	ANTIBIOTIC	DAILY DOSE (mg/kg)	DAYS	ANTIBIOTIC	DAILY DOSE (mg/kg)	DAYS
Fully susceptible	Fluoroquinolone (e.g., ofloxacin)*	15	5–7†	Chloramphenicol	50–75	14–21
				Amoxicillin	75–100	14
				Trimethoprim–sulfamethoxazole	8 (trimethoprim)–40 (sulfamethoxazole)	14
Multidrug-resistant	Fluoroquinolone	15	5–7	Azithromycin	8–10	7
				Third-generation cephalosporin, e.g., cefixime	20	7–14
Quinolone-resistant‡	Azithromycin or fluoroquinolone	8–10 20	7 10–14	Third-generation cephalosporin, e.g., cefixime	20	7–14

*The widely available fluoroquinolones (ofloxacin, ciprofloxacin, and pefloxacin) are all highly active and equivalent in efficacy. Norfloxacin has inadequate oral bioavailability and should not be used to treat typhoid fever.

†Three-day courses are also effective, particularly for the containment of epidemics.

‡The optimal treatment for quinolone-resistant typhoid fever has not been determined. Azithromycin, or a third-generation cephalosporin, or a 10-to-14-day course of high doses of a fluoroquinolone is effective. Combinations of these treatments are now being evaluated.

Figure 5 Treatment of uncomplicated typhoid fever

In areas where quinolone-resistant strains are uncommon, the fluoroquinolones are the current treatment of choice for all age groups. Short courses of treatment (three to five days) are particularly useful to contain epidemics. Among patients with quinolone-resistant *S. enterica* serotype typhi infection, the rate of treatment failure is higher for those treated for less than seven days than for those treated for a longer period. Treatment at the maximal recommended doses (e.g., 20 mg of ofloxacin per kilogram of body weight per day) for 7 to 10 days has been successful in 90 to 95 percent of patients with resistant infections. However, the fever-clearance times are long (seven days, on average), and the rate of fecal carriage during convalescence can be as high as 20 percent (unpublished data). Fluoroquinolones should be used at the maximal possible dose for a minimum of 10 to 14 days, and the patients should be carefully followed to determine whether they are excreting *S. enterica* serotype typhi in their feces. Unfortunately, quinolone-resistant strains are often also multidrug-

resistant, and therefore the choice of drugs is limited to azithromycin or the cephalosporins, which are expensive.

The third-generation cephalosporins (ceftriaxone, cefixime, cefotaxime, and cefoperazone) and azithromycin are also effective drugs for typhoid. In randomized, controlled trials of third-generation cephalosporins, principally ceftriaxone and cefixime, the fever-clearance times averaged one week and the rates of treatment failure were 5 to 10 percent. The relapse rates were 3 to 6 percent, and the fecal-carriage rates were less than 3 percent. Cure rates of 95 percent were achieved with five to seven days of treatment with azithromycin. Fever resolved in four to six days, and the rates of relapse and convalescent fecal carriage were less than 3 percent. Aztreonam and imipenem are potential third-line drugs.

SUSCEPTIBILITY	FIRST-LINE PARENTERAL DRUG			SECOND-LINE PARENTERAL DRUG		
	ANTIBIOTIC	DAILY DOSE (mg/kg)	DAYS	ANTIBIOTIC	DAILY DOSE (mg/kg)	DAYS
Fully susceptible	Fluoroquinolone (e.g., ofloxacin)*	15	10–14	Chloramphenicol	100	14–21
				Ampicillin	100	10–14
				Trimethoprim–sulfamethoxazole	8 (trimethoprim)–40 (sulfamethoxazole)	10–14
Multidrug-resistant	Fluoroquinolone	15	10–14	Ceftriaxone	60	10–14
				or cefotaxime	80	
Quinolone-resistant	Ceftriaxone	60	10–14	Fluoroquinolone	20	10–14
	or cefotaxime	80				

*The widely available fluoroquinolones (ofloxacin, ciprofloxacin, and pefloxacin) are all highly active and equivalent in efficacy.

Figure 6 Treatment of complicated, severe typhoid fever

Chloramphenicol, amoxicillin, and trimethoprim-sulfamethoxazole remain appropriate for the treatment of typhoid fever in areas of the world where the bacterium is still fully susceptible to these drugs and where the fluoroquinolones are not available or affordable. These drugs are inexpensive, widely available, and rarely associated with side effects. They produce relief of symptoms, with defervescence usually occurring within five to seven days; however, two to three weeks of treatment is required, and adherence to a four-times-daily regimen over this period may be low. An adult will often have to take more than 250 capsules of chloramphenicol during a course of treatment. Although the cure rate is approximately 95 percent, the relapse rate is 1 to 7 percent, and the rate of convalescent excretion is 2 to 10 percent.

There are few data on the treatment of pregnant women with typhoid. The beta-lactam antibiotics are considered safe. In addition, there have been several case reports of the successful use of fluoroquinolones. Although these drugs have generally been avoided because of concern about safety, the general consensus is that they are also safe.

Most of the data from randomized, controlled trials come from patients treated in regions where disease is endemic. There are few data from such trials of treatment in patients living in regions where the disease is not endemic or in returning travelers. Knowledge of the antibiotic susceptibility of the infecting strain is crucial in determining which drug to use.

The parenteral fluoroquinolones are probably the antibiotics of choice for severe infections, but there have been no randomized trials of such treatment. In severe typhoid, the fluoroquinolones are given for a minimum of 10 days. Adults and children with severe typhoid characterized by delirium, obtundation, stupor, coma, or shock benefit from the prompt administration of dexamethasone. The mortality rate was reduced from over 50 percent to 10 percent in Indonesian adults and children who were given dexamethasone at an initial dose of 3 mg per kilogram by slow intravenous infusion over a period of 30 minutes, followed by 1 mg of dexamethasone per kilogram given at the same rate every 6 hours for eight additional doses. Hydrocortisone at a lower dose was not effective.

Patients with gastrointestinal perforation during typhoid require resuscitation with fluids, blood, and oxygen, as appropriate, followed by surgery. At operation, the ileum, cecum, and proximal large bowel should be examined for perforations. Several procedures can be performed, including intestinal resection and primary anastomosis or wedge resection or débridement of the ulcer, with primary closure of the perforation. A temporary ileostomy or ileocolostomy is sometimes required. The sites of impending perforation can be sutured with serosa-to-serosa approximation. Lavage of the peritoneal cavity should be followed by closure, with or without drainage. Patients require additional parenteral antibiotics to eliminate enteric aerobes and anaerobes that may contaminate the peritoneal cavity. Early intervention is crucial, and mortality rates increase as the delay between perforation and surgery lengthens. The mortality rate after perforation varies between 10 and 32 percent. Many cases of intestinal hemorrhage are not severe and can be managed without transfusion, but blood should be cross-matched immediately and the surgical team alerted.

Relapses should be treated in the same way as initial infections. The majority of intestinal carriers can be cured by a prolonged course of antibiotics, provided they do not have gallstones. Cure rates of approximately 80 percent have been achieved with 100 mg of ampicillin or amoxicillin per kilogram per day, taken orally, with 30 mg of probenecid per kilogram per day for 3 months; two tablets of trimethoprim–sulfamethoxazole twice daily for 3 months; or 750 mg of ciprofloxacin twice daily for 28 days; the cure rate varies with the susceptibility of the organism. In the presence of cholelithiasis, antibiotic therapy as well as cholecystectomy may be required.

DIFFERENTIAL DIAGNOSIS.

Typhoid must be distinguished from other endemic acute and subacute febrile illnesses. Malaria, deep abscesses, tuberculosis, amebic liver abscess, encephalitis, influenza, dengue, leptospirosis, infectious mononucleosis, endocarditis, brucellosis, typhus, visceral leishmaniasis, toxoplasmosis, lymphoproliferative disease, and connective-tissue diseases should be considered. For patients in countries where typhoid is not endemic, a travel history is crucial. Clinical algorithms have been developed but have not generally been validated (**Table 6-10**)

Diagnostic typhoid fever is very difficult in onset of disease. Epidemiological information allows suspecting typhoid fever. Ciroduol beginning of disease, temperature, intoxication without sepotote damages of organs are very important features of typhoid. Significance of these symptoms is higher, when the temperature graduate goes up and during several days it is accompanied of constant headache, the insomnia, anorexia and constipation.

Typhoid and paratyphoid fever have similar symptomatic. Paratyphoid A and B have acute onset of disease. Chills, sweats, hyperemia of face, coryta, earty rose zash, diarrhea are very commons symptoms. Temperature curve is irregular. Shope in paratyphoid fever. Rose rash is spreading sings in some cases. But, laboratory tests are more informative in diagnostic process.

Clinical peculiarities of Paratyphoid fever :

1. Incubation period (shorter - 5 – 10 days).
2. Disease beginning is more acute.
3. The temperature has waveshape.
4. Headache, rigors, sweatness.
5. Dyspepsia features: nausea, vomiting, pain in the abdomen, diarrhea *(Paratyphoid B).*
6. Sings respiratory tract damage – cough, sore throut, *(paratyphoid A)*
7. General condition: redness of face, *herpes labialis*, *nosalis,* hyperemia of mucous tissue and eye globe.
8. Rash - roseola, roseola-popular, measelslike, petechia.
9. Course of disease with septical features.
10. Purulent meningitis, meningoencephalitis, septicopiemia.
11. Typhoid status can be absent.
12. Relapses and complications are rare.
13. Hemogramm - normocytosis, a little leucocytoses, lymphomonocytosis. There are eosihophils in the blood count.
14. Culture (urine, blood, faces, bile) is diagnostic.

Table 6. Differential criteria typhoid fever and tuberculosis

Symptoms	Typhoid fever	Acute disseminated tuberculosis
Anamnesis	Possible infection (water, contact with patient or bacterio carrier)	Tuberculosis in prenions history, contact with patient
Skin	Dry	Wet
Pulse	Relative bradicardia	Tachicardia
Breathlessness	Not typical	Constant symptom
Tongue	Dry, furred, with bright red tip. There are teeth imprinting on the edge of tongue	Not typical
WBC	After the 3^{d} day – leucopenia with neutropenia, lymphocytosis and anesonophilia	Leucopenia with relative neutrophilosis with lymphocytosis with esonophills (normal quantity) is typical feafure
Platelets	Sever trombocytopenia	Anantity is normal
ESR	Level is normal or slight increased	Higher
X-examination of chest	Bronchitis or bronchopneumonia. Often - it's normal	Features of tuberculosis
Hemoculture	Positive	Negative
Serological test	Positive	Negative

Table 7. Differential criteria typhoid fever and sepsis

Symptoms	Typhoid fever	Sepsis
Skin	Pale, dry	Wet, paint with a little yellow hue.
Rash	Roseola, which appears on the 7 – 8 day.	Often petechia mainly on unbended surfase of arm and around the foints, sometimes it is purelent.
Temperature	Waveshape or trapezium types of fever. Average duration of fever is nearly 2 weaks.	Fever is remittent or irregular. The duration of fever is longer.
Chills	Atypical	Typical symptom
Pulse	Relative bradicardia Pulsus dicroticus	Tachicardia, sometimes There is pulsus dicroticus
Liver	It is enlarged after the 6 – 7^{th} day	Enlarged, but not always.
Urine	Urine specific gravity is normal or slife decreased	Urine specific gravity is low sometimes there is heamaturia
Lien	It is enlarged after the 6 – 7^{th} day	It is enlarged always. In palpation it is soft, in some long cose - solid
Blood	Leucopenia, neutropenia, anesinophilia	Anemia, leucocytosis with neutrophilosis
Blood culture	Salmonella typhi	Different bacteria, strepto- staphylococcus etc

Table 8. Differential criteria typhoid fever and brucellosis

Symptoms	Typhoid fever	Brucellosis
Anamnesis	Epidemiological data possibilities of infection	Contact with ill animals. Consumption of meat and milk products of animals with brucellosis.
Complains bare – muscle system	It is not typical for typhoid fever	Constantly, from firstly days, pain in the loin, in the joint and muscles.
Beginning of disease.	Gradual, with slow increasing of temperature, patient becomes acutely ill.	Acute, sometimes subacute but even on high temperature the general condition is satisfactory.
Lymphoid nodes	Body lymphnodes are not enlarged	mycropolyadenopathy
Sweat	His absent in beginning but period reconvelence period it may be take place.	In a night, plenty sweetness is very typical and even in normal temperature skin of patient is wet.
Chills	It is not typical. Sometimes – cold in high temperature.	Already in half patients chills is constant feature. Often in the second part of day. It may be without temperature.
Abdomen	Distention. Padalka's symptom. Constipation.	Normal
Hepatosplenomegalia syndrom	It s typical	It s typical
Arthralgia	It is not typical	Very often
Pulse	Relative bradycardia, *pulsus dicroticus*.	Pulse lability.
Damage UGS	Seldom	Often
Damage of CNS	Patient is slack, apathetic. Changes in consciousness.	Euphoria, a quickly changes of mood.
Psychiatric disturbance	Seldom	Often, very steady and even after the convalence
Blood culture	*S. typhi*	*Brucella sps.*
Serological test	Positive Widal's test	Pasitive Rait and Heddelson test.

Table 9. Differential criteria typhoid fever and influenza

Symptoms	Typhoid fever	Influenza
Incubation period	7 –21 day, middle – 12-14 days	From few hours to 1 –2 days
Beginning of disease	Gradual increasing of temperature, it reaches maximum figures after the fifth day	Acute, often suddenly, increasing high temperature, in the first day – maximum figures.
Duration of fever	Form 5 day to several weeks	1 – 3 days, seldom 4 – 5 days.
Skin	Pale, dry, hot	Sweetness
Face of patient	Pale, apathetic	Hyperemia, red conjunctiva and something sclera.
Rash	Single, little rose spots on the stomach. It appear after the 6^{th} – 8^{th} day.	Herpes simplex on a lips or a nostrils
Pulse	Relative bradycardia, *pulsus dicrotus*	Pulse corresponds to fever.
Charges in lungs	From the firstly days – bronchitis, sometimes local pneumonia.	Some cases pneumonia with intoxication and shortness of breathing and cyanosis.
Tongue	Furred on the basis of tongue. Dry, tip and edge of tongue are bright red, without fur. There are teeth imprinting.	It is furred, wet.
Abdomen	Meteorismus, retention of stool. Padalka's symptom, from the 5-6^{th} day enlarged lever and lien.	Without abnormalities.
Headache	Long, constant	Severe, localization in foreheads
Sleeplessness	Often in early period	Seldom, in cases with severe intoxication.
CNC	Patient is indifferent, with changes in consciousness	Fatigue, dreaminess, dizziness (vertigo).
Blood	In the firstly 2 – 3 day leucocytosis, after then, lencopenia with anesinophilia, relative lymphomonocytosis nentropenia.	After the second day lencopenia, lympomonocytosis relative neatropenia.
Laboratory diagnostic	Positive heamoculture, coproculture, urineculture. Serological investigation.	Finding of virus, or specific antibody

Table 10. Differential criteria typhoid fever and epidemic typhus

Symptoms	Typhoid fever	Epidemic typhus
Beginning	Gradual show stepshape increasing of temperature	Often acute with fast increasing of temperature
Patient's face	Pale, apathetic. Mucosal tissue of conjunctives and sclera are usual color.	Hyperemia, smelling, odemic, lyes glittes Vesel infection of sclera, hyperemia of conjunctive. Positive Chiari-Avcyna Symptom (after the 3^{d}-4^{th} day – red spots on the transitional fold of conjunctive.
Rash	It appeares on the 8-10^{th} day. It's roseola elevata on the abdomen with little quantity	It's appears on 4-5^{th} day. It's polymorphic, plantiful roseola-pethechia no profrude under the skin. Mainly it localizes on lateral surface of frunk or bended surface of forearm and back and extremites.
Tongue	Dry, the tip is bright red without fur. On the edge of tongue teeth imprintings the basis of tongue is plantiful furred.	It may be wet or dry. It is even covered by grey-white fur. It difficulty hang's out a month. It doesn't fully put out month in order to trembling (Govorova's Symptoms)
Mucosal tissue of mouth cavity	Usual color, the troaf is moderite hyperemia	Hyperemia has high level. Mucosal tissue is day. After the 2^{d}-3^{d} day. There is enanthema on a palatine molis (or it's little petechia in the mucos tissue). Rosemberg's symptom)
Abdomen	Distention, meterismus, retantion of stool.	Without changes
Padalka's symptom	Typical	Negative
Liver and Lien	Enlargement after the 7^{th} day.	Often they enlarge after the 3-4^{th} day
Heatach	Moderate with locatioration in forehead and temple regions	The pain has agonizing, tormented, shrunk, pulsed characteristics. It accompained with noise in ears.
Sleep	Sleeplessness	Uneasy, with horrous dreams
CNS	Patient is slack, apathetic changes in consciousness	Euphoria, talkative.
Blood:	Leucopenia, neutropenia anesinophilia	Lencocytocis, neutrophilosis, in sever cases – anesinophilia and monocytosis.
Blood culture	Positive	Negative
Reaction agglutination with R. prowazekii	Negative	Positive
Conphement sedimintation with R. prowazekii	Negative	Positive
Widal's test	Positive, tytre of antibody is increasing in dynamics.	Negative

PREVENTION

The virtual elimination of typhoid from industrialized countries can be attributed largely to the provision of safe drinking water, the safe disposal of human sewage, legal enforcement of high standards of food hygiene, care in detecting and monitoring chronic carriers, and prompt investigation and intervention on the occasions when these safeguards are broken.

Various typhoid vaccines have bun used for many years, but the immunity engendered by them can casity is overwhelmed by a large inoculums of the organism. At the present time live attenuated oral vaccine appears to be the most effective. In developing countries, reducing the number of cases in the general population requires the provision of safe drinking water, effective sewage disposal, and hygienic food preparation. Mass immunization has been used successfully in some areas. In developed countries, identification of chronic carriers is now less important than formerly. Most cases are the result of travel to areas of endemic disease. Travelers in such areas need to take particular care with food and water. Water for drinking should be boiled or bottled, food should be thoroughly cooked, and ice cream should be regarded with suspicion. Fresh vegetables or fruits that have been washed in local water are potential sources of infection.

The first parenteral whole-cell typhoid vaccine was introduced in 1896. Its efficacy was established in field trials in the 1960s in Poland, Yugoslavia, Guyana, and the Soviet Union. The various vaccines offered 51 to 88 percent protection to children and young adults, lasting for up to 12 years. The chief disadvantages of the whole-cell vaccine are local discomfort and swelling and the systemic side effects that occur in 25 to 50 percent of recipients.

Field studies of Ty21a, a live, attenuated oral vaccine, have shown variable protective efficacy, ranging from 96 percent after 3 years in Egypt to 67 percent after 5 years in Chile and 42 to 53 percent, depending on the formulation, after 2.5 years in Indonesia. The vaccine is given as one capsule on days 1, 3, 5, and 7 and is suitable for adults and children over six years of age. A booster dose is recommended every five years. The vaccine is well tolerated, but because it is a live, attenuated vaccine, it should not be given to immunocompromised patients or patients taking antibiotics. Alternative oral vaccines are at different stages of development.

The parenteral Vi-based vaccine is suitable for adults and children over the age of two years and has no serious side effects. A single dose of 0.5 ml (25 μg) is administered intramuscularly. Booster doses are recommended every two years. A single injection of the Vi vaccine provided a protective efficacy of 72 percent after 17 months in Nepal and 64 percent after 21 months in South Africa. A new modified Vi vaccine conjugated to a nontoxic recombinant *Pseudomonas aeruginosa* exotoxin A (rEPA) was evaluated recently in Vietnam. In an area where the incidence of typhoid in children two to five years of age was 414 cases per 100,000 per year, the protective

efficacy was 91.5 percent. An important advantage of this vaccine is that it has the potential to be immunogenic in infants under the age of two. There is no currently licensed vaccine against *S. enterica* serotype paratyphi A.

The Ty21a and Vi vaccines are recommended for travelers to areas where typhoid is endemic, household contacts of typhoid carriers, and laboratory workers likely to handle *S. enterica* serotype typhi, although there is no evidence from controlled trials that these vaccines are effective outside areas of endemic disease. In areas where epidemic risk is high, mass immunization should be considered during disasters or in refugee camps, in combination with adequate provision of safe water and food.

SALMONELLOSIS

DEFENITION: *acute intestinal infection, caused by different serotypes of nontyphoid salmonella, characterizes by intoxication and predominant disturbances of gastrointestinal system, in rare cases with septic porcess.*

The prototypic Salmonella, *S. choleraesuis*, mistakenly described by Theobald Smith in 1894 as the cause of the viral disease hog cholera, was named in honor of Smith's supervisor, Dr. Daniel Salmon. The genus is both vast and diverse. Of its more than 2300 distinguishable organisms, some can cause infections in humans, including typhoid fever (also known as enteric fever); focal systemic infections; septicemia; and (most commonly) diarrhea, varying from acute watery diarrhea to bloody diarrhea or dysentery. Salmonellae are ecologically entrepreneurial and exist in a multiplicity of habitats; this characteristic adaptability, which accounts for the ubiquity of the organisms in nature and for the many ways in which they encounter potential new human hosts, is related to their genetic plasticity.

Morbidity and mortality rates are highest in infants (most dangerous in infants <3 month with bacteremia), elderly patients, and patients with sickle cell disease, AIDS, neoplasms, or other causes of immunocompromise.

ETIOLOGY

Salmonellae are gram-negative bacillary members of the family Enterobacteriaceae that are almost always motile by means of multiple peritrichous flagella. The salmonellae are facultatively anaerobic and typically do not ferment lactose; these properties form the basis for their identification during initial screening in the microbiology laboratory. Taxonomy, typically the staid and stable domain of a few cognoscenti, has been in a state of flux for Salmonella in recent years, as the number of recognized species classified within the genus has varied from one to a few thousand. The current classification, based on DNA relatedness, recognizes only

two species, *S. enterica* and *S. bongori*, the latter of which is not a human pathogen. The choice of the designation S. enterica reflects a desire to avoid confusion with the prototypic organism described by Smith, *S. choleraesuis*, and the fact that none of the named isolates has previously been called enterica. *S.enterica* encompasses six subspecies, each of which includes multiple members (serovars). Most human pathogenic salmonellae fall within subspecies enterica.

The huge number of salmonellae distinguishable by serologic methods reflects the ability of the organisms to create mosaic flagellin genes through multiple recombinational events and horizontal transfer, point mutations, and gene duplications and alterations in length, all of which together may constitute an adaptive response to host immune defense systems. Since subspecies members are distinguished by serologic markers on polysaccharide somatic O antigens and protein flagellar H antigens, individual salmonellae are properly considered serovars. Thus, *S. typhi* should be called *S. enterica* subspecies enterica serovar typhi, while *S. typhimurium* would properly be designated *S. enterica* subspecies enterica serovar typhimurium. Because the majority of serovars have been named after the place in which they were first detected (for example, *Heidelberg* or *Newport*), Salmonella nomenclature seems more geographic than microbiologic. Nevertheless, clinicians continue to use convenient abbreviated names such as *S.heidelberg* or *S.newport* to refer to these organisms. Therefore, this chapter also makes use of this shorthand system.

Another commonly used historic classification system for salmonellae groups isolates on the basis of the major representatives of the 60 phase-1 somatic antigens they express. These serogroups are designated by letters (A, B, C, etc.). Most human pathogenic salmonellae are members of groups A through D; indeed, the serogroup designation is typically the first piece of specific data about an isolate to emerge from the clinical microbiology laboratory..

Some salmonellae are highly adapted to human or other animal hosts. Animal-adapted strains generally do not cause human disease, while human-adapted strains often cause typhoid fever. The rest of the salmonellae are non-host-adapted organisms that may infect both humans and other animals. These organisms are the most common causes of Salmonella diarrhea.

An infection caused by any Salmonella organism other than *S. typhi* is termed nontyphoidal salmonellosis. Such an infection can present as acute diarrhea, a septicemic syndrome, focal abscesses, meningitis, osteomyelitis, endocarditis, or mycotic aneurysm or can be asymptomatic.

EPIDEMIOLOGY

Salmonella, Shigella, Yersinia, and *Campylobacter* species and pathogenic *Escherichia coli* account for about 10-15% of the diarrheal illnesses of children presenting to the emergency department. In US, *Salmonella* is the most common cause of bacterial gastroenteritis. In most cases, *Salmonella* is a self-limiting disease causing mild gastroenteritis; however, it can lead to a wide spectrum of complications including bacteremia, severe local infections, enterocolitis, and enteric fever.

Salmonella organisms are gram-negative bacilli in the family Enterobacteriaceae. The principal reservoirs for nontyphoidal *Salmonella* organisms are poultry, livestock, reptiles, and pets. The mode of transmission is ingestion of foods of animal origin, including poultry, red meats, unpasteurized milk, and eggs that have been contaminated by infected animals or an infected human. Contact with infected reptiles, such as iguanas, pet turtles, and tortoises, and ingestion of contaminated water are other modes of transmission.

Once ingested, *Salmonella* can gain access to the small intestine. If large enough numbers of bacteria are ingested, they can survive in the normally lethal acidic pH of the stomach.

Two human-adapted serovars, *S. paratyphi A* and *S. schottmuelleri* (more often called *S. paratyphi B*), mimic S. typhi and cause a mild form of typhoid fever. Of the more than 2300 known serovars, just 10 account for two-thirds of all human-disease isolates in US, and four serovars (*S. typhimurium, S. enteritidis, S. heidelberg*, and *S. newport*) cause about three-fifths of all disease cases. Periodic increases in the recovery of certain serovars represent either the introduction of a new transmission source or the occurrence of a large outbreak. A fivefold increase in the recovery of *S. enteritidis* isolates between 1986 and 1999 was due to ingestion of contaminated intact eggs, primarily in Ukraine, Russia, and the northeastern US. The number of infections from this source continued to increase, and by 1992 *S. enteritidis* overtook *S. typhimurium* as the most frequently isolated Salmonella serovar in all countries of Europe and in US. These changes suggested a new global pandemic related primarily to infected poultry eggs.

Surveillance data in US indicate that not only the number but also the incidence of nontyphoidal Salmonella isolates is increasing. The incidence of disease is five times higher among young children than among older subjects and increases again in adults over 70 years of age. Between 1990 and 2002, the median age of infected individuals rose from 6 years to 20 years and has since remained the same. The greatest increase has been in the 20- to 39-year-old population; this observation suggests that foods consumed by young adults are important vehicles or that persons in this age group are traveling more to endemic areas.

For example, the emergence of serious systemic infections in southern California due to *S.dublin* carrying a high-virulence plasmid has been associated with

the ingestion of unpasteurized dairy products or nontraditional nutritional treatments containing raw calf-liver extracts contaminated with this serotype. A reasonable estimate of the total incidence of symptomatic nontyphoidal Salmonella infection in US is around 2 million cases per year. The degree of morbidity represented by this figure implies a significant economic impact in terms of lost productivity and medical costs and, by extension, a serious and underestimated cause of mortality.

Because nontyphoidal salmonellae are so often non-host-adapted, many kinds of domestic animals can harbor the organisms and serve as a source for human infection. From 50-75% of broiler and layer chicken flocks in Canada are infected with a wide variety of Salmonella serovars, many of which are virulent for humans. At laying, intact eggs of naturally infected layer flocks may be positive for low numbers of organisms belonging to serovars virulent for humans; however, growth to large numbers quickly takes place if the eggs are not kept at 4°C. At such levels of contamination, viable organisms will survive cooking by any method. If an egg rests for a short time on infected hen feces or even on the dry bedding of an infected hen, Salmonella can penetrate the surface of the shell through microscopic pores normally present in the shell. Because the epidemic due to *S. enteritidis* is so extensive and thus so unlike salmonellosis associated with cracked eggs, and because it has involved free-range as well as commercial henhouse eggs, a transovarian route is most likely and poses a problem for infection control. The conditions in which raising, shipping, slaughtering, and marketing take place contribute to the spread of Salmonella in the food supply. Introduction of the organism into processed foods, including commercial milk-chocolate products, can result in widespread dissemination, and contamination of such common foods as eggs or milk leads to large-scale outbreaks, including nosocomial epidemics. Dried or frozen foods preserve viable salmonellae. For these reasons, salmonellosis is more a disease of the industrialized world than of the developing world. Additional sources of human infection are animals sold as pets, including baby chicks, ducks, and turtles, and medical products of animal origin, such as carmine dye (from insects), pancreatin, bile salts, or tissue extracts from thyroids, adrenals, stomachs, or rattlesnakes.

A potentially serious problem is the selection of antibiotic-resistant salmonellae by unregulated drug use in animal husbandry. Persistent and severe salmonellosis also has been recognized as a problem among patients with AIDS.

PATHOGENESIS

As with *S. typhi*, the events following ingestion of other salmonellae are determined by environmental factors (dose), microbial factors (the ability to invade epithelial cells, to multiply within mononuclear phagocytes, and to resist intestinal peptide antibiotic defensins), and host resistance factors (the effects of gastric acid, the rapid mobilization of phagocytic cells, and the activation and expansion of clones of T cells involved in protection). As few as 10^3 virulent organisms may cause disease, especially in persons who have achlorhydria or who have recently received antimicrobial therapy.

Systemic invasion is more likely in patients with "reticuloendothelial blockade" due to hemolysis (e.g., in malaria, bartonellosis, leptospirosis, or sickle cell anemia) or intracellular infections (e.g., histoplasmosis) and may be facilitated by the expression of bacterial plasminogen receptors, the conversion of bound plasminogen to enzymatically active plasmin, and subsequent degradation of the extracellular matrix. Documented bacteremia varies in incidence from 5-45% but is assumed to occur early in the course of many, and possibly all, Salmonella infections. Bacteremia is quickly cleared by patients infected with most S. enteritidis serovars. *S. dublin, S. infantis, S. virchow, S. panama, and S. newport* may be especially invasive; virulence is associated with an 80-kb plasmid in *S. dublin. S. typhimurium* isolates from the bloodstream are significantly more likely to hybridize with a probe from the highly conserved EcoRI fragment of the S. dublin plasmid than are fecal isolates (rate of hybridization, 76 vs. 42 percent). Bacteremia may lead to focal tissue infections. S. choleraesuis, a highly invasive serotype, usually causes a septicemia syndrome and is commonly isolated from blood but not from stool. Microbial factors that determine the invasiveness of salmonellae include motility and the presence of chromosomal and plasmid genes needed for invasion and replication within mononuclear phagocytes. Many of these genes are turned on by contact of the organism with host cells and are regulated by a two-component sensing/signaling system, PhoP/PhoQ.

Invasion occurs across the small-intestinal mucosa. In Shigella infection, the organism multiplies within epithelial cells; in contrast, in Salmonella infection, epithelial cells represent a barrier to be crossed by the organism, not an ecologic niche for its survival. Invading salmonellae induce a dramatic ruffling of the plasma membrane of the mammalian cell that is regulated by PhoP/PhoQ and reflects cytoskeletal rearrangements leading to uptake of the organism within phagosome-like vesicles, its transit across the cell, and its release into the lamina propria. A multigene chromosomal locus, inv, encodes the invasive phenotype and shares homology with genes of other invasive bacteria. PhoP/PhoQ also regulates the resistance of salmonellae to host intestinal antibacterial defensins. Invasion activates cell signaling pathways, including mitogen-activated protein kinase; phospholipase A2; release of arachidonic acid; production of prostaglandins and leukotrienes (especially

leukotriene D4); and a sharp increase in intracellular calcium level. Many of these changes are known to alter electrolyte transport and may cause diarrhea. Invasion and inflammation are necessary but not sufficient to cause Salmonella diarrhea in experimental animal models, and transepithelial signals that recruit neutrophils are also involved via induced local chemokine (IL-8) production. Some salmonellae appear to produce a molecule similar to cholera toxin that increases electrolyte and fluid secretion. However, the importance of this molecule in causing diarrhea remains uncertain.

CLINICAL MANIFISTATION

Carefully obtain the patient's history to determine any potential sources of *Salmonella* and to help determine if the correct diagnosis has been made. A patient should be questioned about any recent travel abroad, possible animal exposures, including contact with pet iguanas, turtles, tortoises, or other reptiles, about any family members have current or recent gastroenteritisa and any recent outbreaks have occurred in the community.

Gastroenteritis The incubation period of Salmonella gastroenteritis is generally short (24 to 48 h). Sporadic illness is likely to go undiagnosed because specimens are not taken for culture. Large outbreaks, often considered "food poisoning" and characterized by self-limited fever and diarrhea, are more likely to be investigated and diagnosed. Diarrhea may be associated with nausea, vomiting, and abdominal cramps and occasionally is bloody or even dysenteric when the colon becomes involved. In most cases, children have cramping abdominal pain, nausea, vomiting, and loose watery stools. Fever, which rarely exceeds 39°C, occurs in approximately one half of infected patients.

Direct microscopic examination of stool shows many leukocytes, which offer a clue to the invasive nature of the infection. The illness is generally mild and resolves without specific therapy, but it may cause severe dehydration or disseminate and lead to death in debilitated elderly patients or neonates.

Blood cultures obtained initially often become positive as the patient's condition is improving. Treatment may be discontinued after identification of the organism unless there is an underlying immunosuppressive disease (e.g., sickle cell disease, AIDS, or a malignancy such as a lymphoma) or the patient is receiving glucocorticoid or immunosuppressive drug therapy. In these conditions, an appropriate antibiotic should be administered for 7 to 10 days.

Carriage of salmonellae in the stool continues for several weeks after the resolution of symptomatic disease but rarely persists for longer than 2 months.

On physical examination, patients may have signs of dehydration, such as delayed capillary refill, sunken eyes, dry mucous membranes, or tachycardia. Patients may have tenderness to palpation on abdominal examination, which sometimes can

be difficult to differentiate from appendicitis. Rectal examination may reveal heme-positive stools, gross blood, or mucoid stools.

Localization Of Systemic Infections Bloodborne salmonellae can invade any tissue or organ. The most common isolates are S. typhimurium, S. enteritidis, S. virchow, S. dublin, and S. choleraesuis. Localized infections usually follow intestinal infection, although there may be no prior diarrhea. Endocarditis is rare but, when it occurs, may include destructive cardiac lesions such as valve perforations or ring or septal abscesses. Therapy may require both the administration of appropriate antimicrobials and surgery.

Arterial infection generally occurs in persons with preexisting arteriosclerotic infrarenal aortic aneurysms and is especially likely in men over the age of 50 years. S. choleraesuis accounts for about 20 % of arterial infections but is isolated from fewer than 1 percent of patients with Salmonella diarrhea; this distribution reflects the capacity of this organism to cause systemic invasive disease. S. typhimurium accounts for approximately 25 % of isolates in arterial infections¾a finding consistent with its high prevalence in gastrointestinal salmonellosis. In addition to treatment with antimicrobials, eradication usually requires prompt excision and drainage with bypass through uninvolved tissue. The disease should be suspected when elderly men develop prolonged fever accompanied by back, abdomen, or chest pain following gastroenteritis; when bacteremia occurs or recurs after therapy for the initial illness; or when bacteremia develops in patients with vertebral osteomyelitis or prosthetic valves.

Cholecystitis, other hepatobiliary infection, and splenic abscess are the most common intraabdominal localized infections due to Salmonella. In addition to *S.typhimurium* and *S. enteritidis, S. typhi* is an important cause. Urinary tract infections due to Salmonella sometimes develop. These illnesses are especially likely in patients who have urolithiasis, structural abnormalities, or immunosuppressive diseases or who are receiving immunosuppressive therapy. Salmonella urinary tract infections can coexist with renal tuberculosis or with Schistosoma haematobium infection. Pneumonia or empyema caused by Salmonella is rare. These conditions usually involve patients with preexisting abnormalities of the lungs or pleura or with conditions that predispose to infection, including malignancy, diabetes, glucocorticoid use, sickle cell disease, or alcohol abuse.

Meningitis caused by Salmonella is also rare and is most prevalent among infants and young children. Gram's stains of cerebrospinal fluid are usually positive. Mortality rates of 40 and 60 percent are reported for children and adults, respectively. In survivors, residua include seizures, hydrocephalus, subdural empyemas, and permanent disabilities such as retardation, paresis, athetosis, and visual disturbances.

Septic arthritis due to Salmonella is associated with positive joint-fluid cultures and should not be confused with reactive arthritis (a culture-negative inflammatory

joint disease following invasive diarrheas, especially in HLA-B27-positive patients). Common underlying conditions include glucocorticoid or immunosuppressive drug therapy, sickle cell disease, prosthetic joints, or aseptic necrosis. Drainage may be needed in addition to appropriate antibiotic therapy. Salmonella osteomyelitis is predictably associated with sickle cell disease. It generally affects the long bones and occurs primarily in young patients. Blood cultures are often positive; the most common isolate is S. typhimurium.

Bacteremia Sepsis, with prolonged fever and positive blood cultures but generally without prior diarrhea, occurs most commonly with *S. choleraesuis* or *S.dublin* infection. While this presentation is "typhoidal," typical manifestations of typhoid (rose spots, relative bradycardia, leukopenia) are lacking, and the illness is more acute in onset than typhoid. Enteric fever is caused by several *Salmonella* serotypes. The incubation period for enteric fever is 3-60 days, but symptoms typically occur in 1-2 weeks. Patients may present with fever as high as 39-49^{o}C which rises in a steplike fashion. Other symptoms include anorexia, abdominal pain, malaise, myalgias, headache, cough, diarrhea or constipation, and delirium. A typical finding of enteric fever is relative bradycardia for the height of the fever. Hepatosplenomegaly may be found on examination. Patients with enteric fever may develop rose spots; these spots are blanching pink papules most commonly found on the anterior thorax. They usually fade about 3-4 days after appearance, are 2-4 mm in diameter, and occur in groups of 5-20. *S. choleraesuis* or *S. dublin* sepsis is a severe disease that is associated with high mortality. Intermittent symptomatic Salmonella bacteremia is seen in patients with hepatosplenic or urinary schistosomiasis.

Clinically severe Salmonella sepsis due to *S. typhimurium* also occurs in AIDS patients, is often recurrent, and is an AIDS-defining event. The infection may be refractory to treatment or recurrent despite appropriate therapy.

LABORATORY DIAGNOSIS

Specific diagnosis depends on the isolation of salmonellae from stool, blood, or tissue fluids. All clinical laboratories should be able to make the initial isolation and identify common serovars. Uncommon serovars usually must be sent to reference laboratories for identification.

Complete blood count with differential WBC is often 10,000-15,000 in simple gastroenteritis. Patients with enteric fever commonly have anemia, thrombocytopenia, or neutropenia, although a shift to more immature forms can be seen on the differential count.

Isolation of *Salmonella* from cultures of stool, blood, urine, or bone marrow is diagnostic. Cultures of rose spots and/or bone marrow aspirate may be positive in enteric fever even when stool cultures are negative for *Salmonella.*

Stool may be hemoccult positive and may be stool positive for fecal polymorphonuclear cells.

Electrolyte tests may reveal metabolic acidosis or other abnormalities consistent with dehydration. Patients with enteric fever may have mild hepatitis.

Tests for *Salmonella* agglutinins (febrile agglutinins, Widal test) may suggest infection with *S typhi;* however, they are not recommended because of the number of false-positive and false-negative results.

Imaging studies are not necessary for most patients with simple gastroenteritis and enteric fever without any severe complications. Consider chest radiography if pneumonia is suggested as the result of bacteremia. Perform abdominal radiography if the patient presents with peritoneal signs on physical examination. Consider intestinal perforation as a complication of enteric fever. Perform a bone scan if osteomyelitis is considered as a complication of bacteremia.

TREATMENT

In diet restrict initial oral intake to electrolyte solutions, such as Oralyt, Regidron or clear mineral water. Add solid foods only when the diarrhea appears to be improving and dehydration is not present. Initially, children can be started on a BRAT diet (ie, bananas, rice, applesauce, toast) and then slowly advanced to a regular diet as tolerated.

For uncomplicated gastroenteritis caused by nontyphoidal *Salmonella* species, antimicrobial therapy is not indicated because it does not shorten the duration of illness. Treatment involves monitoring hydration status and IV therapy to correct electrolyte imbalance or restore intravascular volume. Antidiarrheal agents may actually prolong GI transit time and the illness. Antimicrobial agents and hospital admission may be recommended in *Salmonella* gastroenteritis in infants younger than 3 months, infants younger than 12 months with temperatures higher than 39°C and unknown blood culture results, and patients with hemoglobinopathies, HIV infection or other causes of immunosuppression, neoplasms, or chronic GI illnesses. The recommended antibiotics for individuals at high risk of invasive disease include ampicillin, amoxicillin, trimethoprim-sulfamethoxazole (TMP-SMZ), cefotaxime, and ceftriaxone. Treatment of invasive *Salmonella* disease (bacteremia, extraintestinal manifestations) Antibiotic treatment includes ampicillin, amoxicillin, cefotaxime, ceftriaxone, chloramphenicol, TMP-SMZ, or a fluoroquinolone. A 14-day course of antibiotics is recommended for patients with bacteremia. Patients with localized infection, such as osteomyelitis or abscess, or patients with bacteremia and HIV infections should receive 4-6 weeks of therapy. For *Salmonella* meningitis, ceftriaxone or cefotaxime is recommended for 4 weeks or longer.

Choice of antibiotic is complicated by the increasing prevalence of antimicrobial resistance (including multiple-drug resistance) among nontyphoidal

salmonellae as well as in S. typhi. The use of antibiotics in commercial animal rearing, the prevalence of Salmonella in the global food chain, and the growing international commerce in meat, poultry, and processed food products are contributing to the wider distribution of resistant clones.

In the face of these complications, treatment for focal systemic infections requires the selection of the most appropriate antibiotic and, at times, drainage or resection of infected tissue. Bactericidal antibiotics, administered by the parenteral route, are usually chosen. The regimen may include ampicillin (6 to 12 g/d for adults or 100 mg/kg for young children, in divided doses) or appropriate doses of third-generation cephalosporins such as ceftriaxone. Unless resistance is prevalent, chloramphenicol (2 to 4 g/d for adults or 50 mg/kg for children, in divided doses) remains a good choice in developing countries because it can be given orally and is inexpensive. The new quinolones are highly effective, in part because they act on the intracellular compartment and thus affect bacteria within host mononuclear cells; while concerns remain about their safety in infants and children, increasing evidence suggests that the risk of cartilage damage is small.

The proper treatment of Salmonella gastroenteritis is not clear; the traditional dogma has been that antibiotics do not shorten the illness but do increase the duration of convalescent carriage. For this reason, it has generally been recommended that antimicrobial agents not be used in this illness. Initial highly favorable results with the new quinolones are now balanced by a number of contradictory studies. The best recommendation at present is that antimicrobial therapy be reserved for patients with severe disease and for patients at high risk of invasive disease.

Positive blood cultures in the setting of otherwise uncomplicated gastroenteritis do not warrant antibiotic therapy. When an infant under 3 months of age has diarrhea and signs of systemic invasion, a workup to localize the septic process should be initiated and presumptive treatment with a third-generation cephalosporin administered until culture results are available. Fever is often absent in very young infants and is not a reliable indicator of systemic infection. Asymptomatic patients with salmonellae other than *S. typhi* in the stool should not receive antimicrobial treatment, since active disease may be provoked and the carriage state is generally self-limiting. A quinolone would be a good choice for the treatment of long-term carriers.

PREVENTION

It is not possible to eradicate nontyphoidal salmonellosis because the organisms are so widespread in nature. Reduced animal-feed use of antimicrobials employed for the treatment of human infection and improved animal-rearing and animal-marketing practices would be useful. Vigilance in food preparation and in quality testing of the known and commonly contaminated foods should help as well.

It is recommended that eggs not be eaten raw or partially cooked, especially by persons at high risk of infection; however, even fully cooked eggs can harbor viable Salmonella. If universal body-substance precautions are not routinely utilized, hospital staff caring for patients with salmonellosis should observe "enteric precautions," wearing gowns and gloves when handling stool and urine and carefully washing their hands after patient contact.

During outbreaks, food handlers may be responsible for transmission. Much effort is given to the identification (by stool culture) of asymptomatic food handlers who are carriers during food-borne outbreaks; these individuals are usually kept away from work until they become culture-negative. However, it is more important that standards are maintained to ensure the environmental and personal hygiene of food handlers and thus to prevent the problem in the first place, since carriage may be intermittent and is often not uniform within a single stool sample and since foods contaminated with the organism require improper handling to permit the growth of a sufficient inoculum to cause disease. It may be justifiable to restrict carriers from the workplace only in the course of a hospital outbreak or when workers refuse to improve their personal hygiene.

The development of effective vaccines for nontyphoidal salmonellosis may be difficult because of the great number of serovars involved in infection. Some progress has been made with galactose epimerase and aroA vaccine mutants of S. typhimurium for use in animals, and these vaccines may ultimately be tested in humans. It would be most useful to have vaccines for S. choleraesuis, S. typhimurium, and S. enteritidis. S. dublin and S. virchow, while quite virulent, are still uncommon causes of human disease.

BOTULISM

DEFINITION *Botulism is a severe toxic infectious disease which characterized by cranial nerve involvement and progresses caudally to involve the extremities.*

Food-borne botulism was the first of the entities to be described. Byzantine Emperor Leo VI documented cases of fatal food poisoning in the ninth century. In the 1820s, Justinus Kerner, a German physician and romantic poet, scrutinized a number of food poisoning cases and found that most were caused by improperly prepared sausages. As a result, he named the disease botulism, after the Latin word for sausage, botulinus. Kerner correctly deduced the presence of the culpable toxin in the sausages and extracted a compound he termed wurstgift (German for sausage poison).

Kerner continued studying botulism. In an experiment that surely would cause controversy in any modern human investigations committee, Kerner injected himself with the wurstgift extract and demonstrated many of the signs and symptoms so convincingly that the causal relationship was proven. Lastly, Kerner presaged the

therapeutic uses of this toxin in individuals with motor overactivity by some 150 years. Despite his contributions to the field, questions remained regarding how the toxin entered the sausages.

In 1897, the microbiologist Emile-Pierre van Ermengen identified a gram-positive, spore-forming, anaerobic bacterium in a ham that caused 23 cases of botulism in a Belgian nightclub. He termed the bacterium Bacillus botulinus; it was later retermed Clostridium botulinum.

Wound botulism was the next type to be described. C botulinum was cultured from the wounds of asymptomatic patients as early as 1942, but wound botulism was not described as it is known today until 1951. Merson and Dowell reported the 1943 case of a girl who had open leg and ankle fractures. The girl showed clear clinical signs of botulism without any history of food-borne illness or symptomatic family members. Last case of infant botulism was described separately in 1976.

ETIOLOGY

C. botulinum, a heterogeneous group of anaerobic gram-positive organisms that form subterminal spores, is found in soil and marine environments throughout the world and elaborates the most potent bacterial toxin known. Organisms of types A through G have been distinguished by the antigenic specificities of their toxins. *C. botulinum* strains with proteolytic activity can digest food and produce a spoiled appearance; nonproteolytic types leave the appearance of food unchanged. Of the eight distinct toxin types described (A, B, C_1, C_2, D, E, F, and G), all except for C_2 are neurotoxins; C_2 is a cytotoxin of unknown clinical significance. Botulinum neurotoxin, whether ingested or produced in the intestine or a wound, enters the vascular system and is transported to peripheral cholinergic nerve terminals, including neuromuscular junctions, postganglionic parasympathetic nerve endings, and peripheral ganglia. The central nervous system is not involved. Active neurotoxin (150 kDa) is composed of a heavy chain (100 kDa) and a light chain (50 kDa).

Toxin can be inactivated during home cooking by exposure to a temperature of 100°C for 10 min. In the gastrointestinal tract, toxin is complexed with nontoxin proteins and resists degradation. Spores are highly heat-resistant, and their inactivation requires exposure to a temperature of 120°C (e.g., in steam sterilizers or pressure cookers).

Toxin types A, B, E, and (in rare instances) F cause human disease; type G (now called *C. argentinense*) has been associated with sudden death, but not with neuroparalytic illness, in a few patients in Switzerland; and types C and D cause animal disease.

EPIDEMIOLOGY

Human botulism occurs worldwide. The geographic distribution of cases by toxin type parallels the distribution of organism types found in the environment in the world. Types A, B, E predominates in Ukraine. Type E is found in some region Russia. In many countries, food-borne botulism has been associated primarily with home-canned food, particularly mushrooms, meat and fish, condiments, and less

commonly with vegetables, and fruits. Type E outbreaks are frequently associated with fish products.

Commercial products occasionally cause outbreaks, but some of these outbreaks have resulted from improper handling after purchase.

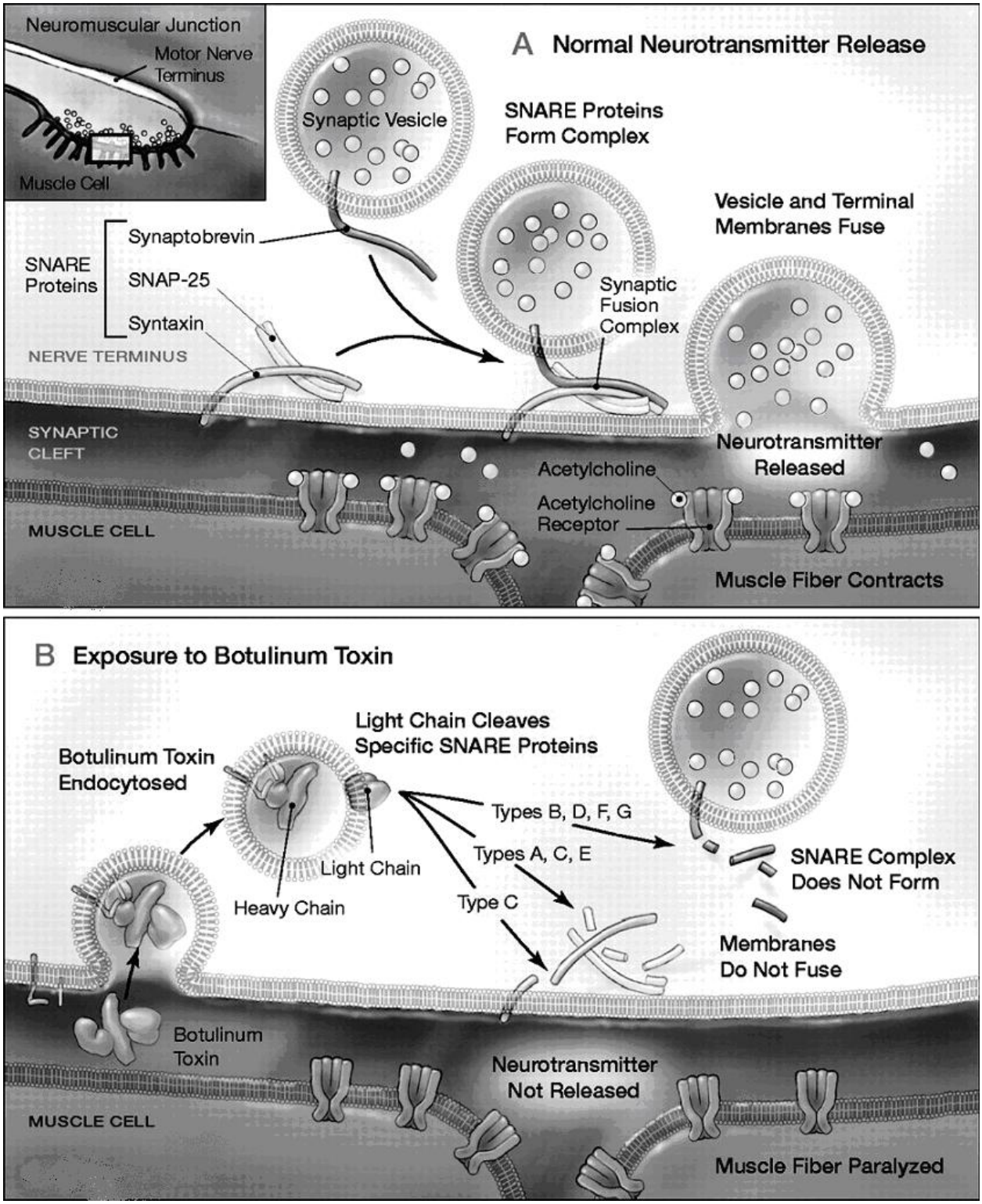


Figure 7.

PATHOGENESIS

Food-borne botulism is not seen after eating fresh foods. Some methods of food preparation, such as home canning, produce an anaerobic, low-acid (ie, pH >4.6), low-solute environment in which the toxin can be propagated. Botulism is caused by potent protein neurotoxins elaborated by Clostridium botulinum. Botulinum toxin is absorbed direcly across mucous membranes of mouth cavity and stomach. Locally acting toxin may produce some lession as a vessel paralysis but cranial nerves paralysis is result of toxin destribution in bloodstream. Toxin act on acetylcholine receptors in neurones. Cranial nerves are preferentially affected because toxin binds more rapidly to sits where the cycles of repolarization are frequent. Binding is irreverseble. All botulinum toxins are zinc metalloproteases that bind to different membrane proteins involved in fusion of the synaptic vesicle to the presynaptic membrane. This fusion allows release of acetylcholine into the synaptic junction. The toxins are classified as types A through G, although only types A, B, E, and F cause human disease. Types A and E bind to synaptosomal-associated protein 25 (SNAP25), type C binds to synapses, and types B, D, and F bind to vesicle-associated membrane protein (VAMP). Inhibition of the proteins effectively blocks acetylcholine transmission across the synapse and functionally denervates the muscle. The magnitude of the clinical effect depends on the proportion of synapses blocked, and the effects can range from weakness to flaccid paralysis and atrophy. Recovery occurs when nerve terminals spout from the axon to form new motor end-plates. (**Figure 7**)

Botulinum toxin blocks impulse transmition mediated by acetylcholine. Motor and parasympatic fiber of cranial nerves, neuromuscular synapses, and spinal motoneurons are the main target for toxin.

Acute respiratory failure may develops in severe cases due to toxic lesion of medulla, respiratory muscular system paralysis. Serious metabolic disorders occur in patient with botulism due to hypoxia.

CLINICAL MANIFESTATIONS

Cases may be classified as (1) *food-borne botulism*, from ingestion of preformed toxin in food contaminated with *C. botulinum*; (2) *wound botulism*, from toxin produced in wounds contaminated with the organism; (3) *infant botulism*, from ingestion of spores and production of toxin in the intestine of infants.

Food-Borne Botulism Incubation period of food borne botulism is range 2 hours to 8 days. There is strictly dependence between severity of diseases and incubation period length.

Patients usually are afebrile. Gastrointestinal tract symptoms usually occur first, beginning 18-36 hours after ingestion and consist of nausea, vomiting, and diarrhea followed by constipation. Constipation is typical symptom in botulism. Patient complains on thirsty, dry mouth, extremity and general weakness, abdominal cramps cramps, dizziness, blurred vision, and diplopia. Motor function symptoms follow, with the cranial nerves usually affected first. As a result, many patients

present with diplopia (eg, often, impaired lateral gaze secondary to sixth cranial nerve involvement) and blurred vision secondary to loss of accommodation.

Cranial nerve involvement, which almost always marks the onset of symptoms, usually produces diplopia, dysarthria, and/or dysphagia; weakness progresses, often rapidly, from the head to involve the neck, arms, thorax, and legs; the weakness is occasionally asymmetric. Since the toxin affects only motor and autonomic systems, sensation and mentation remain intact. Patients with distribution of bulbar palsy complain on difficulties of swallowing, chocking, hoarseness of voice, and speaking trough the nose (rhinolalia). Autonomic dysfunction may lead to orthostatic hypotension, urinary retention, or constipation.

Finally, a rapidly progressive descending weakness or paralysis occurs.

On physical examination patient is pale, and weak. Muscle weakness or flaccid symmetric paralysis and cranial nerve involvement (eg, ptosis, mydriasis, decreased ocular motility, dysphonia, dysphagia, dysarthria) are typical for botulism. Ptosis is frequent; the pupillary reflexes may be depressed, and fixed or dilated pupils are noted in half of patients. Symmetric descending paralysis is characteristic and can lead to respiratory failure and death.

Wound botulism Except for the prerequisite history of a wound, this type of botulism presents in the same way as food-borne botulism. Wound botulism is the least common type of botulism and may follow a penetrating or blunt injury. The incubation period is 4-14 days in wound botulism.

Infant botulism The incubation period is 2-4 weeks in infant botulism. The peak age of incidence is 2-4 months. (This coincides with the peak age for sudden infant death syndrome.) Constipation is the usual presenting symptom in infant botulism, often preceding motor function symptoms by several days or weeks. Other signs of autonomic dysfunction usually present early as well, including those mentioned above. Gag reflexes frequently are impaired, which can lead to aspiration if the airway is unprotected. Infants with botulism are afebrile, suck poorly, and are lethargic and listless; they develop the same descending weakness and paralysis that occurs with food-borne disease. Breastfeeding may protect infants from lethal fulminant infant botulism.

DIAGNOSIS

Although clinical suspicion should be sufficient to prompt supportive therapy for botulism, other differential diagnoses must be excluded. **Differential diagnosis:** Guillain-Barré syndrome, (especially Miller-Fisher variant), acute poliomyelitis, myasthenia gravis, Lambert-Eaton syndrome, tick encephalitis, stroke, aminoglycoside toxicity, atropine poisoning, paralytic shellfish poisoning (saxitoxin), puffer fish ingestion (tetrodotoxin), congenital myopathy.

A diagnosis of botulism must be considered in afebrile, mentally intact patients who have symmetric descending paralysis without sensory findings. The diagnosis must be suspected on clinical grounds in the context of an appropriate history. Conditions often confused with botulism include myasthenia gravis, which may be ruled out by electromyography and antibody studies, and Guillain-Barre syndrome, which is characterized by ascending paralysis, sensory abnormalities, and elevation

of the protein concentration in cerebrospinal fluid. The Fisher variant of Guillain-Barre – a descending paralysis – can indeed be difficult to differentiate from botulism. Other conditions that may resemble botulism include Lambert-Eaton syndrome, poliomyelitis, tick paralysis, diphtheria, and intoxications from mushrooms, medications, or chemicals. Hypermagnesemia should be considered.

The demonstration of toxin in serum by bioassay in mice is definitive, but this test may be negative, particularly in wound and infant botulism. It is performed only by specific laboratories, which can be identified through regional public health authorities. The demonstration of the organism or its toxin in vomitus, gastric fluid, or stool is strongly suggestive of the diagnosis, because intestinal carriage is rare. Obtain stool cultures in all patients, adding wound cultures if wound botulism is suspected. Approximately 60% of food-borne cases yield positive culture results; a positive finding in the presence of flaccid paralysis is diagnostic. At this time, specific assays for the toxin, including enzyme-linked immunoassays (ELISA) and PCR, are investigational. Currently, the mouse inoculation test is the best test available. In the assay, mice are injected with a serum sample from the patient, and test results are considered positive for toxin if the mice die of respiratory arrest within 24 hours. Determination of the exact type of toxin is obtained by pretreating each mouse in a set of mice with a different type-specific antitoxin, then injecting the serum. The mouse left alive the next day is the one that was pretreated with the antitoxin to the toxin affecting the patient.

Wound cultures yielding the organism are suggestive of botulism. The edrophonium chloride (Tensilon) test for myasthenia gravis may be falsely positive in botulism but is usually less dramatically positive than in the former condition. Nerve conduction velocity is normal, but action potentials on routine electromyography are decreased with a supramaximal stimulus, and facilitation is evident after repetitive stimulation at high frequency. Electromyelography (EMG) shows a nonspecific decreased amplitude of action potentials. Rapid repetitive EMG at frequencies of 20-50 Hz is more specific for botulism and useful in excluding Guillain-Barré syndrome, but this response does not distinguish botulism from Lambert-Eaton syndrome. Infant botulism is characterized by a pattern known as BSAP (brief, small, abundant, motor-unit action potential) on EMG in clinically affected muscles. Lumbar puncture usually can exclude Guillain-Barré syndrome, a condition that tends to elicit a higher protein level in cerebrospinal fluid (especially later in the course of the disease) than the reference range levels seen with botulism. The white blood cell count and sedimentation rate are normal.

TREATMENT

In patients with botulism, supportive care is essential, especially ventilatory support. Initiate ventilatory support promptly because respiratory muscle weakness progresses rapidly, and the gag reflex frequently is impaired and predisposes patients to aspiration. Patients need continued suctioning and may require intubation or tracheostomy.

Patients should be hospitalized and monitored closely, both clinically and by spirometry, pulse oximetry, and measurement of arterial blood gases for incipient

respiratory failure. Intubation and mechanical ventilation should be strongly considered when the vital capacity is less than 30 percent of predicted, especially when paralysis is progressing rapidly and hypoxemia with absolute or relative hypercarbia is documented. Serial measurements of the maximal static inspiratory pressure may be useful in predicting respiratory failure.

In food-borne illness, trivalent (types A, B, and E) equine antitoxin should be administered as soon as possible after specimens are obtained for laboratory analysis. Antitoxin dramatically alters the course of the disease, especially if administered within the first 24 hours. The initiation of treatment should not await laboratory confirmation, which may take days. After testing for hypersensitivity to horse serum, two vials of antitoxin are given, one intravenously and one intramuscularly; repeated doses probably are not necessary but may be given 2 to 4 h later. Anaphylaxis and serum sickness are risks inherent in use of the equine product, and desensitization of allergic patients may be required. If there is no ileus, cathartics and enemas may be given to purge the gut of toxin; emetics or gastric lavage can also be used if the time since ingestion is brief (only a few hours). Use of antibiotics to eliminate an intestinal source for possible continued toxin production and of guanidine hydrochloride and other drugs to reverse paralysis is of unproven value.

Antibiotics may be considered to treat secondary bacterial infections. Aminoglycosides, such as gentamicin or tobramycin, may potentiate the neuromuscular blockade and, therefore, are contraindicated. Tube feeding may be useful if gastrointestinal tract motility is intact. If motility is not intact, consider parenteral feeding.

Treatment of infant botulism requires supportive care. Neither equine antitoxin nor antibiotics have been shown to be beneficial, and the value of human botulism immune globulin, an experimental preparation, is still being evaluated. In wound botulism, equine antitoxin is administered. The wound should be thoroughly explored and debrided, and an antibiotic such as penicillin should be given to eradicate *C. botulinum* from the site, even though the benefit of this therapy is unproven. Results of wound cultures should guide the use of other antibiotics.

Type A disease is generally more severe than type B, and mortality from botulism is higher among patients above age 60 than among younger patients. Timing of antitoxin administration greatly influences the prognosis. Retrospective analysis has shown that use of antitoxin within 24 hours is associated with a 10% mortality rate rather than a 15% mortality rate if antitoxin is used more than 24 hours later and a 46% mortality rate if antitoxin is not used at all. Hospital stay also is affected by timing, with a median stay of 10 days when antitoxin is administered within 24 hours rather than 41 days if administered after 24 hours and 56 days if not used at all. Late symptoms may remain after recovery from acute illness, primarily symptoms of muscle weakness including diplopia and fatigue with exertion. Although some patients have reported feeling breathless, pulmonary function tests show that results in lung volumes, forced expiratory volume in 1 second (FEV1)/forced vital capacity (FVC), maximum inspiratory and expiratory pressures, and ventilatory response to exercise lie within reference ranges. Artificial respiratory support may be required for

months in severe cases. Some patients experience residual weakness and autonomic dysfunction for as long as a year after disease onset.

CHOLERA

DEFINITION *Cholera is an acute diarrheal disease caused by an enterotoxin elaborated by V. cholerae serogroup O_1 or O_{139} that have colonized the small bowel, resulting in profound, rapidly progressive dehydration, hypovolaemic shock, metabolic acidosis and if untreated, death.*

Epidemic cholera remains a major public health concern. Cholera has been endemic for two centuries in the Ganges delta of West Bengal and Bangladesh, has caused multiple epidemics thought the Indian subcontinent, and has been responsible for seven global pandemics since 1817. The current seventh pandemic, the first due to the el Tor biotype, began in Indonesia in 1961, rapidly extended from Sulawesi westward throughout Asia displacing the endemic classic strain in many areas, ultimately involved in the early 1970s Africa and Mediterranean Europe, and in 1991 extended to Latin America. In October – December 1992, a new epidemic serogroup O_{139} Bengal emerged in southern India and Bangladesh along the Bay of Bengal. It caused more than 100,000 cases of cholera in the first 3 months of 1993, affecting Pakistan, Nepal, western China, Thailand, and Malaysia by the end of 1994. Emergence of O_{139} serogroup was an unprecedented event in the history of cholera and at that time, thought to be the beginning of the next eighth global pandemic. Indeed, just as O_1 el Tor replaced the classic biotype that preceded it, O_{139} Bengal in 1993 rapidly replaced O_1 el Tor as the most common environmental isolate and the predominant cause of clinical cholera in the areas in which it had appeared. Surprisingly and unexpectedly, however, by the beginning of 1994, O_1 el Tor had resumed its dominance in Bangladesh, relegating O_{139} Bengal cholera to the status of a background endemic infection.

ETIOLOGY

V. cholerae are actively motile, facultatively anaerobic short (0.2-0.4 × 1.5-4.0 μm), slightly curved, gram-negative rods with one or two polar flagella. The species V. cholerae comprises a host of organisms classified on the basis of the carbohydrate determinants of their somatic O antigens. Some 140 serogroups have been recognized. All vibrios are oxidase-positive. V. cholerae can be distinguished from the otherwise similar V. mimicus by its ability to ferment sucrose. They are divided into those that agglutinate in antisera to the O_1 group antigen (V. cholerae O_1) and those that do not (non-O_1 V. cholerae). V. cholerae O_1 exists in two biotypes, classic and el Tor, that are distinguished on the basis of a number of characteristics, including phage susceptibility and hemolysin production. Each biotype is further

subdivided into two serotypes, termed Inaba and Ogawa. Although some strains of non-O_1 V. cholerae occasionally cause sporadic outbreaks of diarrhea, serogroup O_1 was, until recently, the exclusive cause of epidemic cholera. That paradigm changed in late 1992 with the identification of serogroup O_{139} Bengal as the cause of a large epidemic of cholera on the Indian subcontinent. Both phenotypically and genotypically, strain O_{139} Bengal is closely related to the O_1 el Tor strains, and it seems to have arisen from them by horizontal gene transfer. It shares the virulence attributes and general pathogenic mechanisms of O_1 vibrios, including possession of the same enterotoxin genetic element. Those differences are its production of the novel O_{139} lipopolysaccharide and of an immunologically related O-antigen polysaccharide capsule. Encapsulation is not a feature of O_1 strains and may explain the resistance of O_{139} strains to human serum in vitro as well as the occasional development of O_{139} bacteremia.

EPIDEMIOLOGY

Man is the only known mammalian host and victim of V. cholerae. The natural habitat of V. cholerae classic biotype is coastal salt water and brackish estuaries, where the organism lives in close relation to plankton and where it may survive in a viable but noncultivable form. The epidemic el Tor strain proved capable of establishing itself in inland waters rather than in its classic niche of coastal salt waters. V. cholerae proliferate in the summer months when water temperatures exceed about 20°C. Shellfish have the capacity to harbor V. cholerae in high concentration for long periods without obvious damage to the host. Most major epidemics of this disease have been waterborne (ingestion of water contaminated by human feces), and water plays a large part in the transmission of V. cholerae in the epidemic rural areas in the Ganges delta. Consumption of contaminated food in the home, in restaurants, or from street vendors can also contribute to spread. People with mild or asymptomatic infections (contact carriers) may help to disseminate epidemic disease. Asymptomatic infections are frequent and more common with the el Tor than the classic biotype. The clinical case : infection with the classical biotype is about 1:6; with infection due to el Tor biotype, this ratio may be as low as 1:50. A prolonged bladder carrier state occasionally develops in adults convalescing from cholera caused by the el Tor biotype.

For unexplained reasons, susceptibility to cholera is significantly influenced by AB0 blood group status; those with type 0 blood are at greatest risk, while those with type AB are at least risk. While the infectious dose is relatively high, it is markedly reduced in hypochlorhydric persons, in those using antacids, and when gastric acidity is buffered by a meal. In the endemic areas cholera is predominantly a disease of children. Attack rates are 10 times greater in the 1 to 5-year age group than in those over 20 years of age. Children under 2 years of age are less likely to develop severe

cholera than are older children, perhaps because of passive immunity acquired from breast milk. When the disease spreads to previously uninvolved areas, the attack rates arc initially at least as high in adults as in children. Naturally acquired immunity to V. cholerae O_1 does not cross-protect against the O_{139} Bengal strain. Patients convalescent from cholera develop high levels of both agglutinating and vibriocidal antibodies against cell-wall constituents of the vibrio; presumably the short-term protection that follows infection with V. cholerae results from the leakage of such IgG antibodies into the intestinal lumen.

PATHOGENESIS

Cholera is a toxin-mediated disease. V. cholerae cause disease when a large number of viable organisms are ingested, survive passage through the stomach, colonize the small bowel, and produce cholera toxin, a potent protein enterotoxin. Because of the remarkable susceptibility of V. cholerae to gastric acid, an enormous number of microorganisms (more then thousand million) must be ingested to cause illness in previously healthy individuals. If, however, gastric acid is neutralized by sodium bicarbonate, or by a high-protein meal, ingestion of a million viable organisms may produce clinical disease in roughly 50% of normal individuals. The individual with relative or absolute achlorhydria is, therefore, abnormally susceptible to cholera. V. cholerae must next traverse the mucous layer of the upper small bowel. Several properties of the organism enhance its ability to accomplish this feat, including its motility, its chemotaxis, and its production of hemagglutinin/protease. This last substance, originally named cholera lectin, is both an agglutinin and a zinc-dependent protease. It is able to cleave mucin and fibronectin. Hemagglutinin/protease may also serve to detach vibrios bound to the small-bowel surface, thus facilitating their spread within the intestine and excretion in the stool. Having successfully negotiated the barriers of gastric acidity and small-intestinal mucus, the vibrios must finally adhere to the bowel wall. Their attachment is mediated by the toxin-coregulated pilus.

Once vibrios have colonized the small bowel enterotoxin is produced. This is a protein of 84000 Da which consists of a monomeric enzymatic moiety (activating - A) and a pentameric binding moiety (B). Each B subunit (roughly 11500 Da) is capable of combining extraordinarily rapidly to a GM-1 monosialoganglioside molecule (glycolipid receptor on the surface of jejunal epithelial cells). At body temperature, binding becomes irreversible within minutes after the initial contact and B subunits become incorporated into the cell membrane. The A moiety is divided into two unequal subunits: a larger, or A-1, subunit of roughly 23000 Da, and a smaller, or A-2, subunit of roughly 6000 Da. Following binding, the A-l subunit migrates through the epithelial cell membrane to the inner surface, where it stimulates adenosine diphosphate ribosylation of adenylate cyclase component bearing the

guanyl nucleotide site. This results in a modification of the guanosine triphosphate-binding protein, inhibition of the guanosine triphosphate turn-off reaction, and thus increasing of adenylate cyclase activity. The resultant intracellular accumulation of high levels of cyclic adenosine monophosphate leads to rapid excretion of electrolytes into the small-bowel lumen.

The net secretion of fluid and electrolytes by gut mucosal cells in cholera reflects a dual effect on two different intestinal ion-transport sites. In the villous cells the absorption of sodium chloride via the neutral sodium chloride cotransport system is inhibited. In the crypt cells the increased intracellular adenosine monophosphate results in active stimulation of chloride secretion. The net effect of inhibition of sodium absorption and stimulation of chloride secretion is the rapid outpouring of isotonic fluid into the intestinal lumen at a rate that exceeds the absorptive capacity of the colon, thus resulting in the loss of an isotonic fluid. In adults with voluminous diarrhea the electrolyte in cholera stool is remarkably consistent, being nearly isotonic with plasma, with sodium and chloride concentrations slightly less than those of plasma, bicarbonate concentration twice that of plasma, and potassium concentration three to five times that of plasma. In very young children with cholera the mean sodium and chloride concentrations are 15 to 20 mmol/l less than those observed in older patients. Although perturbation of the adenylate cyclase pathway is the primary mechanism by which enterotoxin causes excess fluid secretion, it is not the only one. Increasing evidence indicates that enterotoxin also enhances intestinal secretion via prostaglandins and/or neural histamine receptors. All signs, symptoms, and metabolic derangements in cholera result directly from the rapid loss of these fluids from the gut. Unless the wasted fluid and electrolytes are adequately replaced, shock (due to profound dehydration) and acidosis (due to loss of bicarbonate) follow. All segments of the small bowel participate in the increased secretion of isotonic fluid and the resultant fluid lost represents the sum of the contributions of each of the small-bowel segments, slightly modified during passage through the colon.

CLINICAL MANIFESTATIONS

The incubation period may vary from 12 h to as long as 6 days, but is usually between 24 and 72 h. The clinical onset of cholera is generally abrupt, with painless, watery diarrhea. Fever is usually absent. The stool has a characteristic appearance: a nonbilious, gray, slightly cloudy fluid with flecks of mucus, no blood, and a somewhat sweet, inoffensive odor. It has been called "rice-water" stool because of its resemblance to the water in which rice has been washed. Stool volumes vary greatly, and in all epidemics there are large numbers of mild cases in which the fluid loss is not severe enough to require admission to hospital. In the more severe cases, however, the stool volume can exceed 250 ml/kg in the first 24 h. Clinical symptoms parallel volume contraction: At losses of 3 to 5% of normal body weight, thirst

develops; at 6 to 9%, postural hypotension, weakness, tachycardia, and decreased skin turgor; and above 10%, oliguria, weak or absent pulses, sunken eyes, wrinkled ("washerwoman") skin, prostration (**Table 11**).

Tables 11. Stages of dehydration

	Stage of dehydration			
	I (1-3%)	**II (4-6%)**	**III (7-8%)**	**IV (9-10%>)**
Vomiting (time)	5	6-10	11-20	many times
Periodicity of stool	To 10	10-20	20 more	many times
Thirsty	moderate	marked	severe	the most severe
Dryness of mucous tissues	moderate	marked	severe	the most severe
Voice	normal	little decreased	hoarseness	aphonia
Cyanosis	absent	on lips and nails	acrocyanosis	total
Convulsions	absent	pulling pains	local on legs	generalized
Turgor of the skin	normal	little decreased	decreased	the most decreased
Body temperature	normal	little increased	less than 36^{o}C	lower than 35.5^{o}C
Pulse	normal	100	100-120	Very frequent
Systolic pressure	normal	90-100 mm Hg	80 mm Hg	less 80 mm Hg
Breathing	normal	normal	little increased	tachypnea
Ht	40-50%	51-54%	55-65%	66% and more
Blood pH	7.36-7.4	7.36-7.4	7.3-7.36	less than 7.3
BE	absent	2-5 mEq/l	5-10 mEq/l	more 10 mEq/l
Density of serum	to 1.025	1.026-1.029	1.030-1.035	more 1.036
Electrolytes	normal	hyponatremia	hyponatremia and hypopotassiumemia	hyponatremia and hypopotassiumemia
Urine output	normal	oliguria	oligo-anuria	anuria

Later clinical manifestations depend on the adequacy of therapy. At variable intervals after the onset of diarrhea, vomiting ensues; this is also characteristically effortless and productive of rice-watery material. Muscle cramps, most commonly involving the calf muscles, due to electrolyte disturbances are common. If fluids and electrolytes are not replaced, hypovolemic shock and death ensue. Severely ill cholera patient presents a characteristic appearance: he is collapsed, cyanotic, with no palpable peripheral pulses, pinched facies, and scaphoid abdomen. The skin turgor is remarkably diminished. The voice is weak, high-pitched, and often nearly inaudible. Vital signs include tachycardia, varying degrees of tachypnoea, hypopyrexia, and hypotension, often with no obtainable blood pressure. Heart sounds are faint or inaudible, and bowel sounds are hypoactive or entirely absent. Large alterations in

mental status are not common in adults; the adult usually remains well oriented, although apathetic, even in the face of severe hypovolemic shock. As many as 10 % of small children, however, may have central nervous abnormalities that range from stupor to convulsions.

Laboratory abnormalities include mild neutrophilic leukocytosis, elevated hematocrit and plasma protein (due to hemoconcentration), increased plasma and whole-blood specific gravity, decreased plasma bicarbonate (<15 mmol/l), low arterial pH (about 7.2), normal plasma sodium, slightly increased plasma chloride, and moderately elevated plasma potassium, elevated levels of blood urea nitrogen and creatinine consistent with prerenal azotemia and an elevated anion gap (due to increases in serum lactate, protein, and phosphate). Because the bicarbonate loss is proportional to stool volume, the decrease in whole-blood pH is roughly proportional to the increase in plasma protein concentration at all stages of the untreated disease. The abnormal blood chemical findings are rapidly corrected with appropriate fluid therapy.

With adequate fluid and electrolyte repletion, recovery is remarkably rapid. If therapy is inadequate, the case mortality rate may exceed 50 per cent. The important causes of death are hypovolemic shock, uncompensated metabolic acidosis, and renal failure. When renal failure occurs, the characteristic pathological findings are those of acute tubular necrosis secondary to prolonged hypotension.

DIAGNOSIS

The working diagnosis of cholera should be made on the basis of the clinical picture. Although a cholera-like illness may be caused by microorganisms other than V. cholerae (most frequently by enterotoxigenic Escherichia coli) the resulting physiological and metabolic abnormalities are the same, identical intravenous and oral electrolyte therapy may be used in all such cases. After appropriate therapy has been started, a travel history should be obtained. The diagnosis of cholera is unlikely if the patient has no recently been in a known endemic or epidemic area. Stool examination should then be made. As the cholera enterotoxin causes neither inflammation nor destruction of intestinal mucosa, neither leucocytes or erythrocytes are usually seen on microscopical examination of the cholera stool stained with methylene blue. This, however, is not absolute, as cholera may occasionally be superimposed on other acute or chronic inflammatory bowel disease. With dark-field microscopy, rapid relative diagnosis can be made by direct observation of the characteristic rapid motility of the comma-shaped bacilli in fresh stool. Group- and type-specific antisera immobilize homologous strains and clearly distinguish them from other vibrios. V. cholerae grow rapidly on a number of selective media, including bile-salt agar, glycerine-taurocholate-teliurite agar, and thiosulphate-citrate-bile-salt-sucrose (TCBS) agar. If a delay in sample processing is expected, Carey-

Blair transport medium and/or alkaline-peptone water-enrichment medium should be inoculated as well. Distinction between the two major serotypes - Inaba and Ogawa - is made by slide agglutination with type specific antisera. Distinction between the two major V. cholerae biotypes classical and el Tor, is important for epidemiological purposes. The el Tor is distinguished from the classical biotype by its resistance to polymyxin B as well as its resistance to Mukerjee's choleraphage type IV. Although not generally evaluable in clinical laboratories, serum vibriocidal antibody titers can be used to confirm the diagnosis in non-cholera-endemic regions of the world. Monoclonal antibody-based diagnostic kits and methods based on the polymerase chain reaction and on DNA probes have been developed for V. cholerae O_1 and O_{139} but are unlikely to become available in clinical laboratories.

TREATMENT

Oral Regidration

ORS I generation (glucose-electrolyte solution

Glucose 20g, NaCl 3.5g, $NaHCO_3$ 2.5g, KCl 1.5g to 1 L water Oralitum, Regidronum, Glucosolanum, Citroglucosolanum,

ORS II generation (+starch 50g to 1 L solution)

ORS III generation (+ amylase resistance starch)

Table 12. Intravenous regidration

	Content salts g/L						
	Quartasolum	**Trisolum**	**Acesolum**	**WHO**	**Chlosolum**	**Lactasolum**	**Disolum**
NaCl	**4.75**	**5.0**	**5.0**	**4.0**	**4.75**	**6.2**	**6.0**
KCl	**1.5**	**1.0**	**1.0**	**1.0**	**1.5**	**0.3**	**--**
$NaHCO_3$	**1.0**	**4.0**	**--**	**--**	**--**	**0.3**	**4.0**
CH_3COONa	**2.6**	**--**	**2.0**	**6.5**	**3.6**	**--**	**--**
Na lactat	**--**	**--**	**--**	**--**	**--**	**3.3**	**--**
$CaCl_2$	**--**	**--**	**--**	**--**	**--**	**0.16**	**--**
$MgCl_2$	**--**	**--**	**--**	**--**	**--**	**0.1**	**--**

Cholera is simple to treat; only the rapid and adequate replacement of fluids, electrolytes, and base is required. The mortality rate for appropriately treated disease is usually less than 1%. It has been proved conclusively that fluid may be given orally. Oral replacement of water and electrolytes is remarkably effective in both

adults and children, especially if initiated immediately after onset of watery diarrhea. An oral glucose-electrolyte solution (prepared by the addition of 20 g glucose. 3.5 g sodium chloride, 2.5 g sodium bicarbonate, and 1.5 g potassium chloride to 1 liter of drinking water) can be given in mild cholera cases throughout the course of illness, and is also satisfactory in more severe cases once the hypovolemic shock has been corrected by the initial rapid intravenous fluid therapy. Glucose is an essential component of this solution, in that the success of oral therapy in cholera depends upon enhanced intestinal absorption of sodium in the presence of intraluminal glucose. This approach takes advantage of the hexose-Na^+ cotransport mechanism to move Na^+ across the gut mucosa together with an actively transported molecule such as glucose. Since Na^+ losses in the stool are high, a fluid containing Na^+ at 90 mmol/L has been recommended by the WHO. Cereal-based formulations are receiving increased attention as alternative oral rehydration solutions. Cereals and other starchy foods are rapidly broken down in the gut, providing both glucose and amino acids to facilitate sodium absorption. This increase in substrate at low osmolarity leads to more rapid volume replacement and may result in up to 40 per cent reduction in fluid loss in severe cholera.

For initial management of severely dehydrated patients, intravenous fluid replacement is preferable, if available (table 10). A diarrhea treatment solution, recommended for intravenous therapy by the WHO, may simply be prepared by adding 4 g sodium chloride 6.5 g sodium acetate, and 1 g potassium chloride in one liter of sterile, pyrogen-free, distilled water (**Table 12**). The diarrhea treatment solution, recommended by the WHO for cholera as well as for other acute diarrhoeal diseases, has been used successfully to correct the acidosis, hypokalaemia, and hypoglycemia without provoking hypernatraemia. The total fluid deficit in severely dehydrated patients (10% or more of body weight) can be replaced safely within the first 4 h of therapy, half within the first hour. Thereafter, oral therapy usually can be initiated, with the goal of maintaining fluid intake equal to fluid output. However, patients with continued large-volume diarrhea may require prolonged intravenous treatment to keep up with gastrointestinal fluid losses. The required volume of replacement fluid may be enormous, and in extreme cases, may exceed twice the weight of the patient.

Pulmonary edema may result if fluids are given intravenously at too rapid a rate before the correction of the metabolic acidosis. Cardiac arrhythmias may result from potassium depletion in children, but rarely occur in adults with cholera. Each of these complications can be avoided by the careful administration of intravenous fluids that are designed to replace the faecal electrolyte losses. In the absence of adequate staff to monitor the patient's progress, the oral route of rehydration and potassium replacement is safer than the intravenous route and is physiologically regulated by thirst and urine output.

Adjunctive therapy with antimicrobials to which the organism is susceptible will diminish the duration and volume of fluid loss and will hasten clearance of the organism from the stool. Tetracycline in a dose of 40 to 50 mg/kg body weight daily, given in four equal portions perorally every 6 h for 2 days, was uniformly successful in this regard until 1980, when tetracycline-resistant vibrio strains were first isolated. Emerging drug resistance is an ever-present concern. Fortunately, most V. cholerae strains remain highly sensitive to tetracycline. Tetracycline or doxycycline is effective in adults but is not recommended for children under 8 years of age because of possible deposition in bone and developing teeth. For adults with cholera in areas where tetracycline resistance is prevalent, ciprofloxacin or erythromycin are highly effective in reducing total stool output. For children, furazolidone has been the recommended agent and trimethoprim-sulfamethoxazole the second choice. V. cholerae O_{139} is susceptible to quinolones, erythromycin, tetracycline, and ampicillin. Unlike the O_{139} strains of 1993, the recent strains are susceptible to trimethoprim-sulphamethoxazole and strepomycin but resistant to nalidixic acid.

PREVENTION

At the present time, careful hygiene provides the only certain protection against cholera. Provision of safe water and facilities for sanitary disposal of feces, improved nutrition, and attention to food preparation and storage in the household could significantly reduce the incidence of cholera. In outbreaks, efforts should first be made to identify case contacts and to treat incubating carriers. Epidemiologic studies should be undertaken to establish the modes of transmission to define the best strategy to interrupt them. Immunization has not proved to be effective in altering the transmission of cholera or in altering the convalescent carriage of V. cholerae. Administration of cholera vaccine is therefore not recommended by the WHO for travelers who visit endemic areas.

Current vaccine research is focused on per oral immunization that results in production of IgA antibodies within the intestinal lumen. Two types of oral cholera vaccines are under development. The first is the killed whole-cell vaccine, which has been prepared both with and without the inclusion of the nontoxic B subunit of choleratoxin (WC/BS and WC vaccine, respectively). The second is the live attenuated vaccine (CVD 103-HgR) with genetic deletions of the choleratoxin A subunit gene and the insertion in the hemolysin gene of a mercury resistance marker. This vaccine is more effective against classic than against el Tor cholera. Both of the vaccines conferred moderate (about 60%) protection of recipients, including children between the ages of 2 and 4 years, over a 3-year evaluation period. In comparison standard commercial killed cholera vaccine (containing 1000 million killed vibrios per ml) given intramuscularly provides little protection to nonimmune subjects and predictably causes adverse effects, including pain at the injection site, malaise, and

fever. Immunity was relatively sustained in persons vaccinated at an age of > 5 years but not well sustained in younger vaccines. The vaccine's limited efficacy is at least partially due to its failure to induce a local immune response at the intestinal mucosal surface. Because naturally acquired immunity to V. cholerae O_1 does not cross-protect against the O_{139} Bengal strain, vaccines being developed against the former are unlikely to be effective against the latter.

ENTEROVIRAL INFECTIONS

DEFINITION *Enteroviral infections are responsible for a broad spectrum of disease involving the skin and mucous membranes, muscles, nervous system (frequently associated with aseptic meningitis), the heart and, rarely, other organs, such as the liver and pancreas.*

ETIOLOGY

Enteroviruses are so named because of their ability to multiply in the gastrointestinal tract. Enteroviruses belong to the family of small viruses called picornaviruses. Enteroviruses encompass 67 human serotypes: 3 serotypes of poliovirus, 23 serotypes of coxsackievirus A, 6 serotypes of coxsackievirus B, 31 serotypes of echovirus, and enteroviruses 68 through 71. Human enteroviruses contain a single-stranded RNA genome that is translated to form a polyprotein; this polyprotein is cleaved into 11 different proteins. The RNA is surrounded by an icosahedral capsid comprising four viral proteins (VP1 through VP4). Enteroviruses have no lipid envelope and are stable in acidic environments, including the stomach. These viruses are resistant to inactivation by standard disinfectants (e.g., alcohol, detergents) and can persist for days at room temperature.

EPIDEMIOLOGY

Enteroviral infections have a worldwide distribution and are more common in socioeconomically disadvantaged areas, especially in those where conditions are crowded and in tropical areas where hygiene is poor. Infection is most common among infants and young children. Two-thirds of isolates are from children under 9 years old. Serious illness develops most often during the first few days of life and in older children and adults. In developing countries, where children are infected at an early age, poliovirus infection has less often been associated with paralysis; in countries with better hygiene, older children and adults are more likely to be seronegative, become infected, and develop paralysis. The acquisition of maternal antibody reduces the risk of symptomatic infection in neonates. Young children are the most frequent shedders of enteroviruses and are usually the index cases in family outbreaks. Secondary attack rates in households are as high as 40-70%. In temperate

climates enterovirus infections occur most often in the summer and fall; no seasonal pattern is apparent in the tropics.

Most enteroviruses are transmitted primarily by the fecal-oral route from fecally contaminated fingers or inanimate objects. Patients are most infectious shortly before and after the onset of symptomatic disease, when virus is present in the stool and throat. The virus persists in the oropharynx 1-4 weeks after infection and can be shed in feces for 1-18 weeks. Immunodeficient patients can shed enteroviruses for very long periods. The ingestion of virus-contaminated food or water can also cause disease. Cationic stability of enteroviruses allows these viruses to survive in sewage and chlorinated water in the presence of organic debris. Certain enteroviruses (such as enterovirus 70, which causes acute hemorrhagic conjunctivitis) can be transmitted by direct inoculation from the fingers to the eye. Airborne transmission is important for some viruses that cause respiratory tract disease, such as coxsackievirus A21. Enteroviruses can be transmitted across the placenta from mother to fetus, causing severe disease in the newborn. The transmission of enteroviruses through blood transfusions or insect bites has not been documented. Nosocomial spread of coxsackievirus and echovirus has taken place in hospital nurseries. More than 50% of nonpoliovirus enterovirus infections and more than 90% of poliovirus infections are subclinical.

PATHOGENESIS

Much of what is known about the pathogenesis of enteroviruses has been derived from studies of poliovirus infection. After ingestion, poliovirus is thought to infect epithelial cells in the mucosa of the upper respiratory and gastrointestinal tract and then spread to and replicate in the submucosal lymphoid tissue of the tonsils and Peyer's patches. The virus next spreads to the regional lymph nodes, enters the bloodstream during the first (minor) viremic phase, and replicates in organs of the reticuloendothelial system. In some cases poliovirus again infects the bloodstream (major viremia) and then replicates further in various tissues. Poliovirus can usually be cultured from the blood 3 to 5 days after infection, before the development of neutralizing antibodies. Clinical manifestations are the result of direct lytic action of the virus, but secondary sequelae appear to be immunologically mediated. The target organs depend on the tropism of the particular virus but include CNS, heart, vascular endothelium, liver, pancreas, gonads, and lungs. Experimental studies in a murine model strongly suggest that virus replication occurs in myofibers, resulting initially in scattered necrosis of myofibers and later in focal infiltration of inflammatory cells, including polymorphonuclear leukocytes, lymphocytes, plasma cells, and macrophages. Healing is accompanied by a variable degree of interstitial fibrosis and evidence of loss of myofibers. Recent studies demonstrating the poliovirus receptor in the end-plate region of muscle at the neuromuscular junction suggest that if the

virus enters the muscle during viremia, it could spread across the neuromuscular junction up the axon to the anterior horn cells of the spinal cord and cranial nerve motor neurons.

The pathogenesis of the exanthems is poorly understood. Virus can be isolated from the lesions, which therefore appears to be a direct result of viral invasion of the skin after viremia. There are no reports of attempted virus isolation from the skin in cases of maculopapular and petechial exanthems; consequently, it is not known whether these lesions also are caused by the virus directly or by immunopathologic mechanisms. Humoral and secretory immunity in the gastrointestinal tract is important for the control of enterovirus infections. Enteroviruses induce specific IgM, which usually persists for less than 6 months, and specific IgG, which persists for life. Neutralizing antibody generally confers lifelong protection against subsequent disease caused by the same serotype but does not prevent infection or virus shedding. Enteroviruses also induce cellular immunity, but the importance of this mechanism in limiting infection is uncertain. Patients with impaired cellular immunity are not known to develop unusually severe disease when infected with enteroviruses. In contrast, the severe infections in patients with agammaglobulinemia emphasize the importance of humoral immunity in controlling enterovirus infections. IgA antibodies are important in reducing poliovirus replication in and shedding from the gastrointestinal tract. Breast milk contains IgA specific for enteroviruses and can protect humans from infection.

CLINICAL MANIFESTATION

Coxsackie, ECHO-virus and other enterovirus infection

Echoviruses 9 and 11 alone accounted for 24% of recognized enterovirus infections; echoviruses 4, 6, and 30 and coxsackieviruses A9 and B2 through B5 accounted for 46%. The incubation period for most enterovirus infections ranges from 2 to 14 days but usually is less than a week. When symptoms do develop, they are usually nonspecific and occur in conjunction with fever and sometimes with upper respiratory tract manifestations; only a minority of infections is associated with specific clinical syndromes. Certain clinical syndromes are more likely to be caused by certain serotypes, but there is much overlap. Despite their name, these viruses are not a prominent cause of gastroenteritis.

Acute respiratory disease.

Nonspecific febrile illness (summer grippe) is the most common clinical manifestation of enterovirus infection caused by most enterovirus serotypes. After an incubation period of 3 to 6 days, patients present with an acute onset of fever, malaise, and headache and sometimes accompanied by upper respiratory symptoms, such as sore throat and occasionally cough or coryza. Some cases include nausea and vomiting. Symptoms often last for 3 to 4 days, and most cases resolve in a week. The

role of enteroviruses in lower respiratory illness is not clearly defined; at present, they must be considered rare causes of nonbacterial pneumonia when compared with respiratory syncytial virus, parainfluenza viruses, and influenza viruses, Mycoplasma pneumoniae, and adenoviruses. The best characterized enteroviral respiratory pathogens are coxsackieviruses A21 and A24, which produce illness resembling the common cold except (perhaps) for a higher incidence of fever. Outbreaks of coxsackievirus A21 illness have occurred predominantly in military populations. Although epidemics in civilians have not been recognized, sporadic infections presumably account for antibody prevalence rates of 70% in persons over 50 years of age. Unlike most other enteroviruses, coxsackievirus A21 is more readily recovered from throat swabs than feces. In volunteers receiving small-particle aerosols of the virus, illness has included not only coryza and sore throat, but also tracheobronchitis, bronchiolitis and pneumonia. Among echovirus, type 11 is the most common cause of respiratory disease, although types 4, 8, 9, 20, 22, and 25 appear to be responsible for similar illnesses. Echovirus 11 produces sore throat, coryza, cough, and sometimes fever. It also has been associated with croup. Group B coxsackieviruses have been associated with a variety of respiratory illnesses, especially in infants and children. The spectrum of disease includes coryza, laryngotracheobronchitis, bronchiolitis, and pneumonia. The pneumonia, which may be interstitial or a patchy bronchopneumonia, has occurred in children and rarely in adults. ***Differential diagnosis.*** These illnesses are not clinically distinguishable from similar disease caused by other agents, such as rhinoviruses, parainfluenza viruses, and adenoviruses but in contrast to other respiratory viruses frequently occur in the summer.

Neurological disease.

Enteroviruses can cause a broad range of neurological disease, including meningitis, encephalitis, and a paralytic disease characteristic of poliomyelitis. One of the most frequent manifestations of enterovirus infection is *acute aseptic meningitis.* Enteroviruses account for more than 90% of cases in which an etiologic agent is identified. Approximately 80% of coxsackievirus and echovirus serotypes have been incriminated as causes of aseptic meningitis. Echoviruses are the most common, especially types 4, 6, 9, 11, 16, and 30, all of which have been responsible for both outbreaks and sporadic cases. The coxsackievirus serotypes most frequently implicated are B2-B5, A7, and A9. The attack rates for enteroviral aseptic meningitis are highest in children less than 1 year old. The disease is also seen in older children and young adults, but enteroviral aseptic meningitis after the age of 40 is unusual. The onset may be gradual or abrupt. Typically, patients present with fever, chills, headache, photophobia, and pain on eye movement for only a few hours before frank signs of meningitis are present. Nausea and vomiting are common, especially in children. The illness is sometimes biphasic, as in poliomyelitis; in these patients, fever and myalgia are present for a few days, followed by defervescence and absence

of symptoms for 2-10 days before the sudden reappearance of fever and headache signal the onset of meningitis. The severity of meningeal symptoms and other signs of neurologic disease vary widely. In infants less than 1 year of age, signs of meningeal irritation are absent altogether. Even in older children and adults, meningismus usually is mild. Stiffness of the neck and back, sometimes with muscle spasm, is the only neurologic sign in most cases. Kernig's and Brudzinski's signs are present in only about one-third of the cases. Examination of the cerebrospinal fluid (CSF) invariably reveals pleocytosis; cell count shows a shift to lymphocytic predominance within 24 h of presentation, and the total count generally does not exceed 1000 cells/ml. Additional CSF findings consist of normal glucose content and a normal or only slightly elevated level of protein. Symptoms ordinarily resolve within a week, although CSF abnormalities can persist for several weeks. Neurologic sequelae are rare, and most patients have an excellent prognosis. Only in 5-10% of patients meningitis may be complicated by a mild form of encephalitis that is recognized on the basis of progressive lethargy, disorientation, and sometimes seizures, coma, sensory deficit, or movement disorders. ***Differential diagnosis:*** bacterial meningitis incompletely treated with antimicrobials is the most important condition to be distinguished from enteroviral aseptic meningitis. However, institution of antibiotics prior to lumbar puncture alters the CSF minimally; even when some parameters are altered by therapy (i.e., change from polymorphonuclear to lymphocytic pleocytosis), others continue to indicate bacterial disease (i.e., low glucose or high protein). Other systemic manifestations may provide clues to an enteroviral cause, including pharyngitis and cough, diarrhea, myalgias, rash, pleurodynia, myocarditis, and herpangina. Mumps virus, the arboviruses, lymphocytic choriomeningitis virus, and leptospirosis account for virtually all remaining cases of aseptic meningitis occurring in the absence of other clinical manifestations. Mumps infections occur commonly in late winter and early spring; enteroviruses exhibit peak activity in the late summer and early autumn. Aseptic meningitis associated with parotitis or orchitis is strongly suggestive of mumps. However, approximately 20-50% of patients with mumps aseptic meningitis do not have parotitis. Moreover, orchitis, and parotitis have also been reported with enterovirus infections. While the signs and symptoms of meningeal irritation due to mumps and enteroviruses are usually indistinguishable, disturbances of consciousness suggestive of encephalitis are more characteristic of mumps or arbovirus infections. CSF abnormalities also are usually similar; however, the early preponderance of polymorphs common in enteroviral meningitis is rare in mumps and not seen in lymphocytic choriomeningitis. Profound hypoglycorrhachia (CSF glucose less than 30 mg/dl) occurs in occasional patients with mumps meningitis and lymphocytic choriomeningitis but is very rare in enteroviral aseptic meningitis. Poliovirus aseptic

meningitis is clinically indistinguishable from meningitis caused by coxsackieviruses and enteroviruses.

Primary enteroviral encephalitis is unusual manifestation of central nervous system infection with coxsackieviruses and echoviruses. In perinatally acquired enterovirus infection, encephalitis may be one manifestation of generalized viral infection. It is estimated that 10 to 20% of cases of viral encephalitis are due to enteroviruses. Numerous serotypes have been implicated as causes of encephalitis; coxsackievirus types A9, B2, and B5, and echovirus types 6 and 9 are the serotypes reported most often. Clinical manifestations have ranged from lethargy, drowsiness, and personality change to seizures, paresis, and coma. Although the clinical features of most cases of coxsackievirus and echovirus encephalitis suggest generalized cerebral involvement, it is clear that focal encephalitis does occur. Patients with focal encephalitis have presented with partial motor seizures, hemichorea, and acute cerebellar ataxia. The CSF findings in enteroviral encephalitis are similar to those found in aseptic meningitis. Abnormalities on an electroencephalogram usually reflect the extent and severity of brain involvement. The majority of patients with coxsackievirus and echovirus encephalitis beyond the neonatal period recover fully, although static neurologic sequelae and rare deaths occur. Residual endocrine abnormalities also have been observed after coxsackievirus B5 encephalitis involving the hypothalamic-pituitary axis. Immunocompetent patients generally have a good prognosis. Patients with hypo- or agammaglobulinemia or severe combined immunodeficiency may develop chronic meningitis or encephalitis; about half of these patients have a dermatomyositis-like syndrome, with peripheral edema, rash, and myositis. They may also have chronic hepatitis. Patients may develop neurologic disease while receiving gamma globulin replacement therapy. Echoviruses (especially echovirus 11) are the most common pathogens in this situation. ***Differential diagnosis*** includes encephalitis due to other viruses – especially arboviruses, herpes simplex virus, lymphocytic choriomeningitis and mumps, postinfectious encephalitis after measles, rubella, varicella or pertussis, Reye syndrome, Lyme disease, and toxic encephalopathies. In cases of focal encephalitis, management decisions may be more complicated because herpes simplex infection (the most common and treatable cause of focal encephalitis) only can be diagnosed reliably by a brain biopsy specimen.

Paralysis and other neurological complications. Sporadic cases of flaccid motor paralysis due to enteroviruses other than poliovirus occur sporadically and are usually less severe than poliomyelitis. Most cases are due to enteroviruses 70, 71 or to coxsackieviruses A7, A9, and Bl-5, and echoviruses 6 and 9. Less frequently implicated serotypes are coxsackieviruses A4, A5, and A10 and echoviruses 1-4, 7, 11, 14, 16-18, and 30. Paralysis, which is less common than muscle weakness, is usually not permanent. Cranial nerve involvement has occasionally resulted in

complete unilateral oculomotor palsy. Rare cases of fatal bulbar involvement have been reported. Guillain-Barre syndrome (GBS) in a small number of patients is associated with coxsackievirus serotypes A2, A5, and A9, and with echovirus serotypes 6 and 22. Transverse myelitis has been reported in one patient due to coxsackievirus B4, and in another to echovirus 5. Systemic coxsackievirus B2 disease has been reported with many of the clinical features of Reye syndrome. However, a clear etiologic or epidemiologic link between enterovirus infection and Reye syndrome has not been established. Opsoclonus-myoclonus, or the "dancing eyes" syndrome, has been reported in two children with concurrent coxsackievirus B3 infection.

Epidemic myalgia (pleurodynia, Bornholm disease).

Febrile fever onset and skeletal muscle involvement, particularly of the intercostal muscles characterize this syndrome, which is usually caused by coxsackievirus B serotypes and occur during epidemics. Other agents rarely implicated in pleurodynia include echoviruses 1, 6, 9, 16, and 19 and coxsackieviruses A4, 6, 9. Attack rates during epidemics of pleurodynia have been higher in sparsely populated areas than in cities. It is probable that the disease occurs worldwide. Fever peaks within an hour after the onset of each paroxysm and subsides when pain resolves. Intensity of the pain varies considerably. It is variously described as sticking, a "stitch" in the side, lancinating, stabbing, constricting, or vise-like. Patients asked to localize the pain are likely to indicate a broad area with the palm of the hand, rather than a specific point with the finger. The most common location is the vicinity of the costal margin on one or both sides, or occasionally the subxiphoid region. Approximately half the patients, especially adults, have pain primarily in muscles of the thorax, especially the intercostals, trapezius, and occasionally the erector spinae or pectoralis major. In the other half, pain is primarily in the upper abdomen, especially the hypochondrium (internal and external obliques and transversus abdominis) or the epigastrium (rectus abdominis). Periumbilical pain and pain in the lower abdominal quadrants are also seen, especially in children in whom abdominal localization of pain is the rule.

A few patients experience pain in neither the chest nor the abdomen, but instead in the neck or limbs; in these cases, the diagnosis can only be made by association with other typical cases in the family. Whatever the localization of the pain, it is usual for the individual patient to experience this pain in only one or two areas of the body. If the pain is mild and the patient ambulatory, he stoops forward or leans to the side, splinting the chest. With more severe pain, the patient lies still in bed and appears acutely ill and apprehensive. Chest pain limits deep inspiration, so that respirations are shallow and rapid. Auscultation of the chest reveals no abnormalities. Pleural friction rub has been rare and noted only in 7% of those afflicted. Sore throat and headache may occur, but cough and catarrhal symptoms are

notably absent. Motion also produces pain, and patients resist being turned in bed. Tenderness mimicking spontaneously occurring pain can be elicited by pressure on affected muscles in most cases. Muscle swelling is seen or felt only occasionally and by careful, sequential observations; it is detected most readily when there is involvement of the rectus abdominis or erector spinae. Involvement of the muscles of the hypochondrium does not cause discrete swelling, but spasm of these muscles leads to loss of the upper superficial abdominal reflexes. Paroxysms of spasmodic pain usually last 15 to 30 min and are associated with diaphoresis. Although dull aching of involved muscles usually persists between bouts of sharp pain, the patient may look and feel entirely healthy between paroxysms. The first paroxysm is the most severe, and subsequent paroxysms are shorter and accompanied by less fever. Symptoms resolve in 4-6 days (range: 12 hours to 3 weeks). About one-quarter of patients experience multiple recurrences, often after they have been pain-free for 1 day or more and have felt well enough to return to work or school. In about half of these persons, the recurrence of pain is at the same site; in the remainder a new site is attacked. Late relapses occur in some patients after they have been symptom-free for 1 month or more. The infection may be complicated by aseptic meningitis in 3-6% of the cases, generally 4 or 5 days after the onset of the disease. Orchitis occurs in less than 5% of postpubertal males with epidemic pleurodynia. Pericarditis and pneumonia are rare. Debility out of all proportion to the apparent severity of the illness is occasionally observed for several months during convalescence. ***Differential diagnosis.*** The severity, location, and other characteristics of the pain are so protean that the disease is readily confused with many other illnesses. Pain in the chest may mimic pneumonia, pulmonary infarction, myocardial ischemia, and the preeruptive phase of zoster. Abdominal pain in epidemic pleurodynia may resemble a variety of causes of acute abdomen. Normal auscultatory examination of the chest, together with the characteristic spasmodic and relapsing character of the pain, are helpful in excluding pneumonia. A negative chest radiographic film also is helpful, although rare pleural effusions may be present. The white blood cell and differential cell counts usually are normal. Virologic diagnosis can be achieved in most cases by isolating a group B coxsackievirus from throat washings or feces early in the illness or by demonstrating rising antibody titers to one of these agents in paired acute and convalescent sera.

Acute myocarditis and/or pericarditis. Enteroviruses are estimated to cause up to one-third of cases of acute myocarditis. More then 50% of cases are due to all group coxsackievirus B (especially types 2-5), coxsackievirus A types 4 and 16, and echovirus types 9 and 22. There is less substantive evidence for group A coxsackievirus types 1, 2, 5, 8, and 9, and echovirus types 1-4, 6-8, 11, 14, 19, 25, and 30. Enteroviral myocarditis or pericarditis occurs at all ages but has a special predilection for newborns, adolescents, or active young adults. Involvement of the

heart is a relatively uncommon manifestation of illness even during substantial enterovirus epidemics. In older children and adults, the severity of myopericarditis varies from asymptomatic cardiac involvement to fulminant disease with intractable heart failure and death. More than two-thirds of patients are male. In two-thirds of cases, patients present with an upper respiratory tract infection that is followed by 7-14 days with fever, malaise, chest pain, dyspnea, arrhythmias, and occasionally heart failure. Pain in the precordial area is usually dull, but it may resemble angina pectoris or be sharp, pleuritic, and aggravated by recumbency when there is pericarditis. A pericardial friction rub, often transient, is documented in half of cases. Enlargement of the cardiac silhouette on chest radiograph films, present in about 50%, may be due to either pericardial effusion or cardiac dilatation. A gallop rhythm and other signs of frank congestive heart failure are observed in roughly 20%. Electrocardiographic abnormalities are invariably present. With pericarditis or mild myocarditis, which are the most common, these consist of ST segment elevations or nonspecific ST- and T-wave abnormalities. More severe myocardial disease may lead to the development of Q waves, ventricular tachyarrhythmias, and all degrees of heart block. Serum levels of myocardial enzymes and the white blood cell count are frequently elevated. Other clinical manifestations of systemic enteroviral disease sometimes occur with myopericarditis, including aseptic meningitis, pleurodynia, hepatitis, and orchitis. Neonates commonly have severe disease, while older children and adults recover completely. Most children and adults recover uneventfully. Fatalities during the acute disease occur in only 0-4% of the cases and are essentially restricted to those in whom severe myocarditis predominates over pericarditis. One or more recrudescences of myopericarditis occurring several weeks to more than 1 year after the initial illness have been observed in approximately 20% of the people. Persistent electrocardiographic abnormalities (10-20%), cardiomegaly (5-10%), and chronic congestive heart failure indicate that permanent myocardial injury sometimes occurs. Idiopathic cardiomyopathy may, in some instances, be a sequel of unrecognized coxsackievirus infections. Chronic constrictive pericarditis has occurred after intervals of 5 weeks to 1 year. ***Differential diagnosis.*** Many other viruses have been associated with myopericarditis, although influenza A virus, mumps virus, and vaccinia virus are the only nonenterovirus agents to be recovered directly from pericardial fluid or myocardial tissue. Epstein-Barr virus, adenovirus, varicella virus, and measles virus also can cause myopericarditis. Cardiac disease caused by most of these agents can be distinguished from enteroviral myopericarditis on the basis of associated epidemiclogic and clinical features. Acute myocardial infarction is an important cause of chest pain, arrhythmias, and congestive heart failure that may be difficult to distinguish from myopericarditis. Focal myocardial necrosis has been demonstrated in myopericarditis caused by coxsackievirus B5. In the absence of isolation of virus from heart tissues, the diagnosis rests on circumstantial evidence

provided by recovery of the agent from the oropharynx or feces and/or serologic evidence of recent infection by a group B coxsackievirus. Even serologic diagnosis is difficult; it is often impossible to demonstrate seroconversion, because many patients already have high, stable titers of neutralizing antibodies within a few days of onset of illness. High, stable antibody titers may persist for years in some persons and are of less diagnostic significance than seroconversion. Serodiagnosis of echoviruses and group A coxsackieviruses is not practical.

Generalized disease of the newborn.

This infection develops in infants during the first week of life, although severe disease can occur up to 3 months of age. Neonates often present with an illness resembling bacterial sepsis, with fever, irritability, and lethargy. Laboratory abnormalities include leukocytosis with a left shift, thrombocytopenia, elevated values in liver function tests, and CSF pleocytosis. The illness can be complicated by myocarditis and hypotension, fulminant hepatitis and disseminated intravascular coagulation, meningitis or meningoencephalitis, or pneumonia. ***Differential diagnosis.*** It may be difficult to distinguish enterovirus infection from bacterial sepsis, although a history of a recent virus-like illness in the mother provides a clue.

Exanthems. Enterovirus infection is the leading cause of variety exanthems in the summer and fall. Rashes may be grouped on rubelliform or morbilliform, roseoliform, vesicular, and petechial exanthems. Some overlap between these types of exanthems often is observed in different patients infected with the same enterovirus or even among different lesions in the same patient.

Rubelliform or morbilliform exanthems.

Fine discrete maculopapular rashes resembling rubella, but occurring during summer epidemics, have been reported most often with echoviruses. Thousands of cases and high attack rates in children have been caused by echovirus 9, which is by far the most common serotype associated with rubelliform exanthem. The rash characteristically occurs simultaneously with fever and begins on the face, which is involved in all cases. It then spreads to the neck (75%), chest (64%), and extremities (56%). Usually, there are innumerable faint pink macules, 1-3 mm in diameter, which do not itch or desquamate. Rubelliform rashes may be seen with many echovirus serotypes in addition to type 9. Echoviruses 2, 4, 11, 19, and 25 have each been associated with small outbreaks. Coxsackievirus A9 eruptions may be maculopapular and begin on the face and trunk. Lesions on the limbs are most numerous on the distal parts and extensor surfaces, although the palms and soles are occasionally involved. There are generally also fever and malaise. Posterior cervical or occipital lymphadenopathy similar to that seen in rubella has been present in about half the patients with rash due to coxsackievirus A9. ***Differential diagnosis.*** Maculopapular exanthem is most likely to be confused with rubella, but helpful distinguishing features include the summertime occurrence and absence of pruritis and

lymphadenopathy in the posterior cervical and postauricular regions. In occasional patients with an enanthem resembling Koplik's spots and a blotchy eruption, the disease may be confused with measles, but the coryza and conjunctivitis characteristic of that disease are absent.

Roseoliform exanthems.

The enterovirus exanthems are distinctive not in their appearance, but in their timing; as in roseola, the rash does not appear until defervescence. The prototype is the "Boston exanthem", the first of the enterovirus exanthems to be recognized and now known to be caused by echovirus 16. Multiple cases often occur sequentially in families, with as many as one-quarter of the children in a household developing a rash. The mean age of those affected is 3 years. Most children are mildly ill, but infants often appear ill enough to be suspected initially of having sepsis. The temperature is 38-39°C, and there may be pharyngitis without cough or coryza. The fever lasts 24-36 hours. As it declines discrete, nonpruritic, salmon-pink macules and papules (0.5-1.5 cm) appear first on the face and upper chest. Less commonly, the extremities are involved. The duration of the lesions is 1-5 days. Although the temporal sequence described above is characteristic, it is by no means absolute; also, rashes due to echovirus 16 are occasionally observed simultaneously with fever rather than after defervescence. In addition to echovirus 16, other serotypes (coxsackievirus Bl, B5, and echoviruses 11, 25) also occasionally have been associated with roseola-like illness.

Herpetiform exanthems.

Coxsackievirus A16 (less commonly A5, A7, A10, B2, and B5) is the etiologic agent of a distinctive vesicular eruption known as *hand-foot-and-mouth disease*. The disease is highly infectious involving multiple family members, with attack rates of close to 100% among children under 10 years of age. After an incubation period of 4 to 6 days, patients present with fever, anorexia, and malaise; these manifestations are followed by the development of sore throat or mouth. Most children refuse to eat. Fever of 38-39°C lasts 1-2 days and is accompanied in essentially all cases by vesicles on the buccal mucosa and often on the tongue. About one-third of patients also have lesions on the palate, uvula, or tonsillar pillars. Several lesions may coalesce to form bullae, which frequently ulcerate by the time they are seen by a physician. Cutaneous lesions are less constant, occurring in 75% of the patients and are peripherally distributed. They are located subepidermally and are accompanied by mixed lymphocytic and polymorphonuclear inflammation and extensive acantholysis of the overlying epidermis. Eosinophilic nuclear inclusions and intracytoplasmic picornavirus particles can be seen microscopically within cells surrounding dermal vessels. The skin lesions are tender and consist of mixed papules and clear vesicles with a surrounding zone of erythema. Exanthems are most common on the hands and feet, where either the extensor surfaces or the palms and soles may be involved. Less

commonly, lesions occur more proximally on the extremities or buttocks and rarely on the genitalia. More extensively disseminated lesions have been described in an infant with preexisting atopic eczema and have been given the sobriquet "eczema coxsackium" by analogy, with eczema herpeticum and eczema vaccinatum. The lesions usually resolve in 1 week. Enterovirus 71 also causes hand-foot-and-mouth disease, sometimes in association with central nervous system disease. Generalized vesicular eruptions are reported to be caused by coxsackievirus A9 and echovirus 11. Those eruptions caused by coxsackievirus A9 are similar to the lesions of hand-foot-and-mouth disease, but they occur in crops on the head, trunk, and extremities. The vesicular eruptions caused by echovirus 11 have occurred in immunocompromised adult patients. An acute eruption resembling dermatomal zoster in which echovirus 6 was isolated from the bullous lesions has been reported. *Differential diagnosis.* The vesicular lesions of hand-foot-and-mouth disease superficially resemble those caused by herpes simplex or varicella-zoster viruses. Unlike chickenpox, the vesicles do not evolve to form pustules and scabs. Oral lesions are less common in patients with chickenpox; moreover, they generally appear more ill, and their cutaneous lesions are more extensive and centrally distributed, generally with sparing of the palms and soles. Patients with primary herpetic gingivostomatitis also usually appear more ill and have higher fever and cervical lymphadenopathy; lesions are usually confined to the oral cavity and do not involve the extremities. The enanthem of herpangina also resembles hand-foot-and-mouth disease, but it occurs more posteriorly and typically involves the fauces and soft palate. Laboratory evidence supporting a diagnosis of enteroviral exanthem, at present, rests on isolation of virus from vesicles, blood, feces, or throat secretions.

Petechial exanthems and other cutaneous manifestations.

Petechial and purpuric rashes have been described with echovirus 9 and coxsackievirus A9 infections. When these rashes with a hemorrhagic component occur, the illness is easily confused with meningococcal disease, especially if aseptic meningitis occurs simultaneously. Occasionally, cutaneous eruptions of coxsackievirus A9 disease have an urticarial nature. One child has been reported to have papular acrodermatitis (Gianotti-Crosti syndrome) that was secondary to coxsackievirus A16 infection.

Herpangina.

Herpangina is a specific infectious disease characterized by a vesicular enanthem of the fauces and soft palate accompanied by fever, sore throat, and pain on swallowing. Coxsackieviruses of group A (types 1-10, 16, and 22) are the etiologic agents in the great majority of cases. Other enteroviruses that have been isolated far less commonly from persons with herpangina include coxsackievirus Bl-5 and echoviruses 3, 6, 9, 16, 17, 25, and 30. The disease primarily affects children between the ages of 3 and 10 years, but occasionally attacks teenagers and young adults.

Summer outbreaks of herpangina have been reported more commonly than sporadic, interepidemic illness. Transmission in families usually produces inapparent infections, but one child after another may contact the sore throat at intervals of 2-10 days. Isolated cases without known source are numerous during outbreaks. The illness begins suddenly with fever of 37.7-40.5°C. Vomiting, myalgia, and headache are common at the onset but generally do not persist. Sore throat and pain on swallowing are the most prominent symptoms and precede the appearance of the enanthem by several hours to 1 day. Inspection of the throat reveals erythema and mild exudate of the tonsils, which leads to a diagnosis of pharyngitis or tonsillitis if the characteristic enanthem is missed. The enanthem begins as punctate macules, which evolve over a 24-hour period to 2- to 4-mm grayish-white papulovesicular lesions on an erythematous base that then ulcerate centrally. The lesions, usually two to six but rarely 1 dozen, are moderately painful. They are located on the soft palate, most frequently on the free-hanging margin between the tonsils and the uvula. Less commonly, they are on the tonsils, uvula, the posterior pharyngeal wall, or the buccal mucosa. Fever subsides in 2-4 days, but the ulcers may persist up to 1 week. A variant of the syndrome, acute lymphonodular pharyngitis associated with coxsackievirus A10 presents as tiny white or yellow nodules of packed lymphocytes surrounded by erythema in the posterior oropharynx that eventually recede without undergoing vesiculation or ulceration. Prompt recovery occurs in all cases. ***Differential diagnosis.*** The disease most often is confused with bacterial tonsillitis or other viral causes of pharyngitis, but these infections do not produce vesicular lesions. Herpangina is a disease of the posterior oral cavity, while other vesicular enanthems such as primary herpetic gingivostomatitis or hand-foot-and-mouth disease characteristically occur in the front of the mouth, especially on the inner aspects of the lip, the anterior buccal mucosa, and the tongue. Gingivitis, prominent systemic toxicity, and cervical lymphadenitis are additional features of primary herpes simplex infection that are not seen in herpangina. In hand-foot-and-mouth disease, lesions also occur on the extremities in most cases. Aphthous stomatitis is characterized by larger, ulcerative lesions of the lips, tongue, and buccal mucosa; there is a history of multiple recurrences, and the disease usually occurs in older children and adults.

Acute hemorrhagic conjunctivitis.

Epidemics and nosocomial spread have been associated with enterovirus 70 and coxsackievirus A24. Patients present with an acute onset of severe eye pain, blurred vision, photophobia, and watery discharge from the eye. Examination reveals edema, chemosis, and subconjunctival hemorrhage and often documents punctate keratitis and conjunctival follicles as well. Preauricular adenopathy is often found. Systemic symptoms, including headache and fever, develop in 20% of cases, and recovery is usually complete in 10 days. The sudden onset and short duration of the

illness help to distinguish acute hemorrhagic conjunctivitis from other ocular infections such as those due to adenovirus and Chlamydia. Paralysis has been associated with some cases of acute hemorrhagic conjunctivitis due to enterovirus 70 during epidemics.

Other manifestations. Coxsackievirus B has been isolated at autopsy from the pancreas of a few children presenting with insulin-dependent diabetes mellitus. Other diseases that have been associated with enterovirus infection include infectious lymphocytosis, polymyositis, acute arthritis, and acute nephritis.

POLIOVIRUS INFECTION (POLIOMYELITIS)

DEFINITION: *acute enterovirus infection characterizes by the lesions of grey substance in spinal cord and other parts of CNS with development of flaccid atrophic paralysis and paresis of muscles and disturbances in intestine and upper respiratory tract.*

Poliomyelitis occurs when a susceptible individual is infected with poliovirus type 1, 2 or 3. Poliomyelitis is found world-wide but its incidence has decreased dramatically following improvements in sanitation, hygiene and the widespread use of polio vaccines. Spread is usually via the faecal-oral route, as the virus is excreted in the faeces. Although polio is essentially a disease of childhood, no age is exempt. At present, much of the cases of poliomyelitis are due to live poliovirus vaccine; 5 to 10 such cases are reported each year in the United States. About half of these cases occur in vaccine recipients; vaccine-induced disease is most frequent among infants after the first dose. The median interval from vaccination to the onset of symptoms is 3 weeks. Most of the other cases develop in close contacts of these patients. Usually with persons over 20 years old who have not received a full course of vaccine. About 5% of the cases of poliomyelitis associated with vaccine occur in members of the community who have had no known direct contact with vaccinees. About 15% of all cases of vaccine-associated poliomyelitis involve immunodeficient children or adults, most of whom have hypo- or agammaglobulinemia. In these patients the median interval between vaccination and the onset of symptoms is 6 weeks, but disease can develop up to 6 months after vaccination. The risk of developing poliomyelitis after oral vaccination is estimated at 1 case per 2.5 million doses administered. The risk of developing paralytic disease after oral vaccination is about 2000 times higher among immunodeficient patients than among immunocompetent children.

At least 95% of infections are asymptomatic or inapparent and can be recognized only by the isolation of poliovirus from feces or oropharynx or by a rise in antibody titer. The incubation period is 7-14 days. The clinical manifestations vary considerably. Disease falls into four forms: (1) inapparent infection; (2) abortive

poliomyelitis; (3) non-paralytic poliomyelitis; (4) paralytic poliomyelitis.

Inapparent (subclinical) infection is common and occurs in 90-95% of infected individuals.

Abortive poliomyelitis occurs in approximately 4-5% of cases and is characterized by the presence of nonspecific febrile illness of 2-3 days, malaise, sore throat, listlessness, anorexia, vomiting, myalgias, abdominal pain and headache with no signs of CNS localization. The illness is self-limiting and of short duration. Abortive poliomyelitis is not clinically distinguishable from many other viral infections and can only be suspected clinically during an epidemic.

Nonparalytic poliomyelitis occurs in 1% of patients and differs from abortive poliomyelitis by the presence of signs of meningeal irritation (aseptic meningitis). The systemic manifestations of nonparalytic poliomyelitis are generally more severe than in abortive poliomyelitis. The disease is clinically indistinguishable from aseptic meningitis with other enteroviruses. Examination of CSF reveals lymphocytic pleocytosis, a normal glucose level, and a normal or slightly elevated protein level; CSF polymorphonuclear leukocytes may be present early. In some patients, especially children, malaise and fever precede the onset of aseptic meningitis. Complete recovery in a few days.

Paralytic poliomyelitis occurs in approximately 0.1% of infected children (1.3% of adults). Disease is more common among males, older individuals, pregnant women, and persons exercising strenuously or undergoing trauma at the time of CNS symptoms. Tonsillectomy predisposes to bulbar poliomyelitis, and surgery or intramuscular injection increase the risk of paralysis in the involved limb(s). In children there frequently is a biphasic course with "minor" and "major" illnesses. The minor illness, coinciding with viremia, corresponds with the symptoms of abortive poliomyelitis and lasts 1-3 days. The patient then appears to be recovering and remains symptom-free for 2-10 days before the generally abrupt onset of the major illness. The preparalytic symptoms of the major illness are meningeal irritation, with headache, fever, malaise, vomiting, neck stiffness, and CSF pleocytosis. The temperature is generally 37-39°C, which often is accompanied by chilliness, but rarely by rigors. Patients, especially older persons, produced severe spontaneous muscle pain. The pain may involve one muscle or several, most commonly those of the neck or lumbar region, but also those of the flank, abdomen, or limbs. It is relieved by motion; the patient sometimes paces nervously to "work it off". Localized cutaneous hyperesthesia, paresthesias, involuntary muscle spasm, and muscular fasciculations occasionally are observed during this phase. This phase of the major illness persists for a few days before frank weakness and paralysis ensue. Biphasic pattern (seen in perhaps one-third of the children) is rarely observed in adults, who usually have a single phase but a more prolonged prodrome of symptoms before the more gradual onset of paralysis. Very rarely, paralysis is almost the first

manifestation of illness.

Spinal paralytic poliomyelitis. Signs of aseptic meningitis are followed by the onset of asymmetrical flaccid paralysis without sensory involvement. The severity of the disease varies from weakness of a single portion of one muscle to complete quadriplegia. The maximal extent of involvement usually occurs within a few days after first paralysis and usually does not progress after defervescence. The most characteristic feature of the paralysis is its asymmetric distribution, which affects some muscle groups while sparing others. Proximal muscles of the extremities tend to be more involved than distal muscles. The paralysis is usually confined to the lower limbs in children under 5 years of age and the upper limbs in older children, whereas in adults it manifests as paraplegia or quadriplegia. Paralysis of the bladder usually is associated with paralysis of the legs. It occurs in about one-quarter of the adults, but is uncommon in children. Examination reveals weakness, fasciculations, decreased muscle tone. Deep tendon reflexes, which were initially hyperactive, become diminished or absent. Patients frequently report sensory symptoms, but objective sensory testing usually yields normal results. Sensory loss in poliomyelitis is very rare, and its occurrence should strongly suggest some other diagnosis (e.g., GBS). While occasional cases progress from onset of weakness to complete quadriplegia and bulbar involvement in a few hours, more commonly the paralysis extends over 2-3 days. Most patients with paralysis recover some function weeks to months after infection. About two-thirds of patients have residual neurologic sequelae.

Bulbar paralytic poliomyelitis. Among paralytic cases, 5-25% is bulbar. Mixed bulbospinal involvement is common, with pure bulbar poliomyelitis accounting for not more than about 10% of paralytic poliomyelitis. Bulbar poliomyelitis is characterized by the presence of cranial nerve involvement and respiratory muscle paralysis.

The IX and X cranial nerves are by far the most frequently involved, and pharyngeal paralysis often is the only obvious sign. Bulbar paralysis leads to dysphagia, nasal speech or dysphonia. Pooling of secretions occurs, and patients usually are extremely anxious and agitated about their inability to swallow and breathe. Other cranial nerve nuclei frequently are involved but rarely pose a threat to life. Ocular palsies and pupillary disturbances occur in 11%. V nerve involvement is uncommon and causes difficulty in chewing; it is important when it results in trismus, which may prevent adequate removal of secretions by suction. Paresis of the facial nerve occurs in approximately 50% of the patients; however, unlike in Bell's palsy, it tends to be segmental, resulting in weakness only of muscles supplying the forehead, the cheek, or the lips. Bilateral deafness and vestibular disturbances are rare. Paralysis of the sternomastoid and trapezius muscles is not uncommon, but its importance is overshadowed by difficulties in swallowing and airway obstruction produced by combined involvement of the X, XI, and XII cranial nerves.

Bulbar poliomyelitis involving the respiratory and vasomotor centers is less common than paralysis of the cranial nerve nuclei. Respiratory failure may be caused by paralysis of the respiratory muscles, by airway obstruction from involvement of the cranial nerve nuclei, or by lesions of the respiratory center in the medulla. Paralysis of the respiratory muscles may involve the diaphragm and the intercostal muscles (phrenic or intercostal nerves). These patients have rapid, shallow breathing, which often are difficult 10 evaluating because of superimposed anxiety. With intercostal muscle paralysis, the chest wall is partially or completely immobile, and the accessory respiratory muscles may be in use. Patients with diaphragmatic paralysis are unable to sniff vigorously. Advanced paralysis of the respiratory muscles causes a weak, but otherwise normal cough, because the patient is unable to take a deep breath. In contrast, the patient with pharyngeal paralysis blows rather than coughs, because of inability to close off the glottis. Pharyngeal paralysis typically results in noisy respirations because of pooling of secretions. Lesions of the respiratory center produce irregularities of the rhythm and depth of respiration despite an adequate airway and intact respiratory musculature. Usually a rapid pulse and some elevation in blood pressure are associated with hypoxia. Progression leads to Cheyne-Stokes respiration with associated confusion, delirium, coma, and usually death. Severe medullary involvement may lead to circulatory collapse. Electrocardiographic disturbances are common but usually nonspecific. Disturbances of cardiac rhythm occur, most commonly sinus tachycardia, bradycardia, or prolongation of the Q-T interval. Autonomic manifestations (e.g., flushing, cutaneous vasoconstriction with hyperthermia, or severe hypertension) may be seen.

Nonparalytic respiratory complications include aspiration pneumonia and pulmonary edema associated with bulbar disease, and pulmonary embolism promoted by venous stasis in paralyzed limbs. Myocarditis has been documented by virus isolation and histologic lesions at autopsy, but it rarely is diagnosed clinically. Gastrointestinal complications include hemorrhage, paralytic ileus, and gastric dilatation. Urinary calculi are a common late complication resulting from catheter associated urinary infections and resorption of calcium from bone in immobilized patients with residual spinal paralysis.

Polioencephalitis. Encephalitis, manifested primarily by confusion and disturbances of consciousness, is an uncommon form of poliomyelitis occurring principally in infants. It is the only type of poliomyelitis in which seizures are common. In contrast to spinal paralytic polio, there may be spastic paralysis, which reflects the presence of an upper motor neuron lesion. The illness is not clinically distinguishable from many other infectious causes of encephalitis, and it usually is suspected only in an epidemic.

Postpolio syndrome (postpoliomyelitis neuromuscular atrophy). The syndrome is thought to be due to progressive dysfunction and loss of motor neurons

that compensated for the neurons lost during the original infection and not to persistent or reactivated poliovirus infection. It presents as a new onset of weakness, fatigue, fasciculations, and pain with additional atrophy of the muscle group involved during the initial paralytic disease 20 to 30 years earlier. The onset is insidious, and weakness occasionally extends to muscles that were not involved during the initial illness. The prognosis is generally good; progression to further weakness is usually slow, with plateau periods that range from 1 to 10 years.

Differential diagnosis. Many diseases may mimic the nonspecific signs and symptoms of abortive poliomyelitis. Also, the aseptic meningitis caused by polioviruses is clinically indistinguishable from meningitis due to many other viral causes. Few diseases, however, are likely to be confused with paralytic poliomyelitis. The most important is the GBS. The patient with poliomyelitis is febrile, has signs of meningeal irritation, and appears acutely ill. The paralysis is characteristically asymmetric and virtually never accompanied by sensory loss. In contrast, in GBS there is symmetrical, ascending paralysis with loss of sensation in approximately 80% of the cases. Facial diplegia occurs in about half of patients with GBS, but is very uncommon even in bulbar poliomyelitis. In poliomyelitis, continued extension of paralysis beyond 3-4 days is unusual, whereas in GBS the paralysis may spread in successive stages over a period of up to 2 weeks. Paresthesias are uncommon in poliomyelitis but common in GBS. Characteristics of the CSF are useful in distinguishing the two conditions. In poliomyelitis, pleocytosis and minimally elevated protein concentration are present, whereas in GBS the protein is elevated with absent or minimal pleocytosis (albuminocytologic dissociation). The CSF may be less helpful 2 or 3 weeks into the illness, when (in poliomyelitis) the cell count has returned to normal, but the protein elevation may persist, In acute transverse myelitis, the findings are motor and sensory deficits at a particular level of the spinal cord and spastic paralysis characteristic of an upper motor neuron lesion; prominent sphincter disturbances are also seen. Other diagnoses that may be considered include paralytic disease due to nonpolio enteroviruses, hysteria, neuropathies caused by diphtheria and botulism, tick paralysis, pseudoparalysis in children with arthritis or osteomyelitis of the long bones, and encephalitis with paralysis.

DIAGNOSIS

It is important to identify serious infections with enterovirus during epidemics and to distinguish the vaccine strain of poliovirus from the other enteroviruses. Diagnosis can be established readily by isolation of virus from throat swabs, stool or rectal swabs, and body fluids. Isolation of enterovirus in cell culture is the most common procedure for the diagnosis of infection. While cultures of stool, nasopharyngeal, or throat samples from patients with enterovirus diseases are often positive, isolation of the virus from these sites does not prove that it is directly

associated with disease because these sites are frequently colonized for weeks in patients with subclinical infections. Isolation of virus from the throat is more likely to be associated with disease than isolation from the stool since virus is shed for shorter periods from the throat. Cultures of CSF, serum, fluid from body cavities, or tissues are positive less frequently, but a positive result is indicative of disease caused by enterovirus. In the absence of a positive CSF culture, a positive culture of stool obtained within the first 2 weeks after the onset of symptoms is most often used to confirm the diagnosis of poliomyelitis. In some cases the virus can be isolated only from the blood or only from the CSF; therefore, it is important to culture multiple sites. Cultures are more likely to be positive early than later in the course of infection. Most human enteroviruses can be detected within a week after inoculation of cell cultures. Cultures may be negative because of the presence of neutralizing antibody, lack of susceptibility of the cells used, or inappropriate handling of the specimen. Coxsackievirus A may require inoculation into special cell-culture lines or into suckling mice.

Serologic diagnosis of enterovirus infection is limited by the large number of serotypes and the lack of a common antigen. Demonstration of seroconversion may be useful in rare cases for confirmation of culture results, but serologic testing is usually limited to epidemiologic studies. Serum should be collected and frozen soon after the onset of disease and again about 4 weeks later. Measurement of neutralizing titers (fourfold rises) is the most accurate method for antibody determination; measurement of complement-fixation titers is usually less sensitive. Titers of virus-specific IgM are elevated in both acute and chronic infection.

The polymerase chain reaction (PCR) has been used to amplify viral nucleic acid from CSF, serum, and tissues. The high degree of homology among the different enterovirus serotypes allows the detection of most (more than 92%) of the human serotypes with a single pair of PCR primers. With the proper controls, PCR of the CSF is highly sensitive (95%) and specific (nearly 100%) and is more rapid and probably more sensitive than culture. PCR may be particularly helpful for the diagnosis and follow-up of enterovirus disease in immunodeficient patients receiving immunoglobulin therapy, whose viral cultures may be negative. Antigen detection and hybridization of enterovirus sequences in human tissues with a specific probe are additional options, but these techniques are generally less sensitive than PCR.

Stool and throat samples for culture as well as acute- and convalescent-phase serum specimens should be obtained from all patients with suspected poliomyelitis. If poliovirus is isolated, it should be identified as a wild-type or a vaccine virus.

TREATMENT

Bed rest is essential during the early course of the illnesses. Treatment is directed at symptoms. Most enterovirus infections are mild and resolve

spontaneously; however, intensive supportive care may be needed for cardiac, hepatic, or CNS disease. Supportive treatment of pericardial pain, effusions, arrhythmias, and heart failure is similar regardless of etiology. Respiratory support with intermittent positive-pressure respiration is required if the muscles of respiration are involved. Intravenous, intrathecal, or intraventricular immunoglobulin has been used with apparent success for the treatment of chronic enterovirus meningoencephalitis and dermatomyositis in patients with hypo- or agammaglobulinemia. The disease may stabilize or resolve during therapy; however, some patients decline inexorably despite therapy. Intravenous administration of immunoglobulin with high titers of antibody to the infecting virus has been successful in the treatment of some cases of life-threatening neonatal infection (reduced rates of viremia); neonates with such infection may not have maternally acquired antibody. Antiviral agents that inhibit the growth of enterovirus in vitro and in animal models have not yet undergone clinical trials. Glucocorticoids are contraindicated. Once the acute phase of the illness has subsided, occupational therapy, physiotherapy and occasionally surgery have important roles in patient rehabilitation.

PREVENTION

Good hand-washing practices and the use of gowns and gloves are important in limiting nosocomial transmission of enteroviruses during epidemics. Enteric precautions are indicated for 7 days after the onset of enterovirus infections.

Trivalent (containing all three serotypes) live, attenuated oral poliovaccine (OPV) is currently used. OPV has the advantage of ease of administration and is given at 2, 4, and 6 to 18 months and at 4 to 6 years of age. During replication in the gastrointestinal tract, OPV can mutate, reverting to a more neurovirulent phenotype within a few days. Vaccine-associated paralytic poliomyelitis occurs at a rate of about 1 case per 2.6 million doses of vaccine. OPV should be avoided in immunosuppressed patients or their family members, including patients with HIV, immunosuppressed hosts who are partially immunized to polio and for women in pregnancy. Inactivated poliovirus vaccine (IPV) is recommended for these groups and for adults because of the slightly greater risk of paralysis with OPV in adults than in children. IPV is administered subcutaneously in four doses (starting at 2 months of age), two doses 4-8 weeks apart, a third 6-12 months later, and a booster before school entry. Unnecessary intramuscular injections should be avoided during the first month after vaccination because of the risk of vaccine-associated paralysis.

OPV and IPV induce antibodies that persist for at least 5 years. Compared with recipients of IPV, recipients of OPV shed less virus and less frequently develop reinfection with wild-type virus after exposure to poliovirus. CDC recommended that children receive a sequential schedule of two doses of IPV followed by two doses of

OPV. A four-dose schedule of either IPV or OPV is an acceptable option and may be preferred in certain circumstances. Vaccination with the sequential regimen is expected to reduce the number of cases of vaccine-associated poliomyelitis by 50 to 75%.

SHIGELLOSIS

DEFINITION: *Shigellosis is an acute infectious disease, caused by Shigella and characterized by damage of the mucous membrane of the distal section of the large intestine. The disease is accompanied by symptoms of the general intoxication, abdominal pain, frequent watery stool with admixture of mucus and blood, tenesmus.*

ETIOLOGY

Shigellae are slender, gram-negative, nonmotile bacilli and are members of the family Enterobacteriaceae and the tribe Escherichieae. The four *Shigella* species (*S. dysenteriae*, *S. flexneri*, *S. boydii*, and *S. sonnei*) are defined on the basis of surface somatic O antigens and carbohydrate fermentation patterns. Most are lactose-negative (*S. sonnei* is a late lactose fermenter) and produce acid but not gas from glucose, resulting in a typical acid butt and alkaline slant in triple sugar iron agar without H_2S production.

Shigella species cause damage by 2 mechanisms, invasion of the colonic epithelium, which is dependent on a plasmid-mediated virulence factor, and production of enterotoxin, which is not essential for colitis but enhances virulence. The organism is spread by fecal-oral contact; via infected food or water.

EPIDEMIOLOGY

During last time, major global shifts in the prevalence of four *Shigella* species have been observed. Until begin of 20^{th} century, *S. dysenteriae* type 1 was the predominant isolate, frequently causing epidemics with high mortality until it was replaced by *S. flexneri*. Since middle of 20^{th} century *S. flexneri* has been replaced by *S. sonnei* in the industrialized countries. *S. boydii*, the fourth species, has remained largely confined to the Indian subcontinent.

Shigella is a natural pathogen only of humans. Transmission takes place by the fecal-oral route, generally through contaminated vectors such as food, water, flies, and fomites, but sometimes via direct contact. The organism can even be transmitted during participation in recreational water sports in fecally contaminated pools or lakes and can spread rapidly among confined populations in close contact.

Shigellosis is associated with a high rate of secondary household transmission. As many as 40 percent of children and 20 percent of adults who are household contacts of a case (generally a preschool child) will develop Shigella infection; the

infection is often symptomatic in children but asymptomatic in adults, who seem to have an acquired immunity. In contrast, epidemic disease affects all ages, with clusters of severe and fatal cases in the very young and the very old. Since 1969, epidemic S. dysenteriae type 1 has reappeared in Latin America, in the Indian subcontinent and elsewhere in Asia, and in central and southern Africa and has been associated with relatively high mortality rates due to antimicrobial resistance and inadequate diagnosis and case management. Prolonged asymptomatic carriage is uncommon; unless there is underlying malnutrition, the organisms are generally cleared in a few weeks.

PATHOGENESIS

Shigellae survive in low pH medium more easily than other enteric pathogens and have ability to pass the gastric acid barrier. Invasion of colonic epithelial cells and cell-to-cell spread of infection involves initial attachment of the organism to colonic cells, entry by an endocytic mechanism in which organisms are initially encased in and then escape from plasma membrane-enclosed vesicles, and a jet propulsion-like movement to the epithelial cell surface that is powered by bacterium-induced actin polymerization at the trailing end of the organism. Although invasion is initially innocuous, subsequent intracellular multiplication causes cell damage and death, finally resulting in characteristic mucosal ulcerations.

It was originally thought that shigellae invade the host across the intestinal epithelial cells. Recent studies suggest that the initial invasion may occur via the antigen-sampling M cell. The resulting limited penetration by organisms initiates an inflammatory response and alters the functional integrity of tight junctions between epithelial cells. These changes allow more organisms to breach the mucosal barrier at intercellular junctions. Subsequent neutrophil infiltration of the lamina propria appears to be essential to the development of disease and is associated with increased invasion. If neutrophil migration is directly inhibited by the treatment of animals with antibody to CD18, the escalating invasion by microorganisms does not take place.

Escape from the phagocytic vesicle is necessary for the virulence of shigellae and permits multiplication of the organisms in the cytoplasm. The multiplying organisms spread within the cytoplasm to the plasma membrane of the host cell and then from cell to cell. This spread is achieved by the polymerization of actin at the back end of the dividing bacteria (defined relative to the subsequent direction of motion). Binding and cross-linking by the host protein plastin result in a sphincter-like contraction that provides a forward propulsive force.

One more property of apparent importance in virulence for *S. dysenteriae* type 1 is the ability to produce Shiga toxin, which is encoded by the iron-regulated chromosomal gene *stx*. Shiga toxin is composed of two distinct peptide subunits, each with highly conserved active regions. The first, located on the larger A subunit, is an

N-glycosidase that hydrolyzes adenine from specific sites of ribosomal RNA of the mammalian 60S ribosomal subunit, irreversibly inhibiting protein synthesis. The second common region is a binding site on the B subunit that recognizes glycolipids of target cell membranes that terminate in a galactose $\alpha 1 \rightarrow 4$-galactose disaccharide. The glycolipid Gb3 is a specific receptor present on toxin-sensitive rabbit intestinal villus cells but not crypt cells, and toxin action is specific for the former.

Wild-type toxigenic *S. dysenteriae* causes more severe disease in primates than does an isogenic toxin-negative mutant. The toxin of this organism appears to play a role in the pathogenesis of microangiopathic complications, hemolytic-uremic syndrome (HUS), and thrombotic thrombocytopenic purpura: only toxin-producing shigellae and *E. coli* are associated with these systemic diseasees. Two new *Shigella* enterotoxins, ShET-1 and -2, have been described; the former is restricted almost exclusively to *S. flexneri* 2a, whereas the latter is distributed more. The two enterotoxins are encoded by chromosomal and plasmid genes, respectively. Both toxins alter electrolyte transport by segments of gut in vitro and cause net fluid secretion in vivo. Moreover, both toxins induce antibody in infected humans.

In shigellosis, the epithelial surface of the human colon shows extensive ulcerations, with an exudate consisting of desquamated colonic cells, polymorphonuclear leukocytes, and erythrocytes; the ulcerations may resemble a pseudomembrane in severely affected areas. Marked mucus depletion and increased mitotic activity are evident in the crypt regions and presumably reflect a response to the loss of surface colonic cells. The lamina propria is edematous and hemorrhagic and is infiltrated by neutrophils and plasma cells. There is also swelling of capillary and venular endothelial cells, with margination of neutrophils. At the ultrastructural level, bacteria can be seen within vesicles as well as free in the cytoplasm. Histologic examination of colon from dysenteric humans shows an alteration of mucosal endothelial cells similar to that induced by endotoxin lipopolysaccharide (LPS). Shiga toxin (protein) targets endothelial cells as well, especially when toxin receptor expression is upregulated by exposure to LPS or proinflammatory cytokines. Levels of circulating LPS are high in *S. dysenteriae* type 1 infection and somewhat lower in *S. flexneri* infection, even without bacteremia. The frequency of endotoxemia in shigellosis suggests a broader role for LPS in the pathogenesis of the disease. One likely mechanism is related to the ability of LPS to induce cytokine gene transcription and the strong association of cytokine secretion and inflammation. Bacterial invasion of the mucosa activates the transcription factor NF-kappa B, which is involved in regulation of cytokine synthesis. Cytokine-producing cells are present in the mucosa of patients infected with *S. dysenteriae* or *S. flexneri* and in their stools as well. In fact, the number of cells producing interleukin 1, interleukin 6, interferon ά, and tumor growth factor is directly related to the severity of the inflammation. Inflammatory changes in *Shigella* infection thus appear to be components of the

pathogenesis of dysentery as much as they are a consequence of the bacterial invasive process.

Epidemiologic evidence indicates that immunity develops and is serotype specific. Common surface outer-membrane proteins involved in invasion elicit serum antibodies.

CLINICAL MANIFESTATION

Incubation period vary from 12 hrs to 7-10 days, on average 2-3 days. Onset of shigellosis is usually acute. The duration of incubation period depends from infective dose of the pathogen, conditions of infection, virulence of the pathogen and condition of human organism. The temperature can rise rapidly up to 38° - 41°C, accompanied by chill and general unwell. Shigellosis is characterized by frequent passage (usually 10 to 30 times per day) of small-volume stools consisting of blood and mucus. Diarrhea is accompanied by abdominal cramps and tenesmus - the painful straining with stooling that may lead to rectal prolapse, especially in young children. Severe forms of shigellosis are most likely in infection due to *S. dysenteriae* type 1 or *S. flexneri*. Patients with mild disease generally recover without specific therapy in a few days to a week. Severe shigellosis can progress to toxic dilatation and colonic perforation, which may be fatal.

In case of colitic form of shigellosis (most frequent, more then 90%) the temperature increases up to 38-39°C for 2-3 days. Severe abdominal pain develops in the lower part of the abdomen, mainly in the left iliac area. Stools at first have usual character, then mucus and fibers of the blood is marked. Tenesmus are very typical.

Gastroenterocolitic form is characterized with acute onset of the disease after short incubation period (6-8 hours) that more usual for food intoxications. The factors of transmission are usually milk and meat products.

Intoxication syndrome and symptoms of gastroenteritis are observed in the initial period. The manifestations of enterocolitis predominate in the climax period. Intoxication and diarrhea lasts for 2-7 days, but pain, infiltration and tenderness on palpation of sigmoid colon lasts quite longer. Full recover after acute shigellosis become in 1-1,5 month. In some patients postinfective colitis occurs.

Clinical classification

By duration:

- acute;
- lingering;
- chronic.

By character:

-gastroenterocolitic;
- enterocolitic;
- colitic form.

By gravity:

- effaced;
- mild;
- moderate;
- severe;
- grave.

There are mild, moderate, severe and grave course of the gastroenterocolitic form of acute shigellosis. For estimation of gravity of course of the disease it is necessary to take into account not only the degree of intoxication and gastrointestinal tract damage, but also degree of dehydration due to repeated vomiting and plentiful diarrhea.

Enterocolitic form of acute shigellosis. The main feature of this variant of the course of acute shigellosis is predominance of the clinical symptoms of enteritis together with symptoms of colitis – pain in left iliac area, stools with admixture of fibers of the blood and tenesmus. Changes in blood analysis include neutrophil leukocytosis, ESR increasing.

LABORATORY DIAGNOSIS

The specific diagnosis is based on culture of *Shigella* from the stool samples. The yield of *Shigella* is increased if the organism is sought by stool culture when the patient has leukocytes in a coprocytogramm or bloody diarrhea. The organism is very labile and must be transferred quickly to plates or holding media (such as buffered glycerol saline) if it is to survive. Stool samples are preferable to swabs for a rectal sample obtaining. More than one selective medium should be used for culture – Endo, Ploskirev or other. Diagnosis by the polymerase chain reaction is also possible.

Serologic tests can be performed, e.g. reaction of indirect agglutination (RIAG), since antibodies to somatic antigens develop early in the acute phase of disease. Diagnostic titer is 1:200 or more. But serologic assessments usually are used mainly for epidemiologic studies.

Rectosigmoidoscopy shows the mucosa to be hemorrhagic, with mucous discharge and focal ulcerations and sometimes with overlying exudate. The majorities of lesions are in the distal colon and progressively diminish in the more proximal segments of large bowel. Mild dehydration is common among patients with watery diarrhea; severe dehydration is very rare. With extensive colonic involvement, protein-losing enteropathy can occur and can have important adverse nutritional consequences, especially for already poorly nourished children.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis includes inflammatory colitis due to other microbial agents: enteroinvasive E. Coli, *Campylobacter jejuni*, *Salmonella enteritidis*, *Yersinia enterocolitica*, *Clostridium difficile*, and the protozoan *Entamoeba histolytica*. Ulcerative colitis and Crohn's colitis are among the conditions with "noninfectious" causes that should be considered. All these infections except that due to *E. histolytica* are associated with the presence of large numbers of fecal leukocytes. Amebiasis can be diagnosed by the detection of erythrophagocytic trophozoites in the stool.

Other laboratory studies are nonspecific and may disclose in clinical blood analysis: neutrophilic leukocytosis, anemia due to blood loss with hemorrhagic diarrhea; prerenal azotemia, or (if watery diarrhea has been pronounced) hyperchloremic acidosis.

TREATMENT

Diet is very impotent measure in treatment. In acute period there is diet N 4 by Peuzner, then after normalization of gut function patients diet N 2 can be indicated with further transmission on diet N 15.

In case of gastroenterocolitic form of shigellosis gastric lavage is a first aid measure. It must be performed with cool water or 0,5% solution of sodium bicarbonate in quantity of 3 – 5 liters. Usage of stomach pump is preferable.

Antibiotic treatment is indicated in most patients. Resistance to sulfonamides, streptomycin, levomicetin (chloramphenicol) and tetracyclines is almost universal. Many shigellae are now resistant to ampicillin and trimethoprim-sulfamethoxazole as well. Ciprofloxacin (Cipro, Ciloxan) in dose 500 mg per os (PO), trimethoprim - sulfamethoxazole (Bactrim, Septra, Bactrim DS, Biseptol 480) can be used in doses two tablets three time a day, for 3 days.

It is necessary to avoid narcotic-related antidiarrheals. Antimotility drugs are suspected of enhancing the severity of disease by delaying excretion of organisms and thus facilitating further invasion of the mucosa. Therefore, they are contraindicated for the treatment of infants and young children. In adults, these agents are contraindicated for use in the acute phase of disease.

In case of severe intoxication there is indicated IV infusion of polyionic crystalloid solutions (trisolum, lactosolum, acesolum). In case of mild or moderate infection and absence of repeated vomiting oral rehydration solutions (Rehydron, Glucosolan, Cytroglucosolan) are preferable.

Treatment of shigellosis

1. **Regidration** ORS **(Table 12)**
2. **Desintoxication**

A. Enterosorbents

COAL: Polyphepam, Carbolenum
SILICON POLIMERS: Enterosgelum, Sorbogelum, Polysorbum
POLYVYNILPYROLIDON: Enterodesum

B. Intravenous desintoxication

POLYVINYLPYROLIDON: Haemodesum, gluconeodesum
COLOID SOLUTION: Rheopolyglucinum, Rheosorbilactum

3. Antibiotic therapy

A. Nitrofurans

Furasolidonum, Furodoninum 0.1g 4 time per day
Nifuroxazidum 0.1g 2 time per day

B. Sulphanilamids

Sulphamethoxazole/trimethoprim 800/40 mg 2 time per day

C. Fluorinequinolones

Norfloxacinum 400 2 time per day
Ciprofloxacinum 500 2 time per day
Lomefloxacinum 500 1 time per day

D. Antibiotics

Chloramphenicol 0.5-1.0 4 time per day
Ampicillin 1.0 4 time per day
Aminoglycosids (Kanamycin, Gentomycin, Amicin)
Cefolosporins III generation (Ceftriaxon)

E. Probiotics and prebiotics

Acute period: **Bactisubtilum** (B.subtilis), **Aerobactum** (Aerococcus sp.) **Enterol 250** (Sacharomyces boulardii), **Carbolevuer** (Sacharomyces cerevaisae), Bifiform (Bifidobacterium + Enterococcus)
Reconvalescence period: Linex (Lactobacterium + Enterococcus), Bifiform, Colibacterinum (E.coli), Normase (lactulose), Hilac-forte, cellulose

F. Local treatment

Lavement with plant oils, plant extracts (Recutan, Chlorophyliptum, Ectericidum).

PREVENTION

Direct-contact transmission of shigellosis can be prevented by appropriate environmental and personal hygiene. Hand washing with soap and water, decontamination of water supplies, use of sanitary latrines or toilets, and precautions in the preparation and storage of food can all reduce the primary and secondary transmission of *Shigella* infection. In highly endemic developing countries, infants are protected during the period of exclusive breast feeding, which should be encouraged. Any measures that reduce the burden of malnutrition will also reduce the burden of shigellosis in the population. Stool precautions should be instituted for hospitalized infected patients to ensure safe disposal of infected excreta and linens,

and hospital personnel must wash their hands and medical instruments (such as stethoscopes) after each contact with an infected patient. Cohorting of asymptomatic infected children, use of antibiotics to reduce infectiousness, and scrupulous attention to hygiene are usually successful in nosocomial outbreaks. Children in day care must be kept at home while clinically ill and ideally should have a negative stool culture before returning to the day-care facility.

Likewise, food handlers and food industry workers, who develop shigellosis, should be culture-negative before returning to work and need supervision after convalescence in outpatient department. Antibiotic treatment is not indicated for the asymptomatic carrier state.

No effective vaccine is available.

YERSINIOSIS

DEFENITION: *Yersiniosis (syn.: intestinal yersiniosis) is an acute infectious disease from the group of bacterial zooanthroponoses, characterized by the primary affection of gastrointestinal tract, with tendency to generalization of process with involving of different organs and systems.*

History. Yersinia enterocolitica was first cultured from human in the USA in 1939 by G. Shleifstein and M. Koleman. The first cases of disease of yersiniosis in people were registered in France, Belgium and Sweden in 1962 – 1963.

ETIOLOGY

Y. enterocolitica and *Y. pseudotuberculosis* are pleomorphic gram-negative bacilli in the family Enterobacteriaceae. They are aerobic or facultatively anaerobic, motile at 25°C, nonmotile at 37°C, oxidase negative, urease positive, able to ferment glucose, unable to ferment lactose, and usually able to reduce nitrates. They grow well, if slowly, on nonselective media (e.g., blood agar) and on most of the routine media used to select for enteric bacteria. They can multiply within a wide temperature range (-1°C to 45°C). The most clinically and epidemiologically useful methods for identifying pathogenic *Y. enterocolitica* isolates are biotyping based on biochemical profiles and serotyping according to somatic O and H antigens, of which serotypes O:3, O:8, O:9 and 5,27 cause infection in human. Serotype 3 strains are found in Europe, Canada, Africa, and Asia; serotype 8 is the predominant type in the United States; serotype 9 has been reported frequently from Finland and other European countries; serotype 5,27 is reported in association with bacteraemic complications in compromised patients. *Y. pseudotuberculosis* strains comprise a homogenous species characterized by six serological types (I to VI). In Europe serotype I strains are most frequently recognized in man and animals; types II and III

are less common. Serotypes IV and V are rarely isolated while serotype VI has been isolated only from rabbits in Japan.

EPIDEMIOLOGY

Y. enterocolitica is distributed worldwide and has been isolated from soil, fresh water, contaminated foodstuffs (meat, milk, and vegetables), and a wide variety of wild and domestic animals, including mammals, birds, amphibians, fish, and shellfish. Many serotypes isolated from environmental sources, however, evidently are not human pathogens.

There are marked differences in the reported frequency and distribution of *Y. enterocolitica* infections. There is general agreement that in Europe, especially in Scandinavia and Belgium, sporadic infection with *Y. enterocolitica* serotypes O3 and O9 are common while outbreaks with these or other serotypes are rare. The most important sources of these infections are thought to be pork, especially when tongues are eaten undercooked or raw, and contact with household pets, especially sick puppies and kittens.

In North America numerous outbreaks of *Y. enterocolitica* have been recognized, several have been caused by serotype O8. Epidemics have usually been caused by contamination of a food vehicle from a meat source or water. Sporadic cases in the United States are less common than in England and associated with multiple serotypes. Transmission is by the faecal-oral route after eating or drinking food or water contaminated by colonized or infected animals or people. Hospital acquired infection occurs by nosocomial transmission and by the use of stored blood from asymptomatic donors or individuals who had gastrointestinal disease within 2 weeks of their blood donation. Because of the ability of Y. enterocolitica to multiply both in food products under refrigeration and in aerobic conditions, at risk products are raw or undercooked pork or any uncooked meat stored in evacuated plastic bags.

Except in rare instances of transmission via contaminated blood products or direct cutaneous inoculation, the enteropathogenic yersiniae are thought to enter the host via the oral route. The 50 percent infectious dose in humans is uncertain but may be more then 10^9/ bacteria.

Cases and outbreaks of yersiniosis due to *Y. pseudotuberculosis* are less commonly recognized. Not unexpectedly this zoonotic infection results from contact with animals or birds and there has been no evidence of person to person transmission.

PATHOGENESIS

The organisms initially invade the ileal epithelium, then are translocated via M cells into the lamina propria, and finally enter Peyer's patches, where they are able to replicate. They subsequently drain into the mesenteric lymph nodes, which undergo

hyperplasia and from which the bacteria can be distributed systemically. The mesenteric lymph nodes can become intensely swollen and matted and are occasionally detected on physical examination as a tender right lower quadrant mass. Intestinal inflammation (most commonly of the distal ileum and less commonly of the ascending colon) develops and may be accompanied by mucosal ulcerations. In relatively severe cases, thrombosis of mesenteric blood vessels, intestinal hemorrhage, and necrosis can occur. In patients with enteropathogenic yersinial infections who undergo exploratory laparotomy, the appendix usually is histologically normal or shows only lymphoid hyperplasia, but frank suppuration is sometimes evident.

Both *Y. enterocolitica* and *Y. pseudotuberculosis* can express at least one protein superantigen that selectively stimulates the proliferation of T cells. Many strains of *Y. enterocolitica* produce a heat-stable enterotoxin that is similar to *Escherichia coli* enterotoxin. The cell walls of *Y. enterocolitica* and *Y. pseudotuberculosis* contain a lipopolysaccharide (endotoxin). However, they can exploit host-chelated iron stores and the drug deferoxamine (a siderophore produced by *Streptomyces pilosus*). Therefore, iron overload (e.g., caused by hemodialysis or multiple transfusions) and deferoxamine therapy appear to be independent risk factors for *Y. enterocolitica* bacteremia (especially that involving serotypes O:3 and O:9) and to a lesser degree for *Y. pseudotuberculosis* bacteremia.

Immunogenetic factors are clearly involved in the pathogenesis of reactive arthritis following infection with the enteropathogenic yersiniae. As noted above, most patients with *Yersinia* - induced reactive arthritis express HLA-B27. In addition, *Y. pseudotuberculosis* shares at least one cross-reactive epitope with HLA-B27. In patients with reactive arthritis following *Y. enterocolitica* infection, yersinial antigens are commonly detectable in synovial fluid cells in the apparent absence of whole organisms. Thus, it is unknown whether the arthritis results from occult bacterial persistence through self-tolerance of HLA-B27 with a failure of cross-reactive immune responses to yersiniae, from an immune response to common antigenic determinants shared by the bacteria and host HLA-B27 (i.e., molecular mimicry), or from other mechanisms. Local T-cell immune responses appear to be particularly important in the pathogenesis of reactive arthritis. The pathogenesis of *Yersinia*-induced erythema nodosum is obscure.

CLINICAL MANIFESTATION

Clinical classification (WHO, 1981)

1. Mesenteric lymphadenitis;
2. Enteritis;
3. Septicemia;
4. Polyarthritis;

5. Erythema nodosum;
6. Reyter's syndrome.
7. Extramesenteric forms:

- acute meningitis;
- pneumonia, pleurisy;
- purulent arthritis and osteomyelitis;
- abscesses of lever, spleen.

The incubation period for primary yersiniosis is probably 3 to 7 days and generally under 10 days; secondary arthritis and erythema nodosum follow 4 to 14 days after the prodromal disease. The inflammatory arthritis may persist for 1 to 4 months followed by a prolonged period of stiffness and arthralgia.

The most commonly recognized form of yersiniosis is an acute enteritis due to *Y. enterocolitica* with acute onset, watery diarrhea, abdominal pain in epigastria and umbilical regions, nausea and vomiting. This contrasts with the pseudoappendicitis syndrome of abdominal pain caused by acute mesenteric lymphadenitis. The majority of patients diagnosed as having *Y. pseudotuberculosis* infection present with mesenteric lymphadenitis while only 15 to 20 per cent of *Y. enterocolitica* infections present with this syndrome. The clinical picture is that of acute or subacute appendicitis with pain in the middle or lower right quadrant of the abdomen and a temperature of 35 to 40°C. Signs of peritoneal irritation are observed but at laparotomy the appendix usually appears normal or is mildly congested with some clear fluid in the peritoneal cavity. Pathognomonic is the finding of enlarged mesenteric lymph nodes in the ileocaecal angle with a hyperemic mesentery in the region of the affected nodes with or without swelling of the terminal ileum and caecum. These clinical presentations must be distinguished from Crohn's disease, tuberculosis, and neoplasia. Most cases are self limiting but complications include diffuse ulceration of the small intestine and colon, perforation, intussusception, toxic megacolon, cholangitis, and mesenteric vein thrombosis.

Patients with *Y. enterocolitica* may present with focal infection in a variety of extraintestinal sites in the absence of bacteraemia: pharyngitis with cervical lymphadenopathy, osteomyelitis, conjunctivitis, urinary tract infections, renal disease, pneumonia, and lung abscesses.

Secondary immunological implications occur 1 or 2 weeks after the onset of gastrointestinal symptoms and are typically a polyarticular arthritis or erythema nodosum; less common are Reiter's syndrome, glomerulonephritis, or myocarditis.

LABORATORY DIAGNOSIS

Results of routine laboratory tests in most patients with yersiniosis are nonspecific. Leukocyte counts are usually normal or slightly elevated, often with a modest left shift. Standard microbiologic methods are sufficient to isolate *Y.*

enterocolitica and *Y. pseudotuberculosis* from otherwise-sterile sites, such as blood, CSF, lymph node tissue, and peritoneal fluid, and from abscesses. Isolation of these organisms from feces is impeded by their slow growth and the overgrowth of normal fecal flora on culture media routinely used to select for enteric bacteria. When routine enteric media are used, the yield of yersinial isolates from feces is increased by incubation at 22 to 25°C for 48 h. The yield from feces and other grossly contaminated specimens can be further increased by the use of *Yersinia*-selective cefsulodin – Irgasan - novobiocin (CIN) agar and by cold enrichment (i.e., inoculation of feces into buffered saline and incubation at 4°C for 2 to 4 weeks, with periodic plating onto enteric media). Because bacteriologic procedures designed to isolate yersiniae from feces are not considered cost -effective, many laboratories undertake them by special request only.

The results of serologic tests can be used to support a diagnosis of yersiniosis. Agglutination tests or ELISAs are used most commonly. The existence of multiple serotypes makes routine serologic tests laborious; thus these tests are generally conducted only in research laboratories or large commercial laboratories. Since these tests are experimental and are neither standardized nor well validated, and since some strains of *Yersinia* cross-react with other bacteria (e.g., *Brucella*, *Salmonella*, and *Vibrio*) and with serum from some patients with thyroiditis, results should be interpreted with caution. In typical uncomplicated cases of yersiniosis, agglutinin titers begin to rise within the first week of disease, peak in the second week, and then gradually diminish and return to normal within 3 to 6 months, although agglutinating antibody may remain detectable for several years in some cases. Because an initial serum specimen is often collected a week or more after the onset of disease, when agglutinin titers are already high, it is usually impossible to document a fourfold or greater rise in titer between paired specimens (although a fourfold or greater fall in titer may be found).

In patients with *Yersinia*-induced reactive arthritis, synovial fluid is sterile and the leukocyte count ranges from a few hundred to 60,000/uL, with a majority of neutrophils. The erythrocyte sedimentation rate is often >100 mm/h. Rheumatoid factor and antinuclear antibodies are usually absent. The diagnosis of *Yersinia*-induced reactive arthritis or other nonsuppurative inflammatory sequelae can be difficult, especially when triggering infections are asymptomatic or clinically mild or occur several weeks before the diagnosis is attempted. Because the isolation of a pathogenic *Yersinia* strain from feces is the most specific diagnostic test in such cases, it should be attempted. Since culture is of limited sensitivity in this clinical setting, a high index of suspicion and positive results of serologic tests for *Y. enterocolitica* or *Y. pseudotuberculosis* usually are required for diagnosis.

TREATMENT

Antimicrobial therapy is not indicated in uncomplicated enterocolitis or pseudoappendicitis syndrome resulting from yersiniosis. Localized infection in the gastrointestinal tract, septicemia, and enterocolitis in compromised patients requires appropriate antimicrobial treatment with third generation cephalosporins, quinolones, or aminoglycosides. *Y. enterocolitica* isolates are usually resistant to most penicillins and first generation cephalosporins. *Y. pseudotuberculosis* isolates are usually sensitive to ampicillin, while both species are sensitive to tetracyclines. Patients with reactive arthritis may benefit from treatment with nonsteroidal anti-inflammatory drugs, intraarticular steroid injections, and physical therapy.

PREVENTION

The importance of safe food-handling and food-preparation practices in the prevention of yersiniosis cannot be overemphasized. Caution is particularly warranted in the case of pork and other animal products. The consumption of raw or undercooked meats, especially pork, should be avoided. Increased efforts to prevent the spread of enteric pathogens in household, pet-care, day-care, and hospital settings and in the food industry would be likely to decrease the incidence of yersiniosis.

Yersiniosis is not routinely reportable to public health authorities in most jurisdictions. However, clinicians who suspect a common-source outbreak (e.g., because they have documented a familial case cluster or have diagnosed the disease in several apparently unrelated patients over a short period) or some other public health threat should consult promptly with local public health officials.

PSEUDOTUBERCULOSIS

DEFINITION: *Pseudotuberculosis is an acute infectious disease caused by Y. pseudotuberculosis, characterized by polymorph clinical manifestations with primary affection of gastrointestinal tract, skin and locomotor system.*

ETIOLOGY

Y pseudotuberculosis belongs to the genus *Yersinia*, which has 2 other pathogens that infect humans – *Y enterocolitica* and *Y pestis*.

The bacillus was first described in 1889 and was later renamed twice before the current name, *Y pseudotuberculosis*, was established in the 1960s. From the late 1920s to the mid 1960s, the organism was identified as *Pasteurella* and then *Shigella pseudotuberculosis*. A Russian researcher named Znamenskiy demonstrated that the organism was, in fact, a causative agent for clinical disease through self-inoculation.

Y pseudotuberculosis and *Y pestis* have a remarkable 97-100% homology. Y pseudotuberculosis is a gram-negative, non–lactose-fermenting coccobacillus that chemically is differentiated from other species, such as Y enterocolitica, by its fermentation of sorbitol, ornithine decarboxylase activity, and other tests. The optimum growth of yersinia occurs on MacConkey medium at 20-35°C. The organism is urease positive. *Y pseudotuberculosis* is both aerobic and facultatively anaerobic; it is a gram-negative coccobacillus that grows slowly on blood and chocolate agar plates, forming small colonies with a gray and translucent characteristic at 24-72 hours. It has a good growth pattern on MacConkey or eosin-methylene blue (EMB) agar plates but is enhanced noticeably at lower temperatures (e.g., 4°C cold enrichment in buffered saline) and is in fact motile at temperatures lower than 28°C. Biochemically, it is oxidase-negative, urea-splitting, and catalase-producing, and it does not ferment lactose.

EPIDEMIOLOGY

Yersinia pseudotuberculosis is the least common of the 3 main Yersinia species to cause infections in humans. It is primarily a zoonotic infection with variable hosts, including domestic and sylvan animals and birds. The condition has been associated with food-borne infection, including a few outbreaks.

Y. pseudotuberculosis infection has zoonotic forms; the animal reservoirs for such transmission include many mammalian and avian hosts, such as dogs, cats, horses, cattle, rabbits, deer, rodents, and birds (geese, turkey, ducks, canaries, cockatoos).

Distribution is worldwide; most cases occur in the winter season, probably because of the increased seasonal incidence of infection among animals. The increased prevalence in winter may also be due to the enhanced growth characteristics in cold temperatures. Although many cases have been reported in Europe, large-scale outbreaks in the Aomori region of Japan were noted in the early 1990s. Fewer than 30 cases of septicemia have been reported in the literature.

In the 1980s, outbreaks in Finland and Japan constituted most of the sporadic cases reported in the literature. In 1995, 8 cases were reported in a Belgian hospital that involved gastrointestinal complaints caused by *Y. pseudotuberculosis*, which were obtained from stool analysis and careful isolation techniques involving cold-enriched media.

In November 1998, 4 laboratory-confirmed cases of Y pseudotuberculosis were reported to the British Columbia Centre for Disease Control Society (BCCDCS). Through a follow-up case-control study evaluating risk factors in a multivariate analysis, it was ascertained that possibly contaminated homogenized milk was implicated in the outbreak. In 1991, children consuming untreated drinking water in

Okayama, Japan, were exposed to Y pseudotuberculosis that led to clinical disease. Isolation of the organism also has been reported in well water (in Czechoslovakia).

Infections in humans are primarily acquired through the gastrointestinal tract as a result of contaminated food products.

Fecal excretion of the microorganism can occur several weeks after disease but often does not result in secondary person-to-person cases or clinical relapses. Latent times from 2-20 days have been reported in sporadic outbreaks with peak incidence rates at 4 days after ingestion.

PATHOGENESIS

Main infection route is through contaminated food or water. Although the bacterial organism generally does not result in diarrheal symptoms, it can cause a range of morbidities including forms of mesenteric lymphadenitis, granulomatous disease, and dissemination with sepsis. On first stage (lymphadenitis) there are no clinical symptoms. But in case of insufficiency of lymphatic barrier bacteremia and clinical manifestation occurs.

The following is a list of the major virulence factors associated with *Y.pseudotuberculosis* (specific pathogenic mechanisms have not been fully elucidated). Yersinia species have encoded several plasmid virulence factors. More specifically, *Y pseudotuberculosis* has a 70-kd plasmid that encodes for a contact-dependent type III secretion system that delivers virulence factors known as *Yersinia* outer proteins (Yops). This mode of delivery is crucial for the pathogenicity of Y pseudotuberculosis.

Another virulence factor is the superantigen *Y pseudotuberculosis* - derived mitogen (YPM), an exotoxin. Generally, superantigens are bacterial or viral classes of proteins that are mediators of immune system activation. YPM selectively stimulates T lymphocytes that have V beta–containing gene segments and induce excessive amounts of inflammatory cytokines that appear to correlate to an increase in systemic symptoms. This is analogous to the role of superantigens in a similar disease, such as Kawasaki disease and even staphylococcal and streptococcal toxic shock syndromes.

Another group of mediators of *Y pseudotuberculosis* pathogenesis is collectively known as adhesion molecules.

These proteins bind onto the host cell and aid in facilitating the internalization of *Y pseudotuberculosis* into the host. Two major proteins in this group are invasin and yadA. *Y pseudotuberculosis* strains that have the Inv gene (which encodes invasin) have enhanced invasion properties for epithelial host cells. Invasin of Y pseudotuberculosis binds to integrins on the M cells of Peyer patches. These integrins also bind to collagen and fibronectin.

Additionally, invasin is involved in promoting the internalization of bacteria across these eukaryotic M cells. The yadA outer membrane protein binds to laminin, collagen, and fibronectin that are themselves bound to their respective beta-1 integrin receptors on the cell surface. These binding interactions contribute to the processes of bacterial adhesion onto the host cell surface and bacterial internalization into the host cell.

Another molecular mechanism of pathogenesis is the high pathogenicity island (HPI) of *Y pseudotuberculosis*. It contains the gene that codes for yersiniabactin, the important siderophore used for iron uptake. HPI has been shown to be common among the highly pathogenic species of Yersinia. Furthermore, the level of virulence increased when genes of HPI were transferred to a biotype 2 strain of Y enterocolitica that is ordinarily observed to display low pathogenicity.

Because the organism does not produce iron-binding compounds, patients with iron-overload states such as hemochromatosis, venous congestion, hemolytic anemia, and cirrhosis are at risk for sepsis. In 1959, an epidemic that occurred on the Pacific coast of Russia was termed the Far East scarlatinoid fever. Interestingly, virulence factors such as the *Y pseudotuberculosis* - derived mitogen (YPM) - a superantigen - are likely related to the atypical scarlet fever syndromes more recently reported, such as Izumi fever in Japan.

Histologic Findings: Although the affected appendix may even be normal in appearance, involved lymph nodes (mesenteric) typically show epithelioid granulomatous changes, lymphoid hyperplasia, coagulative necrosis, and histiocytic cell hyperplasia. Enteric lesions may be associated with crypt hyperplasia, microabscesses, and villus shortening.

CLINICAL MANIFESTATION

There are several clinical classifications of pseudotuberculosis.

Clinical classification

Abdominal form – predominance of symptoms of gastrointestinal tract affection: abdominal pain, tenderness on palpation, nausea, vomiting

- terminal ileitis;
- mezadenitis;
- appendicitis.

Icteric form – pain in right part of abdomen, darkening of urine, jaundice of skin and mucous layers, enlargement of liver, elevation of serum bilirubin, alaninaminotranspherace.

Arthritis – pain and swelling in big joints.

Exantematous – erythematous sock- gloves- and hood - like rush on skin of extremities end trunk.

Catharal – symptoms of pharingitis, rhinitis, accompanied with sore throat, hyperemia end edema of mucous of nasopharings.
Mixed – diseases with signs of different forms (e.g. abdominal and icteric).
Generalized – all syndromes expressed highly, it is difficult to distinguish.
The incubation period varies from 5-10 days. Most Y pseudotuberculosis infections are self-limited with a low case-fatality rate. However, the infrequent sepsis - associated diseases in patients with chronic liver disease may be associated with a greater than 75% mortality among these patients.
Effaced, cryptic – can be diagnosed only by serological methods in case of outbreak.

Onset of the disease is usually acute. Initial symptoms include fever and abdominal pain (often right lower quadrant location). Diarrhea is not common. The recently described syndrome of Izumi fever also can include more systemic symptoms. Other symptoms may include joint effusion, tenderness, or decreased range of movement and may be asymmetric in distribution.

Other clinical problems associated with the enteric form have included terminal ileitis and intussusception, especially in children. In two thirds of clinical cases, enterocolitis may result and generally lasts 1-3 weeks.
Izumi fever, a syndrome, has been characterized by acute onset, scarlatiniform rash, systemic symptoms, and features shared with Kawasaki disease, such as coronary artery aneurysms. Acute renal failure has been reported, although this is distinctly a rare manifestation.

Other manifestations of infection can include erythema nodosum, arthralgias, reactive arthritis, and ankylosing spondylitis.
The Far East scarlatinoid fever was first described in the context of Y pseudotuberculosis infection. A scarlatinoid-appearing rash involving the head and neck, upper and lower extremity erythema, mucous membrane enanthem, and strawberry tongue characterize this syndrome.

Physical findings may be grouped into 3 main categories, systemic, enteric, and rheumatologic. The predominant and often self-limited presentation is that of a febrile gastroenteritis with right lower quadrant abdominal pain.

Systemic findings may include fever, skin rash, strawberry tongue, hypotension, and lymphadenopathy.
Enteric findings include abdominal tenderness with or without rebound indicative of peritoneal involvement. Tenderness may be exquisite over McBurney point.
Complications: Late complications of yersinial infection also can include reactive arthritis and rheumatologic manifestations, uveitis and conjunctivitis.

LABORATORY DIAGNOSIS

The laboratory diagnosis of Y pseudotuberculosis infection is a matter of confirming the presence of the organism to support the clinical diagnosis of the associated syndromes.

Because this is a bacterial infection and it ought not to be present in sterile fluids, the acquisition by culture from sources such as blood, CSF, peritoneal fluid, synovial fluid, or other organ-based biopsy (intestinal tissue, skin) is confirmatory.

Besides diagnostic measures that include serological tests, also developed various PCR methods that are sensitive, efficient, and accurate tools for identifying and serotyping *Y pseudotuberculosis*.

Histologic examination of specific tissue, such as mesenteric lymph nodes, may yield both pathologic and microbiologic presence of organism.

Isolation of organism from stool is difficult given the slow growth pattern and overgrowth of normal fecal flora. However, stool culture yield may be increased by means of cold enrichment, special culture media (CIN agar), or alkali treatment. These methods generally are not cost effective.

Blood, peritoneal fluid, pharyngeal exudate, and synovial fluid may yield the organism.

ELISA and agglutination tests may be ordered; the antibodies (against the O antigen) may appear soon after the onset of disease and are expected to wane over 2-6 months. Paired serum specimens taken 2 weeks apart that indicate a 4-fold rise in agglutinating antibodies can support the diagnosis. Hemagglutination reaction tests that detect the pili (fimbriae) of either *Y pseudotuberculosis* has also been developed. Hemagglutination titers of 1:160 or higher are considered generally significant and indicative of true infection.

However, cross-reaction between antibodies against other organisms may obscure the diagnostic picture. These other organisms include other *Yersinia, Vibrio, Salmonella, Brucella,* and *Rickettsia* species.

Researchers have developed monoclonal antibodies that can identify serogroup-specific protein epitopes of *Y pseudotuberculosis* strains (grown at specific temperatures) from each of the 6 serogroups of the species. These monoclonal antibodies have been shown to not positively react with other *Yersinia, Salmonella, Shigella, Escherichia*, and *Proteus* species. This research has great potential to be developed into a potent serotyping tool for *Y pseudotuberculosis*.

TREATMENT

Bed regimen through the acute phase of disease is recommended. Activity as tolerated can be resumed once the enteric and systemic symptoms resolve.

No special diet is recommended. It is expected that with the resolution of enteric syndromes, the natural appetite will improve, and, accordingly, it is appropriate to ensure adequate caloric intake.

It often is not necessary to treat *Y pseudotuberculosis* infection with antibiotics. However, if critical disease along with younger age or immunosuppressed status is present, it may be prudent to treat with beta-lactam antibiotic therapy. Antibiotic therapy (initially IV) is warranted if the septic form of the disease occurs. Guidance by in vitro testing may be helpful; initial empiric therapy should include an aminopenicillin (Ampicillin 500 mg O with 6 hr interval for 7 days, or combination with a beta-lactamase inhibitor) and ideally, an aminoglycoside. Combination therapy is not absolutely needed in most cases. The aminoglycoside streptomycin 1 g IM one time a day has been used to treat Yersinia infections, although gentamicin (3 mg/kg/d IV q8h) and tobramycin (5 mg/kg/d IV q24h, reduce to 3 mg/kg/d as soon as clinically indicated), are considered appropriate. Third-generation cephalosporins have also been used. Another antibiotic that may have an important role is levomycetin (chloramphenicol 500 mg PO/IV q6h for 10 days) for patients with allergies to penicillin or aminoglycoside.

PREVENTION

Food-borne epidemics can occur. Contact precautions, especially in the inpatient setting, apply to appropriate barriers (eg, gown, gloves) to exposure to enteric secretions, such as with diarrhea. Avoid ingestion of uncooked meat, contaminated water, or unpasteurized milk. Careful handwashing should follow consumption or handling of chitterlings (pork intestines).

CAMPYLOBACTER INFECTION

DEFINITION: *acute intestinal infection characterizes by intoxication, gastroenterocolitis and possible development of septic process.*

Estimated rates for symptomatic enteric *Campylobacter* infection are 2 million infections per year or 1% of the US population per year. Incidence in the rural population is 5-6 times higher because of increased consumption of raw milk. A 5-year national laboratory study from 1982-1986 showed an isolation rate of *Campylobacter* species of 5.5 per 100,000 person-years. *C jejuni* accounts for 99% of the *Campylobacter* species isolated.

In developing countries, *C jejuni* often is isolated from stools of healthy individuals and is especially common during the first 5 years of life. Isolation rates in children who are asymptomatic or children with diarrhea range from 8-45%, with an annual incidence as high as 2.1 episodes of Campylobacter-associated diarrhea per

child. In developed countries, average incidence of Campylobacter bacteremia is estimated to be 1.5 per 1000 patients with enteritis.

The vast majority of patients recover fully after *C jejuni* infection within 5 days (range 2-10 d), either spontaneously or after appropriate antimicrobial therapy. Symptomatic Campylobacter infection-associated mortality rate in the US is estimated as 24 per 10,000 culture-confirmed cases or 200 deaths per year.

Infection with C fetus is of concern in patients who are immunocompromised, women who are pregnant, and neonates. Previously healthy patients usually recover without complications.

ETIOLOGY

Bacteria of the genus Campylobacter and of the related genera *Arcobacter* and Helicobacter cause a variety of pyogenic infections. Although acute diarrheal illnesses are most common, these organisms may cause infections in virtually all parts of the body, especially in compromised hosts, and these infections may have late nonsuppurative sequelae. The designation Campylobacter comes from the Greek for "curved rod" and refers to the organism's vibrio-like morphology.

Campylobacters are motile, non-spore-forming, curved gram-negative rods. Originally known as *Vibrio fetus*, these bacilli were reclassified as a new genus in 1973 after it was recognized that they were quite dissimilar from other vibrios. Since then, more than 15 species have been identified. These species are currently divided into three genera: *Campylobacter, Arcobacter,* and *Helicobacter*. Not all of the species are pathogens of humans. The human pathogens can be divided into two major groups: those that primarily cause diarrheal disease and those that cause extraintestinal infection. The principal diarrheal pathogen is *Campylobacter jejuni*, which accounts for 80 to 90 percent of all cases of recognized illness due to campylobacters. Other organisms that cause diarrheal disease include *Campylobacter coli, Campylobacter upsaliensis, Campylobacter lari,* and *Campylobacter fetus*. The major species causing extraintestinal illnesses is *C. fetus*; however, any of the diarrheal agents may cause systemic or localized infection as well. Neither aerobes nor strict anaerobes, these microaerophilic organisms are adapted for survival in the gastrointestinal mucous layer. This chapter will focus on *C. jejuni* and *C. fetus* as the major pathogens and prototypes for their groups; the key features of infection are listed by species:

Enteric

C jejuni subspecies jejuni
C jejuni subspecies doylei
Campylobacter coli
Campylobacter upsaliensis
Campylobacter lari

C fetus subspecies fetus
Campylobacter hyointestinalis
Campylobacter concisus

Extraintestinal

C jejuni subspecies jejuni
Campylobacter upsaliensis
C lari
C fetus subspecies fetus
C concisus
Campylobacter sputorum
Campylobacter curvus
Campylobacter rectus

EPIDEMIOLOGY

Campylobacters are found in the gastrointestinal tract of many animals used for food (including poultry, cattle, sheep, and swine) and of many household pets (including birds, dogs, and cats). These microorganisms usually do not cause illness in their animal hosts. In most cases, campylobacters are transmitted to humans in raw or undercooked food products or through direct contact with infected animals. In the United States and other developed countries, ingestion of contaminated poultry that has not been sufficiently cooked is the most common means of acquiring infection (50 to 70 percent of cases). Other modes of transmission include ingestion of raw (unpasteurized) milk or untreated water, contact with infected household pets, travel to developing countries (campylobacters being among the causes of traveler's diarrhea), and (occasionally) contact with an index case who is incontinent of stool.

Campylobacter infections are not rare. Several studies indicate that, in US, diarrheal disease due to campylobacters is more common than that due to Salmonella and *Shigella* combined. Infections occur throughout the year, but their incidence peaks during summer and early autumn. Persons of all ages are affected; however, attack rates for *C. jejuni* are highest among young children and young adults, while those for *C. fetus* are highest at the extremes of age. Systemic infections due to *C.fetus* (and to other *Campylobacter* and related species) are most common in compromised hosts. Persons at increased risk include those with AIDS, hypogammaglobulinemia, neoplasia, liver disease, diabetes mellitus, and generalized atherosclerosis as well as pregnant women. However, apparently healthy nonpregnant persons occasionally develop transient Campylobacter bacteremia.

In developing countries, *C. jejuni* infections are hyperendemic, with the highest rates among children <2 years old. Infection rates fall with age, as does the illness-to-infection ratio; these observations suggest that frequent exposure to C. jejuni leads to the acquisition of immunity.

PATHOGENESIS

Many *C. jejuni* infections are subclinical, especially in partially immune hosts. Most illnesses occur within 2 to 4 days (range, 1 to 7 days) of exposure to the organism in food or water. The sites of tissue injury include the jejunum, ileum, and colon. Biopsies show an acute nonspecific inflammatory reaction, with neutrophils, monocytes, and eosinophils in the lamina propria, as well as damage to the epithelium, including loss of mucus, glandular degeneration, and crypt abscesses. Biopsy findings may be consistent with Crohn's disease or ulcerative colitis, but these "idiopathic" chronic inflammatory diseases should not be diagnosed unless infectious colitis, specifically including that due to infection with *Campylobacter*, has been ruled out.

The high frequency of *C. jejuni* infections and their severity and recurrence among hypogammaglobulinemic patients suggest that antibodies are important in protective immunity. The pathogenesis of infection is uncertain. Both the motility of the strain and its capacity to adhere to host tissues appear to favor disease, but classic enterotoxins and cytotoxins (although described) do not appear to play any substantial role in tissue injury or disease production. In contrast, the organisms have been visualized in the epithelium, albeit in low numbers. The documentation of a significant tissue response and occasionally of *C. jejuni* bacteremia further suggests that tissue invasion is clinically significant.

The pathogenesis of *C. fetus* infections is better defined. Virtually all clinical isolates of *C. fetus* possess a proteinaceous capsule-like structure (an S layer) that renders the organism resistant to complement-mediated killing and opsonization. As a result, C. fetus can cause bacteremia and can seed sites beyond the intestinal tract. The ability of the organism to switch the S-layer proteins expressed, a phenomenon that results in antigenic variability, may contribute to the chronicity and high rate of recurrence of these infections in compromised hosts.

CLINICAL MANIFESTATION

Clinical manifestations of infection by all Campylobacter species that cause enteric illness overlap and appear identical. Diarrhea is one of the main symptoms of disease. Mild episodes subside within 7 days in 60-70% of cases, last for 2 weeks in 20-30%, and persist longer in 5-10% of cases. In one third to one half of patients, initial symptoms include periumbilical cramping, intense abdominal pain that mimics appendicitis, malaise, myalgias, headache, and vomiting.

Watery secretory diarrhea consists of more than 10 stools per day and is frequently seen in younger children. Dehydration occurs in approximately 10% of these children.

Inflammatory diarrhea symptoms are indistinguishable from those caused by Shigella organisms, Escherichia coli, and Salmonella species. They are characterized by malaise, fever, abdominal cramps, tenesmus, bloody stools, and fecal leukocytes on light microscopy. Rarely, in young adults and adolescents, inflammatory diarrhea can be severe and confused with Crohn disease and ulcerative colitis. Toxic megacolon with massive bleeding may occasionally occur. In asymptomatic neonates, *C jejuni* has been isolated from blood-streaked formed stools or hematochezia.

Extraintestinal infections cased by bacteremia is very severe clinical form of campylobacteriosis. Bacteremia with *C jejuni* is uncommon, occurring most in patients with immunodeficiency, chronic illness, and at extremes of ages. Bloodstream infections and systemic infections by *C fetus* are rare. The 3 patterns of bacteremia are as follows:

Transient bacteremia in a normal host with acute Campylobacter enteritis: These patients usually recover completely without treatment.

Secondary bacteremia or deep focus of infection such as meningitis, pneumonia, endocarditis, and thrombophlebitis in a normal host: Bacteremia usually originates from the intestinal tract and responds to antimicrobial therapy.

Chronic bacteremia with relapses that can persist for several months occurring in an immunocompromised host: In these patients, bacteremia also can arise from an infected indwelling catheter. Many such patients do not have acute enteritis.

Localized extraintestinal infections are uncommon manifestations and include cholecystitis, arthritis, urinary tract infection, pancreatitis, osteomyelitis, and meningitis. These manifestations may be the initial presentation of *C jejuni* infection or may occur simultaneously with bacteremia. They frequently are seen in patients who are immunocompromised or at extremes of age. Appropriate treatment is necessary.

Because of the affinity of *C fetus* for the genital tract—and by the tropism for fetal tissue – *C fetus* and, rarely, *C jejuni* are associated with perinatal infection. Abortion or stillbirth and premature labor have been described. Infants are often premature and develop signs and symptoms suggestive of sepsis including fever, cough, respiratory distress, vomiting, diarrhea, cyanosis, convulsions, and jaundice. Infection typically progresses to meningitis, which may be rapidly fatal or may result in serious neurologic sequelae. The source of the organism in these cases has been the mother.

On physical examination the abdomen is frequently tender on palpation, especially the right lower quadrant. Rarely, splenomegaly may be present.

C. jejuni and C. fetus infections The clinical features of infections due to all of the Campylobacter and related species causing enteric disease appear to be highly similar. There is often a prodrome, with fever, headache, myalgia, and/or malaise, 12

to 48 h before the onset of diarrheal symptoms. The most common symptoms of the intestinal phase are diarrhea, abdominal pain, and fever. The degree of diarrhea varies from several loose stools to grossly bloody stools; most patients presenting for medical attention have 10 or more bowel movements on the worst day of illness. Abdominal pain usually consists of cramping and may be the most prominent symptom. Pain usually is generalized but may become localized; *C. jejuni* infection may cause pseudoappendicitis. Fever may be the only initial manifestation of *C. jejuni* infection, a situation mimicking the early stages of typhoid fever. Febrile young children may develop convulsions. *Campylobacter* enteritis generally is self-limited; however, symptoms persist for longer than 1 week in 10 to 20 percent of patients seeking medical attention, and relapses occur in 5 to 10 percent of untreated patients.

C. fetus may cause a diarrheal illness similar to that due to *C. jejuni*, especially in normal hosts, or may cause either intermittent diarrhea or nonspecific abdominal pain without localizing signs. Sequelae are uncommon, and outcome is benign. *C.fetus* also may cause a prolonged relapsing systemic illness (with fever, chills, and myalgias) that has no obvious primary source; this manifestation is especially common in compromised hosts. Secondary seeding of an organ (e.g., meninges, brain, bone, urinary tract, or soft tissue) complicates the course, which may be fulminant. *C. fetus* infections have a tropism for vascular sites: endocarditis, mycotic aneurysm, and septic thrombophlebitis all may occur. Infection during pregnancy often leads to fetal death. Helicobacter cinaedi causes recurrent cellulitis with fever and bacteremia in immunocompromised hosts.

COMPLICATION

Except in the case of infection with *C. fetus* or *H. cinaedi*, bacteremia is uncommon, developing most often in immunocompromised hosts and at the extremes of age. Three patterns of extraintestinal infection have been noted:

1. Ttransient bacteremia in a normal host with enteritis (benign course, no specific treatment needed);

2. Ssustained bacteremia or focal infection in a normal host (bacteremia originating from enteritis, with patients responding well to antimicrobial therapy);

3. Ssustained bacteremia or focal infection in a compromised host. Enteritis may not be demonstrated. Antimicrobial therapy, possibly prolonged, is necessary for suppression or cure of the infection.

Campylobacter infections in patients with AIDS or hypogammaglobulinemia may be severe, persistent, and extraintestinal; relapse after cessation of therapy is common. Hypogammaglobulinemic patients also may develop osteomyelitis and an erysipelas-like rash.

Local suppurative complications of infection include cholecystitis, pancreatitis, and cystitis; distant complications include meningitis, endocarditis, arthritis, peritonitis, cellulitis, and septic abortion. All are rare. Hepatitis, interstitial nephritis, and the hemolytic-uremic syndrome occasionally complicate acute infection. Reactive arthritis and other rheumatologic complaints may develop several weeks after infection, especially in persons with the HLA-B27 phenotype. Guillain-Barre syndrome follows Campylobacter infections uncommonly (i.e., in 1 of every 1000 to 2000 cases). However, because of their high incidence, it is now estimated that Campylobacter infections may trigger 20 to 40 percent of all cases of Guillain-Barre syndrome.

LABORATORY APPROACHES

In patients with Campylobacter enteritis, peripheral leukocyte counts reflect the severity of the inflammatory process. Stools containing leukocytes or erythrocytes is typical for campylobacteriosis. Fecal smears should be treated with Gram's or Wright's stain and examined in all suspected cases. When the diagnosis of Campylobacter enteritis is suspected on the basis of findings of inflammatory diarrhea (fever, fecal leukocytes), clinicians can ask the laboratory to attempt the visualization of organisms with characteristic vibrioid morphology by direct microscopic examination of stools with Gram's staining or to use phase-contrast or dark-field microscopy to identify the organisms' characteristic "darting" motility.

Confirmation of the diagnosis of *Campylobacter* infection is based on identification of an isolate from cultures of stool, blood, or another site. *Campylobacter*-specific media should be used to culture stools from all patients with inflammatory or bloody diarrhea. Since all *Campylobacter* species are fastidious, they will not be isolated unless selective media or other selective techniques are used. Not all media are equally useful for isolation of the broad array of campylobacters; therefore, failure to isolate campylobacters from stool does not entirely rule out their presence. The detection of the organisms in stool almost always implies infection; there is a brief period of postconvalescent fecal carriage and no commensalism. In contrast, *Campylobacter sputorum* and related organisms found in the oral cavity are commensals without known pathogenic significance.

Presumptive diagnosis can be made by examination of fecal specimens by darkfield or phase-contrast microscopy, which demonstrate the characteristic darting motility, and Gram stain of the stool, which shows Vibrio forms (slim, short, curved rods). Red blood cells and neutrophils are present in stool in approximately 75% of patients with *Campylobacter enteritis*.

Definitive diagnosis of infection is based on isolation of organisms from stool culture or from another site.

Culture of *C jejuni* from stool requires special isolation techniques and special media such as Campy-BAP or Skirrow. These media contain antibiotics that reduce the emergence of other enteric microorganisms. Inoculated media should be incubated in 5% oxygen and 10% carbon dioxide at 42°C. If C fetus or other atypical enteric species are suspected, isolation from stool requires inoculation on media lacking antibiotics and at 37°C. Filtration technique may be needed. Routine media are adequate for isolation of Campylobacter from normally sterile sites such as blood, body fluids, and tissues.

Hematology and blood chemistries Peripheral white blood cell count is usually normal; however, a left shift may occur. Alanine aminotransferase and the erythrocyte sedimentation rate (ESR) may be slightly elevated.

Diagnostic rise usually occurs after symptoms have resolved. Since the median duration of fecal excretion in the convalescent phase is less than 3 weeks, serology testing may be more sensitive than culture for the diagnosis of recent C jejuni infection.

While it is also useful for epidemiological investigations, serologic testing is not recommended for routine diagnosis.

Deoxyribonucleic acid (DNA) probes and polymerase chain reaction are mainly research tools at this time and are not routinely performed.

In patients who undergo proctoscopy secondary to a prolonged course of Campylobacter enteritis, normal mucosa is found 50% of the time. Mucosal edema, congestion, friability, and granularity are seen in the remaining half.

Histologic Findings: The spectrum of histologic findings in the intestinal tract ranges from minimal edema with acute and chronic inflammatory cells without vascular congestion, to moderate inflammation and cryptitis, to crypt abscess formation. For perinatal infections secondary to C jejuni and C fetus, the placenta may have areas of necrosis, infarction, microabscesses, and inflammation.

DIFFERENTIAL DIAGNOSIS

The symptoms of Campylobacter enteritis are not sufficiently unusual to distinguish this illness from that due to *Salmonella, Shigella*, or *Yersinia*, among other pathogens. The combination of fever and fecal leukocytes or erythrocytes is indicative of inflammatory diarrhea, and definitive diagnosis is based on culture. Similarly, extraintestinal *Campylobacter* illness is diagnosed by culture. Infection due to *Campylobacter* should be suspected in the setting of septic abortion and that due to *C. fetus* specifically in the setting of septic thrombophlebitis. It is important to reiterate that the presentation of *Campylobacter enteritis* may mimic that of ulcerative colitis or Crohn's disease, that *Campylobacter enteritis* is much more common than either of the latter (especially among young adults), and that biopsy may not distinguish among these entities. Thus a diagnosis of inflammatory bowel

disease should not be made until *Campylobacter* infection has been ruled out, especially in persons with a history of foreign travel, significant animal contact, immunodeficiency, or practices incurring a high risk of transmission.

TREATMENT

Fluid and electrolyte replacement is central to the treatment of diarrheal illnesses. Even among patients presenting for medical attention with Campylobacter enteritis, fewer than half will clearly benefit from specific antimicrobial therapy. Indications for such therapy include high fever, bloody diarrhea, severe diarrhea, persistence for more than 1 week, and worsening of symptoms. For patients who are severely dehydrated and cannot tolerate oral hydration, intravenous hydration and inpatient care may be necessary.

Occasionally, acute abdominal pain may be the only presenting symptom, often mimicking acute appendicitis and resulting in immediate laparotomy. Consultation with an infectious disease specialist and a gastroenterologist may be necessary for complicated cases.

Because rehydration and electrolyte replacement are the mainstays for treating diarrheal disease, oral rehydration with an electrolyte and glucose solution is necessary.

Most *C jejuni* infections are mild and self-limited; therefore, they do not usually require antibiotic therapy. Correction of electrolyte abnormalities and rehydration are usually sufficient. Treatment often is reserved for compromised hosts or persons with fever, increasing bloody diarrhea, or symptoms that last longer than 1 week.

C jejuni is usually sensitive to erythromycin, gentamicin, tetracycline, ciprofloxacin, and clindamycin. Reports of erythromycin- and ciprofloxacin-resistant strains are increasing. In adults, placebo-controlled studies of erythromycin demonstrate no improvement in the clinical symptoms if given late in the course of illness but have resulted in decreased fecal shedding. If an appropriate antibiotic therapy was initiated within the first 4 days of illness, there was a reduction in the excretion of the organism; however, results regarding the resolution of symptoms were controversial. In contrast, early erythromycin treatment for children with bloody diarrhea shortened both the duration of diarrhea and excretion of microbes in the stool.

Recommended duration for antibiotic treatment given for gastroenteritis is 5-7 days. Antimicrobial therapy for all bacteremic and mmunocompromised patients with C jejuni should be selected based on a laboratory susceptibility test. Begin therapy with gentamicin, imipenem, third-generation cephalosporins, or chloramphenicol until susceptibility test results are available. Because infections with C fetus usually

are systemic, IV antibiotics usually are required. Aminoglycosides, such as gentamicin, are usually the drug of choice (DOC).

Alternatives for *C fetus* bacteremia include ampicillin, imipenem, chloramphenicol, and third-generation cephalosporins. Reported synergistic combinations include ampicillin with gentamicin and imipenem with gentamicin. Duration of therapy is empiric.

Patients with central nervous system infection require treatment for 2-3 weeks with a third-generation cephalosporin, ampicillin, or chloramphenicol. Those with endovascular infection should be treated for at least 4 weeks with gentamicin as the DOC. Treatment with ampicillin or third-generation cephalosporins are other alternatives. Erythromycin is the DOC for patients with diarrheal illness secondary to *C fetus*.

VIRAL HEPATITIS

DEFENITION: acute viral hepatitises are *infectious diseases with fecal-oral or parenteral way of transmission, and characterize by cyclic clinical course with apperence of intoxication, jaundice, hepatosplenomegaly and in severe cases – acute hepatic failure.*

The last two decades have witnessed an explosion in knowledge of viral hepatitis, a major public health problem throughout the world affecting several hundreds of millions of people. The term viral hepatitis is often thought to be synonymous with diseases caused by the known hepatotropic viruses, including hepatitis viruses A, B, C, D, and E. There will not considering other various of viral hepatitis there (F, TTV, SEN-V). Infections with hepatitis viruses, especially hepatitis viruses B and C, have been associated with a wide variety of extrahepatic manifestations. Infrequent causes of viral hepatitis include adenovirus, cytomegalovirus, Epstein-Barr virus, and, rarely, herpes simplex virus infection, but that is other problem.

The term hepatitis describes inflammation of the liver. Hepatitis may be caused by alcohol, drugs, autoimmune diseases, metabolic diseases, and viruses. Viral infection accounts for more than half the cases of acute hepatitis in the United States. The term viral hepatitis can describe either a clinical illness or the histological findings associated with the disease. Acute infection with a hepatitis virus may result in conditions ranging from subclinical disease to self-limited symptomatic disease to fulminant hepatic failure (as usually this is complication in cases of acute hepatitis B) . Adults with acute hepatitis A or B are usually symptomatic. Persons with acute hepatitis C may be either symptomatic or asymptomatic (i.e., subclinical). Typical symptoms of acute hepatitis are fatigue, anorexia, nausea, and vomiting. Very high

aminotransferase values (>1000 U/L) and hyperbilirubinemia are often observed. Severe cases of acute hepatitis may progress rapidly to acute liver failure, marked by poor hepatic synthetic function. This is often defined as a prothrombin time of 16 seconds or an international normalized ratio of 1.5 in the absence of prior liver disease. Fulminant hepatic failure, due to virus hepatitis B, is defined as acute liver failure that is complicated by hepatic encephalopathy. In contrast to the encephalopathy associated with cirrhosis, the encephalopathy of fulminant hepatic failure is attributed to increased permeability of the blood-brain barrier and to impaired osmoregulation in the brain, which leads to brain-cell swelling. The resulting brain edema is a potentially fatal complication of fulminant hepatic failure. Fulminant hepatic failure may occur in as many as 1% of cases of acute hepatitis due to hepatitis B. Hepatitis E is a common cause in Asia. Whether hepatitis C is a cause remains controversial. Although fulminant hepatic failure may resolve, more than one half of all cases result in death unless liver transplantation is performed in time. Providing that acute viral hepatitis does not progress to fulminant hepatic failure, many cases resolve over a period of days, weeks, or months. Alternatively, acute viral hepatitis may evolve into chronic hepatitis. Hepatitis A and hepatitis E never progress to chronic hepatitis, either clinically or histologically.

ETIOLOGY

Hepatitis A Hepatitis A virus is a nonenveloped 27-nm, heat-, acid-, and ether-resistant RNA virus in the hepatovirus genus of the picornavirus family . HAV is the only one of the human hepatitis viruses that can be cultivated in vitro.

Hepatitis B Hepatitis B virus is a DNA virus with a remarkably compact genomic structure; despite its small, circular, 3200-base-pair size, HBV DNA codes for four sets of viral products and has a complex, multiparticle structure. Once thought to be unique among viruses, HBV is now recognized as one of a family of animal viruses, hepadnaviruses (hepatotropic DNA viruses), and is classified as hepadnavirus type 1. Although HBV is difficult to cultivate in vitro in the conventional sense from clinical material, several cell lines have been transfected with HBV DNA. Such transfected cells support in vitro replication of the intact virus and its component proteins. There is HBs Ag, HBe Ag, HBc Ag by hepatitis B virus.

Hepatitis C. Hepatitis C virus, is a linear, single-stranded, positive-sense, 9500-nucleotide RNA virus, the genome of which is similar in organization to that of flaviviruses and pestiviruses; HCV constitutes its own genus in the family Flaviviridae. Because HCV does not replicate via a DNA intermediate, it does not integrate into the host genome. Because HCV tends to circulate in very low titer, visualization of virus particles has been difficult. Although in vitro HCV replication remains difficult to accomplish convincingly, the chimpanzee has proven to be an invaluable experimental animal model. HCV is a spherical, enveloped, single-

stranded RNA virus belonging to the Flaviviridae family and Flavivirus genus. In 2001, Lauer and Walker reported that HCV is closely related to hepatitis G, dengue, and yellow fever viruses. HCV can produce at least 10 trillion new viral particles each day. RNA-dependent RNA polymerase, an enzyme critical in HCV replication, lacks proofreading capabilities and generates a large number of mutant viruses known as quasispecies. These represent minor molecular variations with only 1-2% nucleotide heterogeneity. HCV quasispecies pose a major challenge to immune-mediated control of HCV and may explain the variable clinical course and the difficulties in vaccine development. The nonstructural components include NS2, NS3, NS4A, NS4B, NS5A, NS5B, and p7, whose proteins function as helicase-, protease-, and RNA-dependent RNA polymerase, although the exact function of p7 is unknown. One region within NS5A is linked to an interferon (IFN) response and is called the IFN sensitivity-determining region. These enzymes are critical in viral replication and are attractive targets for future antiviral therapy. Six major HCV genotypes and numerous subtypes have been identified. Genotypes 1a and 1b are prevalent in the United States, whereas in other countries, genotype 1a is less frequent. Genotypes 2 and 3 are also found globally and account for a significant minority of infections. HCV genotype 1, particularly 1b, does not respond to therapy as well as genotypes 2 and 3. Genotype 1 also may be associated with more severe liver disease and a higher risk of HCC.

Hepatitis D. Mario Rizzetto and colleagues discovered HDV, also known as the delta virus, in 1977. Hepatitis D virus. HDV is a single-stranded, 1.7-kb RNA virus. The viral particle is 36 nm in diameter and contains HDAg and the RNA strand. It uses HBsAg as its envelope protein. Thus, HBV co-infection is necessary for the packaging and release of HDV virions from infected hepatocytes. Natural history of HDV co-infection. The resulting acute hepatitis may be mild or severe. Similarly, the risk of developing chronic HBV and HDV infection after acute exposure to both viruses is the same as the rate of developing chronic HBV infection after acute exposure to HBV (approximately 5% in adults). However, chronic HBV and HDV disease tends to progress more rapidly to cirrhosis than chronic HBV infection alone. Natural history of HDV superinfection Introduction of HDV into an individual already infected with HBV may have dramatic consequences. Superinfection may give HBsAg-positive patients the appearance of a sudden worsening or flare of hepatitis B. HDV superinfection may result in fulminant hepatic failure.

Hepatitis E. Previously labeled *epidemic* or *enterically transmitted non-A, non-B hepatitis,* HEV is an enterically transmitted virus that occurs primarily in India, Asia, Africa, and Central America. This agent, with epidemiologic features resembling those of hepatitis A, is a 32- to 34-nm, nonenveloped, HAV-like virus with a 7600-nucleotide, single-stranded, positive-sense RNA genome. HEV,

resembling calciviruses, appears to be sufficiently distinct from any known agent to merit a new classification of its own within the alphavirus group. The virus has been detected in stool, bile, and liver from infected patients as well as from experimentally infected nonhuman primates. Studies in humans and experimental animals have shown that HEV is excreted in the stool during the late incubation period and that immune responses to viral antigens occur very early during the course of acute infection. Both IgM anti-HEV and IgG anti-HEV can be detected, but both fall rapidly after acute infection, reaching low levels within 9 to 12 months. Currently, serologic testing for HEV infection is not available routinely.

Hepatitis G A sixth hepatitis virus was discovered independently by two different groups, one calling it hepatitis G (HGV), the other calling it GB virus C (GBV-C; a viral agent isolated in the 1960s from a surgeon with viral hepatitis and transmitted in tamarins). This agent may contribute to cases of acute and chronic viral hepatitis unaccounted for by the other five hepatitis viruses. Like HCV, HGV is a bloodborne RNA virus with a flavivirus-like genomic structure. Infection with this agent, identified reliably by PCR amplification of RNA (much less reliably by antibody testing), occurs in approximately 1.5 percent of blood donors, is transmitted by blood transfusion, and can be detected in some patients with acute, chronic, and fulminant hepatitis. Data available to date, however, indicate that a sizable proportion of clinically apparent HGV infections occur in patients coinfected with hepatitis C, that HGV does not alter the severity of hepatitis C, and that most isolated instances of HGV infection are not associated with acute or chronic liver injury. Thus, although HGV may play a small role in viral hepatitis and may be transmitted by transfusion, its contribution to acute and chronic liver disease requires better definition.

EPIDEMIOLOGY

Hepatitis A virus (HAV); hepatitis B virus (HBV); hepatitis C virus (HCV); hepatitis D virus (HDV), which requires coexisting HBV infection; and hepatitis E virus (HEV) cause 95% of cases of acute viral hepatitis observed in US and South Europe. Whether hepatitis G virus (HGV) is pathogenic in humans remains unclear. HAV is the most common cause of acute hepatitis in developing countries. HCV is the most common cause of chronic hepatitis.

Fecal-oral transmission is main way of transmission in cases of HAV, HEV infections. Parenteral transmission is typical for HBV, HCV, HDV, and HGV. Sexual transmission and perinatal transmission – HBV, HDV, and HCV. There some examples of parenteral transmission of HAV-infection via contaminated blood from donor. Nearly 25-30% cases of HBV and HCV-infections the way of tramnsmission remains unknown.

Prior to the availability of serologic tests for hepatitis viruses, all viral hepatitis cases were labeled either as "infectious" or "serum" hepatitis. Modes of transmission

overlap, however, and a clear distinction among the different types of viral hepatitis cannot be made solely on the basis of clinical or epidemiologic features. The most accurate means to distinguish the various types of viral hepatitis involves specific serologic testing.

Hepatitis A. This agent is transmitted almost exclusively by the fecal-oral route. Person-to-person spread of HAV is enhanced by poor personal hygiene and overcrowding, and large outbreaks as well as sporadic cases have been traced to contaminated food, water, milk, and shellfish. Intrafamily and intrainstitutional spread are also common. Early epidemiologic observations suggested that there is a predilection for hepatitis A to occur in late fall and early winter. In temperate zones, epidemic waves have been recorded every 5 to 20 years as new segments of nonimmune population appeared; however, in developed countries, the incidence of type A hepatitis has been declining, presumably as a function of improved sanitation, and these cyclic patterns are no longer being observed. No HAV carrier state has been identified after acute type A hepatitis; perpetuation of the virus in nature depends presumably on nonepidemic, inapparent subclinical infection. Hepatitis A has an incubation period of approximately 4 weeks. Its replication is limited to the liver, but the virus is present in the liver, bile, stools, and blood during the late incubation period and acute preicteric phase of illness. Despite persistence of virus in the liver, viral shedding in feces, viremia, and infectivity diminish rapidly once jaundice becomes apparent.

Hepatitis B. It has long been recognized that a major route of hepatitis B transmission is percutaneous, but the outmoded designation "serum hepatitis" is an inaccurate label for the epidemiologic spectrum of HBV infection recognized today. As detailed below, most of the hepatitis transmitted by blood transfusion is not caused by HBV; moreover, in approximately half of patients with acute type B hepatitis, there is no history of an identifiable percutaneous exposure. We now recognize that many cases of type B hepatitis result from less obvious modes of nonpercutaneous or covert percutaneous transmission. HBsAq has been identified in almost every body fluid from infected persons — saliva, tears, seminal fluid, cerebrospinal fluid, ascites, breast milk, synovial fluid, gastric juice, pleural fluid, and urine, and even rarely in feces. Although there is abundant evidence to suggest that feces are not infectious, at least some of these body fluids — most notably semen and saliva — have been shown to be infectious, albeit less so than serum, when administered percutaneously or nonpercutaneously to experimental animals. Among the nonpercutaneous modes of HBV transmission, oral ingestion has been documented as a potential route of exposure but one whose efficiency is quite low. On the other hand, the two nonpercutaneous routes considered to have the greatest impact are intimate (especially sexual) contact and perinatal transmission.

Hepatitis C. Hepatitis C is the major cause of chronic hepatitis in the United States. HCV infections account for 20% of all cases of acute hepatitis. HCV accounts for more than 40% of all referrals to active liver clinics. HCC develops in 1-4% of patients with cirrhosis each year. El-Serag et al reported in 2003 that HCV is largely responsible for the recent increase in the incidence of HCC in the United States. In the United States, the number of deaths due to HCV-related complications has increased from fewer than 10,000 in 1992 to just fewer than 15,000 in 1999.

HCV can be transmitted parenterally, perinatally, and sexually. HCV is transmitted most reliably through transfusion of infected blood or blood products, transplantation of organs from infected donors, and sharing contaminated needles among intravenous drug users. Needlestick injuries among health care workers place them at significant risk of infection. Incidence of HCV infection in health care workers with history of needlestick exposure to infected blood approaches 10%. Even more concerning is the 0.4-1% chance of developing irreversible liver injury from a needlestick infection in this setting.

WHO estimates 170 million individuals worldwide are infected with hepatitis C virus (HCV). However, the prevalence of HCV infection varies throughout the world. For example, Egypt has the highest number of reported infections, largely attributed to the use of contaminated parenteral antischistosomal therapy. This has led to a mean prevalence of HCV antibodies in persons in Egypt of 22%.

According CDC, an estimated 1.8% of the US population is positive for HCV antibodies. Because 3 of 4 seropositive persons are also viremic, this corresponds to an estimated 2.7 million people with active HCV infection nationwide. Infection due to HCV accounts for 20% of all cases of acute hepatitis, an estimated 30,000 new acute infections, and 8000-10,000 deaths each year in US.

Medical care costs associated with the treatment of HCV infection US are estimated to be more than $600 million a year. Most patients infected with HCV have chronic liver disease, which can progress to cirrhosis and hepatocellular carcinoma (HCC). Chronic infection with HCV is one of the most important causes of chronic liver disease and, according to a report by Davis et al from 2003, the most common indication for orthotopic liver transplantation. HCV may also be transmitted by means of acupuncture, tattooing, and sharing razors. Needlestick injuries in the health care setting result in a 3% risk of HCV transmission, but, according to Rischitelli et al in 2001, HCV prevalence among health care workers is similar to that of the general population. Nosocomial patient-to-patient transmission may occur by means of a contaminated colonoscope, via dialysis, or during surgery, including organ transplantation before 1992.

Co-infection with HIV type 1 appears to increase the risk of both sexual and maternal-fetal transmission of HCV. Casual household contact and contact with the

saliva of those infected are inefficient modes of transmission. No risk factors are identified in approximately 10% of cases.

Hepatitis D. Infection with HDV has a worldwide distribution, but two epidemiologic patterns exist. In Mediterranean countries (northern Africa, southern Europe, the Middle East), HDV infection is endemic among those with hepatitis B, and the disease is transmitted predominantly by nonpercutaneous means, especially close personal contact. In nonendemic areas, such as US and northern Europe, HDV infection is confined to persons exposed frequently to blood and blood products, primarily drug addicts and hemophiliacs. HDV infection can be introduced into a population through drug addicts or by migration of persons from endemic to nonendemic areas. Thus, patterns of population migration and human behavior facilitating percutaneous contact play important roles in the introduction and amplification of HDV infection. Occasionally, the migrating epidemiology of hepatitis D is expressed in explosive outbreaks of severe hepatitis, such as those which have occurred in remote South American villages as well as in urban centers in US.

Ultimately, such outbreaks of hepatitis D – either of coinfections with acute hepatitis B or of superinfections in those already infected with HBV – may blur the distinctions between endemic and nonendemic areas. HDV is believed to infect approximately 5% of the world's 300 million HBsAg carriers. The prevalence of HDV infection in South America and Africa is high. Italy and Greece are areas of intermediate endemicity and are well studied. The sharing of contaminated needles in intravenous drug use is thought to be the most common means of transmitting HDV. Persons who use intravenous drugs who are also positive for HBsAg have been found to have HDV prevalence rates ranging from 17-90%. Sexual and perinatal transmissions are also described. The prevalence of HDV in prostitutes in Greece and Taiwan is high.

Hepatitis E. The enteric form of hepatitis E identified in India, Asia, Africa, and Central America resembles hepatitis A in its primarily enteric mode of spread. The commonly recognized cases occur after contamination of water supplies such as after monsoon flooding, but sporadic, isolated cases occur. An epidemiologic feature that distinguishes HEV from other enteric agents is the rarity of secondary person-to-person spread from infected persons to their close contacts. Infections arise in populations that are immune to HAV and favor young adults. Cases imported from endemic areas have been found in Europe.

Hepatitis G. Hepatitis G is a bloodborne agent whose modes of transmission have not been defined adequately but tend to parallel those of HCV infection. Evidence for infection occurs in approximately 1.5 percent of blood donors, but the frequency of infection is the same in blood donors with normal and with elevated ALT levels. Among sporadic, community-acquired cases of acute viral hepatitis

unexplained by hepatitis viruses A through E, HGV accounts for only 10 to 15 percent, which represents less than 0.5 percent of all community-acquired cases.

PATHOGENESIS

Under ordinary circumstances, none of the hepatitis viruses is known to be directly cytopathic to hepatocytes. Evidence suggests that the clinical manifestations and outcomes following acute liver injury associated with viral hepatitis are determined by the immunologic responses of the host. Among the viral hepatitides, the immunopathogenesis of hepatitis B has been studied most extensively. Certainly for this agent, the existence of asymptomatic hepatitis B carriers with normal liver histology and function suggests that the virus is not directly cytopathic.

The facts that lymphoid cells are juxtaposed with necrotic hepatocytes in the livers of patients with liver injury and that patients with defects in cellular immune competence are more likely to remain chronically infected rather than to clear the virus are cited to support the role of cellular immune responses in the pathogenesis of hepatitis B-related liver injury. The model that has the most experimental support involves cytolytic T cells sensitized specifically to recognize host and hepatitis B viral antigens on the liver cell surface. Although HBsAg was initially thought to be the most likely viral target antigen on the hepatocyte surface, recent laboratory observations suggest that nucleocapsid proteins (HBcAg and possibly HBeAg), present on the cell membrane in minute quantities, are the viral target antigens that, with host antigens, invite cytolytic T cells to destroy HBV-infected hepatocytes. Still, this hypothesis is insufficient to explain differences in outcomes between those who recover after acute hepatitis and those who progress to chronic hepatitis or between those with mild and severe (fulminant) acute HBV infection. As convincing as are the cumulative data supporting nucleocapsid proteins as the target of cell-mediated immunologic injury, attention has been refocused on the envelope protein, HBsAg, by the demonstration that in transgenic mice with the gene for HBsAg inserted into their, genomes, cytolytic T cells directed against HBsAg can be shown to destroy hepatocytes. Therefore, HBsAg cannot be dismissed as a potential immunologic target.

The typical morphologic lesions of all types of viral hepatitis are similar and consist of panlobular infiltration with mononuclear cells, hepatic cell necrosis, hyperplasia of Kupffer cells, and variable degrees of cholestasis. Hepatic cell regeneration is present, as evidenced by numerous mitotic figures, multinucleated cells, and "rosette" or "pseudoacinar" formation. The mononuclear infiltration consists primarily of small lymphocytes, although plasma cells and eosinophils are occasionally seen. Liver cell damage consists of hepatic cell degeneration and necrosis, cell dropout, ballooning of cells, and acidophilic degeneration of hepatocytes (forming so-called Councilman-like bodies). Large hepatocytes with a

ground glass appearance of the cytoplasm may be seen in chronic but not in acute HBV infection; these cells have been shown to contain HBsAg and can be identified histochemically with orcein or aldehyde fuchsin. In uncomplicated viral hepatitis, the reticulin framework is preserved. In hepatitis C, the histologic lesion is often remarkable for a relative paucity of inflammation, a marked increase in activation of sinusoidal lining cells, lymphoid aggregates, the presence of fat, and, occasionally, bile duct lesions in which biliary epithelial cells appear to be piled up without interruption of the basement membrane. Occasionally, microvesicular steatosis occurs in hepatitis D.

In hepatitis E, a common histologic feature is marked cholestasis. A cholestatic variant of slowly resolving acute hepatitis A also has been described. A more severe histologic lesion, bridging hepatic necrosis, also termed subacute or confluent necrosis, is occasionally observed in some patients with acute hepatitis. "Bridging" between lobules results from large areas of hepatic cell dropout, with collapse of the reticulin framework. Characteristically, the bridge consists of condensed reticulum, inflammatory debris, and degenerating liver cells that span adjacent portal areas, portal to central veins, or central vein to central vein. This lesion had been thought to have prognostic significance; in many of the originally described patients with this lesion, a subacute course terminated in death within several weeks to months, or severe chronic hepatitis and postnecrotic cirrhosis developed.

More recent investigations have failed to uphold the association between bridging necrosis and such a poor prognosis in patients with acute hepatitis. Although the frequency of bridging may be higher among hospitalized patients with severe acute hepatitis, and although cirrhosis, chronic hepatitis, and even death have been observed in this group, the frequency of bridging necrosis in uncomplicated acute viral hepatitis is probably on the order of 1 to 5 percent.

Prospective studies have failed to demonstrate a difference in prognosis between patients with acute hepatitis who have bridging necrosis and those who do not. Therefore, although demonstration of this lesion in patients with chronic hepatitis has prognostic significance, its demonstration during acute hepatitis is less meaningful, and liver biopsies to identify this lesion are no longer undertaken routinely in patients with acute hepatitis. In massive hepatic necrosis (fulminant hepatitis, acute yellow atrophy), the striking feature at postmortem examination is the finding of a small, shrunken, and soft liver.

Histologic examination reveals massive necrosis and dropout of liver cells of most lobules with extensive collapse and condensation of the reticulin framework. Immunofluorescence and immunoperoxidase antibody studies have localized HBsAg to the cytoplasm and plasma membrane of infected liver cells. In contrast, HBcAg predominates in the nucleus, but occasionally, scant amounts are also seen in the cytoplasm and on the cell membrane. Electron-microscopic studies of liver biopsy

material have demonstrated the presence of HBsAg particles in the cytoplasm and HBcAg particles in the nucleus of liver cells during hepatitis B infection. These morphologic observations suggest that DNA is synthesized and packaged within core particles in the nucleus, while the envelope is assembled in the cytoplasm, resulting in the formation of intact hepatitis B virus. HDV antigen is localized to the hepatocyte nucleus, while HAV, HCV, and *HEV* antigens are localized to the cytoplasm.

CLINICAL MANIFISTATION

Clinical current and presentation of infectious hepatitis varies from person to person as well as with the etiology of infection. Some patients may present as entirely asymptomatic or only mildly symptomatic. Others may present with rapid onset of fulminant hepatic failure. The classic presentation of infectious hepatitis involves 4 clinic periods.

Period (incuation) 1 - Viral replication. Patients are asymptomatic during this phase. Laboratory studies demonstrate serologic and enzyme markers of hepatitis.

Period 2 - Prodromal phase. There is syndrome like acute gastrointestinal infectious (food poisoning, salmonellas), syndrome arthralgias, syndrome like acute respiratory virus infectious, asthenia – vegetative syndrome and mixed. In more cases the temperature up to febrile and sub febrile. Patients experience anorexia, nausea, vomiting, alterations in taste, arthralgias, malaise, fatigue, urticaria, and pruritus. Some even develop an aversion to cigarette smoke. When seen by a health care provider during this phase, patients are often diagnosed as having gastroenteritis or a viral syndrome. After second half of this period black colour urine and enlargement liver as usually to appear.

Period 3 - Icteric phase. Patients may note darkening of the urine, followed by pale-colored stools. In addition to the predominant gastrointestinal symptoms and malaise, patients become icteric and may develop right upper quadrant pain with hepatomegaly.

Period 4 - Convalescent phase.Symptoms and icterus resolve.Liver enzymes return to normal.

Symptoms and Signs. Acute viral hepatitis occurs after an incubation period that varies according to the responsible agent. Generally, incubation periods for hepatitis:

- ✓ Acute viral hepatitis A – 15-45 days (mean 4 weeks);
- ✓ Acute viral hepatitis B or D – 30-180 days (mean 4 to 12 weeks);
- ✓ Acute viral hepatitis C – 15-160 days (mean 7 weeks);
- ✓ Acute viral hepatitis E – 14-60 days (mean 5 to 6 weeks).

As has been said, the prodromal symptoms of acute viral hepatitis are systemic and quite variable. Constitutional symptoms of anorexia, nausea and vomiting,

fatigue, malaise, arthralgias, myalgias, headache, photophobia, pharyngitis, cough, and coryza may precede the onset of jaundice by 1 to 2 weeks.

The nausea, vomiting, and anorexia are frequently associated with alterations in olfaction and taste. A low-grade fever between 38 and 39°C is more often present in hepatitis A and E than in hepatitis B or C, except when hepatitis B is heralded by a erum sickness-like syndrome; rarely, a fever of 39.5 to 40°C may accompany the constitutional symptoms. Dark urine and clay-colored stools may be noticed by the patient from 1 to 5 days prior to the onset of clinical jaundice.

With the onset of clinical jaundice, the constitutional prodromal symptoms usually diminish, but in some patients mild weight loss (2.5 to 5 kg) is common and may continue during the entire icteric phase. The liver becomes enlarged and tender and may be associated with right upper quadrant pain and discomfort. Infrequently, patients present with a cholestatic picture, suggesting extrahepatic biliary obstruction. Splenomegaly and cervical adenopathy are present in 10 to 20 percent of patients with acute hepatitis. Rarely, a few spider angiomas appear during the icteric phase and disappear during convalescence.

During the *recovery phase,* constitutional symptoms disappear, but usually some liver enlargement and abnormalities in liver biochemical tests are still evident. The duration of the posticteric phase is variable, ranging from 2 to 12 weeks, and usually is more prolonged in acute hepatitis B and C. Complete clinical and biochemical recovery is to be expected 1 to 2 months after all cases of hepatitis A and E and 3 to 4 months after the onset of jaundice in three-quarters of uncomplicated cases of hepatitis B and C.

Biochemical recovery may be delayed. A substantial proportion of patients with viral hepatitis never become icteric. Infection with HDV can occur in the presence of acute or chronic HBV infection; the duration of HBV infection determines the duration of HDV infection. When acute HDV and HBV infection occur simultaneously, clinical and biochemical features may be indistinguishable from those of HBV infection alone, although occasionally they are more severe.

As opposed to patients with *acute* HBV infection, patients with *chronic* HBV infection can support HDV replication indefinitely. This can happen when acute HDV infection occurs in the presence of a nonresolving acute HBV infection. More commonly, acute HDV infection becomes chronic when it is superimposed on an underlying chronic HBV infection. In such cases, the HDV superinfection appears as a clinical exacerbation or an episode resembling acute viral hepatitis in someone already chronically infected with HBV.

Superinfection with HDV in a patient with chronic hepatitis B often leads to clinical deterioration. In addition to superinfections with other hepatitis agents, acute hepatitis-like clinical events in persons with chronic hepatitis B may accompany spontaneous HbeAg-to-anti-HBe seroconversion or spontaneous reactivation, i.e.,

reversion from nonreplicative to replicative infection. Such reactivations can occur as well in therapeutically immunosuppressed patients with chronic HBV infection when cytotoxic-immunosuppressive drugs are withdrawn; in these cases, restoration of immune competence is thought to allow resumption of previously checked cell-mediated cytolysis of HBV-infected hepatocytes. Occasionally, acute clinical exacerbations of chronic hepatitis B may represent the emergence of a precore mutant.

Clinical course of HAV

The incubation period of HAV is 2-7 weeks, with an average of 28 days. Clinical symptoms then develop, often with a presentation similar to that of gastroenteritis or a viral respiratory infection. Most common signs and symptoms include fatigue, nausea, vomiting, fever, hepatomegaly, jaundice, dark urine, anorexia, and rash. HAV infection usually occurs as a mild self-limited disease and confers lifelong immunity to HAV. Chronic infection with HAV does not occur.

Morbidity and death . Although HAV usually causes mild disease, the older the patient, the more severe the disease is likely to be. While icteric disease occurs in fewer than 10% of children younger than 6 years with HAV, it occurs in 40-50% of older children and in 70-80% of adults with HAV. Other complications can include acute liver failure, cholestatic hepatitis, and relapsing hepatitis.

The overall mortality rate for HAV is approximately 0.01%. Children younger than 5 years and adults older than 50 years have the highest case-fatality rates.

Clinical course of HBV

The incubation period for HBV varies from 30-180 days, with the average approximately 75 days. Patients then enter the prodromal or preicteric phase, developing gradual onset of anorexia, malaise, and fatigue. During this phase, as the liver becomes inflamed, liver enzymes start to elevate, and the patient may experience right upper quadrant pain. Fifteen percent of patients develop an illness resembling serum sickness. These patients may experience fever, arthritis, arthralgias, or an urticarial rash. As the disease progresses to the icteric phase, the liver becomes tender, and jaundice develops. Patients may note that their urine darkens and that their stools lighten in color. Other symptoms in this stage include nausea, vomiting, and pruritus. From this point on, patients may have quite a variable course. Some experience fairly rapid improvements in their symptoms, while others go on to a prolonged disease course with slow resolution. Still others may have symptoms that periodically improve, only to worsen later (relapsing hepatitis). Finally, an unfortunate subset of patients suffers rapid progression of their disease to the point of fulminant hepatic failure. This may occur over days to weeks.

Complications

One of the major complications of HBV infection is the development of chronic infection. Patients with chronic HBV infection are at risk of later developing chronic active hepatitis, cirrhosis of the liver, and eventual hepatocellular cancer. Patients infected at an early age have the greatest risk of developing chronic HBV infection. While 90% of those infected at birth develop chronic HBV, only 5-10% of older children or adults go on to develop chronic infection. The risk of chronic infection is also higher in patients who are immunocompromised. Patients with chronic HBV infection have a significantly increased risk of developing hepatocellular cancer. In fact, hepatocellular cancer is the leading cause of cancer-related deaths in areas where HBV is endemic. The cancer is believed to result from repeated bouts of chronic inflammation and cellular regeneration. Hepatocellular cancer develops an average of 25-30 years after initial infection. Another major complication of HBV infection is development of **fulminant hepatic failure**. In approximately 0.5-1% of HBV-infected patients, the disease progresses to fulminant hepatic failure, with coagulopathy, encephalopathy, and cerebral edema. The case-fatality rate for these patients approaches 80%.

Clinical course of HCV

Incubation period for HCV runs 15-150 days, with symptoms developing anywhere from 5-12 weeks after exposure. During acute infection with HCV, symptoms may appear similar to those of HBV infection. In up to 80% of cases, however, patients are asymptomatic and do not develop icterus.

Complications .Acute infection with HCV may cause fulminant hepatic failure and is associated with aplastic anemia. Approximately 50-85% of patients with HCV become chronically infected with HCV; of those, 29-76% later develop chronic active hepatitis or cirrhosis. In fact, HCV is a leading cause of chronic hepatitis and cirrhosis worldwide. In the United States and Europe, chronic HCV infection is the leading indication for liver transplant. Moreover, chronic HCV infection causes 10,000 deaths per year in the United States. Chronic HCV infection is also strongly linked to the development of hepatocellular cancer, which usually develops after 30 years in patients who are chronically infected and have cirrhosis.

Clinical course of HDV

The incubation period of HDV is approximately 35 days. Patients co-infected with HBV and HDV tend to have a more severe disease course than those infected with HBV alone. As many as one third of those with co-infection go on to develop fulminant hepatitis.

Chronic HBV carriers superinfected with HDV usually also develop chronic HDV infection. Chronic co-infection often leads to rapidly progressive subacute or chronic hepatitis, resulting in a more rapid progression to cirrhosis.
Over the long term, as many as 70-80% of these patients have evidence of chronic liver disease with cirrhosis, compared to only 15-30% of patients with chronic HBV alone.

Clinical course of HEV

The incubation period is 2-9 weeks with an average of 45 days. HEV usually causes an acute self-limited disease similar to HAV. Fulminant disease does occur in about 10% of cases. In women who are pregnant, HEV infection has a case fatality rate of 15-20%. No reports of chronic infection with HEV exist.

LABORATORY DIAGNOSIS

The serum aminotransferases AST and ALT (previously designated SGOT and SGPT) show a variable increase during the prodromal phase of acute viral hepatitis and precede the rise in bilirubin level. The acute level of these enzymes, however, does not correlate well with the degree of liver cell damage. Peak levels vary from 400 to 4000 IU or more; these levels are usually reached at the time the patient is clinically icteric and diminish progressively during the recovery phase of acute hepatitis.

The diagnosis of anicteric hepatitis is difficult and requires a high index of suspicion; it is based on clinical features and on aminotransferase elevations, although mild increases in conjugated bilirubin also may be found. Jaundice is usually visible in the sclera or skin when the serum bilirubin value exceeds 43 umol/L (2.5 mg/dL). When jaundice appears, the serum bilirubin typically rises to levels ranging from 85 to 340 umol/L (5 to 20 mg/dL). The serum bilirubin may continue to rise despite falling serum aminotransferase levels. In most instances, the total bilirubin is equally divided between the conjugated and unconjugated fractions. Bilirubin levels above 340 umol/L (20 mg/dL) extending and persisting late into the course of viral hepatitis are more likely to be associated with severe disease. In certain patients with underlying hemolytic anemia, however, such as glucose-6-phosphate dehydrogenase deficiency and sickle cell anemia, a high serum bilirubin level is common, resulting from superimposed hemolysis. In such patients, bilirubin levels greater than 513 umol/L (30 mg/dL) have been observed and are not necessarily associated with a poor prognosis.

Neutropenia and lymphopenia are transient and are followed by a relative lymphocytosis. Atypical lymphocytes (varying between 2 and 20 percent) are common during the acute phase. These atypical lymphocytes are indistinguishable from those seen in infectious mononucleosis.

Measurement of the prothrombin time (PT) is important in patients with acute viral hepatitis, for a prolonged value may reflect a severe synthetic defect, signify extensive hepatocellular necrosis, and indicate a worse prognosis. Occasionally, a prolonged PT may occur with only mild increases in the serum bilirubin andaminotransferase levels. Prolonged nausea and vomiting, inadequate carbohydrate intake, and poor hepatic glycogen reserves may contribute to hypoglycemia noted occasionally in patients with severe viral hepatitis. Serum alkaline phosphatase may be normal or only mildly elevated, while a fall in serum albumin is uncommon in uncomplicated acute viral hepatitis. In some patients, mild and transient steatorrhea has been noted as well as slight microscopic hematuria and minimal proteinuria.

A diffuse but mild elevation of the gamma globulin fraction is common during acute viral hepatitis. Serum IgG and IgM are elevated in about one-third of patients during the acute phase of viral hepatitis, but serum IgM elevation is seen more characteristically during acute hepatitis A. During the acute phase of viral hepatitis, antibodies to smooth muscle and other cell constituents may be present, and low titers of rheumatoid factor, antinuclear antibody, and heterophil antibody also can be found occasionally.

In hepatitis C and D, antibodies to liver-kidney microsomes (LKM) may occur; however, the species of LKM antibodies in the two types of hepatitis are different from each other as well as from the LKM antibody species characteristic of autoimmune chronic hepatitis type 2. The autoantibodies in viral hepatitis are nonspecific and also can be associated with other viral and systemic diseases. In contrast, virus-specific antibodies, which appear during and after hepatitis virus infection, are serologic markers of diagnostic importance.

As described above, serologic tests are available with which to establish a diagnosis of hepatitis A, B, D, and C. Tests for fecal or serum HAV are not routinely available. Therefore, a diagnosis of type A hepatitis is based on detection of IgM anti-HAV during acute illness . Rheumatoid factor can give rise to false-positive results in this test. A diagnosis of HBV infection can usually be made by detection of HBsAg in serum. Infrequently, levels of HBsAg are too low to be detected during acute HBV infection, even with the current generation of highly sensitive immunoassays. In such cases, the diagnosis can be established by the presence of IgM anti-HBc. The titer of HBsAq bears little relation to the severity of clinical disease. Indeed, there may be an inverse correlation between the serum concentration of HBsAg and the degree of liver cell damage. For example, titers are highest in immunosuppressed patients, lower in chronic liver disease (but higher in mild chronic than in severe chronic hepatitis), and very low in acute fulminant hepatitis. These observations suggest that in hepatitis B the degree of liver cell damage and the clinical course are probably related to variations in the patient's immune response to HBV rather than to the amount of

circulating HBsAg. In immunocompetent persons, however, there is a correlation between markers of HBV *replication* and liver injury.

Another serologic marker that may be of value in patients with hepatitis B is HBeAq. Its principal clinical usefulness is as an indicator of relative infectivity. Because HBeAg is invariably present during early acute hepatitis B, HBeAg testing is indicated primarily during follow-up of chronic infection.

In patients with hepatitis B surface antigenemia of unknown duration, e.g., blood donors found to be HBsAq-positive and referred to a physician for evaluation, testing for IgM anti-HBc may be useful to distinguish between acute or recent infection (IgM anti-HBc-positive) and chronic HBV infection (IgM anti-HBc-negative, IgG anti-HBc-positive). A false-positive test for IgM anti-HBc may be encountered in patients with high-titer rheumatoid factor.

Anti-HBs is rarely detectable in the presence of HBsAg in patients with *acute* hepatitis B, but 10 to 20 percent of persons with *chronic* HBV infection may harbor low-level anti-HBs. This antibody is directed not against the common group determinant, a, but against the heterotypic subtype determinant (e.g., HBsAg of subtype *ad* with anti-HBs of subtype y). In most cases, this serologic pattern cannot be attributed to infection with two different HBV subtypes, and the presence of this antibody is not a harbinger of imminent HBsAg clearance. After immunization with hepatitis B vaccine, which consists of HBsAq alone, anti-HBs is the only serologic marker to appear. Tests for the detection of HBV DNA in liver and serum are now available (with help PCR). Like HBeAq, serum HBV DNA is an indicator of HBV replication, but tests for HBV DNA are more sensitive and quantitative. These markers are useful in following the course of HBV replication in patients with chronic hepatitis B receiving antiviral chemotherapy, e.g., with interferon. In immunocompetent persons, a general correlation does appear to exist between the level of HBV replication, as reflected by the level of HBV DNA in serum, and the degree of liver injury. High serum HBV DNA levels, increased expression of viral antigens, and necroinflammatory activity in the liver go hand in hand unless immunosuppression interferes with cytolytic T cell responses to virus-infected cells; reduction of HBV replication with antiviral drugs, such as interferon, tends to be accompanied by an improvement in liver histology.

In patients with hepatitis C, an episodic pattern of aminotransferase elevation is common. A specific serologic diagnosis of hepatitis C can be made by demonstrating the presence in serum of anti-HCV. When a second- or later-generation immunoassay (that detects antibodies to nonstructural and nucleocapsid proteins) is used, anti-HCV can be detected in acute hepatitis C during the initial phase of elevated aminotransferase activity. This antibody may never become detectable in 5 to 10 percent of patients with acute hepatitis C, and levels of anti-HCV may become undetectable after recovery from acute hepatitis C. In patients with chronic hepatitis

C, anti-HCV is detectable in >90 percent of cases. Because nonspecificity can confound immunoassays for anti-HCV, a supplementary recombinant immunoblot assay should be done, especially in persons with a low prior probability of infection, to establish the specific viral proteins to which anti-HCV is directed. Assays for HCV RNA are the most sensitive tests for HCV infection. HCV RNA can be detected even before acute elevation of aminotransferase activity and before the appearance of anti-HCV in patients with acute hepatitis C. In addition, HCV RNA remains detectable indefinitely, continuously in most but intermittently in some, in patients with chronic hepatitis C (even detectable in some persons with normal liver tests, i.e., asymptomatic carriers). Thus a diagnosis of hepatitis C can be supported by detection of anti-HCV and by exclusion of false-positive reactivity. In the small minority of patients with hepatitis C who lack anti-HCV, a diagnosis can be supported by detection of HCV RNA.

If all these tests are negative and the patient has a well-characterized case of hepatitis following percutaneous exposure to blood or blood products, a diagnosis of hepatitis G or, perhaps, hepatitis caused by another agent as yet unidentified can be entertained. A proportion of patients with hepatitis C have isolated anti - HBc in their blood, a reflection of a common risk in certain populations to multiple bloodborne hepatitis agents. The anti-HBc in such cases is almost invariably of the IgG class and usually represents HBV infection in the remote past, rarely current HBV infection with low-level virus carriage.

The presence of HDV infection can be identified by demonstrating intrahepatic HDV antigen or, more practically, an anti-HDV seroconversion (a rise in titer of anti-HDV or de novo appearance of anti-HDV). Circulating HDV antigen, also diagnostic of acute infection, is detectable only briefly, if at all. Because anti-HDV is often undetectable once HBsAg disappears, retrospective serodiagnosis of acute self-limited, simultaneous HBV and HDV infection is difficult. Early diagnosis of acute infection may be hampered by a delay of up to 30 to 40 days in the appearance of anti-HDV.

When a patient presents with acute hepatitis and has HBsAg and anti-HDV in the serum, determination of the class of anti-HBc is helpful in establishing the relationship between infection with HBV and HDV. Although IgM anti-HBc does not distinguish *absolutely* between acute and chronic HBV infection, its presence is a reliable indicator of recent infection and its absence a reliable indicator of infection in the remote past. In simultaneous acute HBV and HDV infections, IgM anti-HBc will be detectable, while in acute HDV infection superimposed on chronic HBV infection, anti-HBc will be of the IgG class. Tests for the presence of HDV RNA are useful for determining the presence of ongoing HDV replication and relative infectivity. Currently, probes for this marker are restricted to a limited number of research laboratories. Similarly, diagnostic tests for hepatitis E and G are confined to a small number of research laboratories.

Liver biopsy is rarely necessary or indicated in acute viral hepatitis, except when there is a question about the diagnosis or when there is clinical evidence suggesting a diagnosis of chronic hepatitis. A diagnostic algorithm can be applied in the evaluation of cases of acute viral hepatitis. A patient with acute hepatitis should undergo four serologic tests, HBsAg, IgM anti-HAV, IgM anti-HBc, and anti-HCV. The presence of HBsAg, with or without IgM anti-HBc, represents HBV infection. If IgM anti-HBc is present, the HBV infection is considered acute; if IgM anti-HBc is absent, the HBV infection is considered chronic. A diagnosis of acute hepatitis B can be made in the absence of HBsAg when IgM anti-HBc is detectable. A diagnosis of acute hepatitis A is based on the presence of IgM anti-HAV. If IgM anti-HAV coexists with HBsAg, a diagnosis of simultaneous HAV and HBV infections can be made; if IgM anti-HBc (with or without HBsAg) is detectable, the patient has simultaneous acute hepatitis A and B, and if IgM anti-HBc is undetectable, the patient has acute hepatitis A superimposed on chronic HBV infection. The presence of anti-HCV, if confirmable, supports a diagnosis of acute hepatitis C. Occasionally, repeat anti-HCV testing later during the illness is necessary to establish the diagnosis. Absence of all serologic markers is consistent with a diagnosis of "non-A, non-B, non-C" hepatitis, if the epidemiologic setting is appropriate.

In patients with chronic hepatitis, initial testing should consist of HBsAg and anti-HCV. Anti-HCV supports the diagnosis of chronic hepatitis C. If a serologic diagnosis of chronic hepatitis B is made, testing for HBeAg and anti-HBe is indicated to evaluate relative infectivity. Testing for HBV DNA in such patients provides a more quantitative and sensitive test for the level of virus replication and, therefore, is very helpful during antiviral therapy . In patients with hepatitis B, testing for anti-HDV is useful under the following circumstances: severe and fulminant cases, severe chronic cases, cases of acute hepatitis-like exacerbations in patients with chronic hepatitis B, persons with frequent percutaneous exposures, and persons from areas where HDV infection is endemic.

PROGNOSIS

Virtually all previously healthy patients with hepatitis A recover completely from their illness with no clinical sequelae. Similarly, in acute hepatitis B, 95 percent of patients have a favorable course and recover completely. There are, however, certain clinical and laboratory features that suggest a more complicated and protracted course. Patients of advanced age and with serious underlying medical disorders may have a prolonged course and are more likely to experience severe hepatitis. Initial presenting features such as ascites, peripheral edema, and symptoms of hepatic encephalopathy suggest a poorer prognosis. In addition, a prolonged FT, low serum albumin level, hypoglycemia, and very high serum bilirubin values suggest severe hepatocellular disease. Patients with these clinical and laboratory

features deserve prompt hospital admission. The case-fatality rate in hepatitis A and B is very low (approximately 0.1%) but is increased by advanced age and underlying debilitating disorders. Among patients ill enough to be hospitalized for acute hepatitis B, the fatality rate is 1%.

Hepatitis C occurring after transfusion is less severe during the acute phase than type B hepatitis and is more likely to be anicteric; fatalities are rare, but the precise case-fatality rate is not known. In outbreaks of waterborne hepatitis E in India and Asia, the case-fatality rate is 1-2% and up to 10-20% in pregnant women. Patients with simultaneous acute hepatitis B and hepatitis D do not necessarily experience a higher mortality rate than do patients with acute hepatitis B alone; however, in several recent outbreaks of acute simultaneous HBV and HDV infection among drug addicts, the case fatality rate has been approximately 5 percent. In the case of HDV superinfection of a person with chronic hepatitis B, the likelihood of fulminant hepatitis and death is increased substantially. Although the case-fatality rate for hepatitis D has not been defined adequately, in outbreaks of severe HDV superinfection in isolated populations with a high hepatitis B carrier rate, the mortality rate has been recorded in excess of 20%.

Chronic hepatitis is an important late complication of acute hepatitis B and C occurring in a small proportion of acute cases but more common in those who present with chronic infection without having experienced an acute illness. Certain clinical and laboratory features suggest progression of acute hepatitis to chronic hepatitis:

- lack of complete resolution of clinical symptoms of anorexia, weight loss, and fatigue and the persistence of hepatomegaly;
- the presence of bridging or multilobular hepatic necrosis on liver biopsy during protracted, severe acute viral hepatitis;
- failure of the serum aminotransferase, bilirubin, and globulin levels to return to normal within 6 to 12 months following the acute illness;
- the continued presence of HBsAg and HBeAg 6 months or more after acute hepatitis, suggesting chronic, replicative viral infection of the liver.

TREATMENT

There is no specific treatment for typical acute viral hepatitis. Although hospitalization may be required for clinically severe illness, most patients do not require hospital care. Forced and prolonged bed rest is not essential for full recovery, but many patients will feel better with restricted physical activity. A high-calorie diet is desirable, and because many patients may experience nausea late in the day, the major caloric intake is best tolerated in the morning. Intravenous feeding is necessary in the acute stage if the patient has persistent vomiting and cannot maintain oral intake. Drugs capable of producing adverse reactions such as cholestasis and drugs

metabolized by the liver should be avoided. If severe pruritus is present, the use of the bile salt-sequestering resin cholestyramine will usually alleviate this symptom.

Glucocorticoid therapy has no value in acute viral hepatitis. Even in severe cases associated with bridging necrosis, controlled trials have failed to demonstrate the efficacy of steroids. In fact, such therapy may be hazardous.

Physical isolation of patients with hepatitis to a single room and bathroom is rarely necessary except in the case of fecal incontinence for hepatitis A and E or uncontrolled, voluminous bleeding for hepatitis types B (with or without concomitant hepatitis D) and hepatitis C. Because most patients hospitalized with hepatitis A excrete little if any HAV, the likelihood of HAV transmission from these patients during their hospitalization is low. Therefore, burdensome enteric precautions are no longer recommended. Although gloves should be worn when the bedpans or fecal material of patients with hepatitis A are handled, these precautions do not represent a departure from sensible procedure for all hospitalized patients. For patients with hepatitis types B and C, emphasis should be placed on blood precautions, i.e., avoiding direct, ungloved hand contact with blood and other body fluids. Enteric precautions are unnecessary. The importance of simple hygienic precautions, such as hand washing, cannot be overemphasized. Universal precautions that have been adopted for all patients apply to patients with viral hepatitis.

Hospitalized patients may be discharged when there is substantial symptomatic improvement, a significant downward trend in the serum aminotransferase and bilirubin values, and a return to normal of the protrombin. Mild aminotransferase elevations should not be considered contraindications to the gradual resumption of normal activity. In fulminant hepatitis, the goal of therapy is to support the patient by maintenance of fluid balance, support of circulation and respiration, control of bleeding, correction of hypoglycemia, and treatment of other complications of the comatose state in anticipation of liver regeneration and repair. Protein intake should be restricted, and oral lactulose or neomycin administered. Glucocorticoid therapy has been shown in controlled trials to be ineffective. Likewise, exchange transfusion, plasmapheresis, human cross-circulation, porcine liver cross-perfusion, and hemoperfusion have not been proven to enhance survival. Meticulous intensive care is the one factor that does appear to improve survival. Orthotopic liver transplantation is resorted to with increasing frequency, with excellent results, in patients with fulminant hepatitis.

For patients with chronic HCV infection, one current treatment option is combination therapy with pegylated interferon (PEG-IFN) [PEG-Intron® or Pegasys®] and the antiviral ribavirin (Rebitol® or Kapegus®). This regimen may be recommended for a certain subset of patients with moderate or severe inflammation and/or moderite fibrosis (**Table 13**). The combination of the 2 drugs provides a more

sustained clearance of HCV RNA from the serum of infected individuals when compared to monotherapy.

Table 13. Treatment of chronic viral hepatitis C

Genotypes of HCV-infection and body weight of patient		PEG-IFN		Ribavirin	Duration of therapy
		PEG-Intron®	Pegasys®		
2 & 3 genotypes	less 80 kg	180 mcg/week	1,5 mcg/kg/week	800 mg/day	24 week
	more 80 kg	180 mcg/week	1,5 mcg/kg/week	1000 mg/day	
1 & 4 genotypes	less 80 kg	180 mcg/week	1,5 mcg/kg/week	1000 mg/day	48 week
	more 80 kg	180 mcg/week	1,5 mcg/kg/week	1200 mg/day	

Other therapeutic options are being explored for treatment of chronic HCV with the goals of increasing efficacy and decreasing toxicity. These include protease inhibitors, ribozymes, and viral vaccines.

PEG-INF interferon is indicated for the treatment of chronic hepatitis B, but due to issues of cost and associated side effects, is not as widely used as the oral antiviral therapies. However, a finite duration of treatment and the lack of concern for viral resistance still make interferon-based therapy a viable option for some patients. Monotherapy with INF viral hepatitis B or D is not so effective then combined treatment INF with antiviral drugs such as Adefovir or Entecavir, and Tebivudine.

Lamivudine is a potent nucleoside analog and was the first oral therapy approved for the treatment of hepatitis B. Unfortunately, high rates of viral resistance, manifesting as the mutation of HBV, emerged after even short periods of lamivudine therapy (24% resistance at 1 year, increasing up to 70% by 4 years of therapy). However, despite this high rate of viral resistance, due to its relatively low cost and ready availability, lamivudine remains widely used worldwide.

Adefovir is a nucleotide analog with effective antiviral activity against the lamivudine-resistant viral strain.

Entecavir was approved for the treatment of hepatitis B in 2005, and data continue to be reported on the long-term outcomes of patients. The phase 3 randomized study comparing entecavir with lamivudine in the treatment of nucleoside-naive HBeAg-positive patients was continued for a total of 96 weeks.

Telbivudine is the most recent Food Drug Administration approved therapy for the treatment of chronic HBV infection, and is a nucleoside analogue that inhibits the HBV polymerase.

PROPHYLAXIS

Because there is no therapy for acute viral hepatitis, and because antiviral therapy for chronic viral hepatitis is effective in only a proportion of patients , emphasis is placed on prevention through immunization. The prophylactic approach differs for each of the types of viral hepatitis. In the past, immunoprophylaxis relied exclusively on passive immunization with antibody - containing globulin preparations purified by cold ethanol fractionation from the plasma of hundreds of normal donors. Currently, for hepatitis A and B, active immunization with vaccines is available as well.

Hepatitis A. Both passive immunization with immune globulin (IG) and active immunization with a killed vaccine are available. All preparations of IG contain anti-HAV. Although the titers may vary, all IG preparations have an antibody concentration sufficient to be protective. When administered before exposure or during the early incubation period, IG is effective in preventing clinically apparent type A hepatitis. In some cases, IG does not abort infection but, by attenuating it, renders it inapparent. As a result, long-lasting "passive-active" immunity occurs; however, this is now considered to be the exception rather than the rule. For postexposure prophylaxis of intimate contacts (household, institutional) of persons with hepatitis A, administration of 0.02 mL/kg is recommended as early after exposure as possible; it may be effective even when administered as late as 2 weeks after exposure. Prophylaxis is not necessary for casual contacts (office, factory, school, or hospital), for most elderly persons, who are very likely to be immune, or for those known to have anti-HAV in their serum. In day-care centers, recognition of hepatitis A cases in children or staff should provide a stimulus for immunoprophylaxis in the center and in the children's family members. By the time most common-source outbreaks of type A hepatitis are recognized, it is usually too late in the incubation period for IG to be effective; however, prophylaxis may limit the frequency of secondary cases. For travelers to tropical countries, developing countries, and other areas outside standard tourist routes, IG prophylaxis had been recommended, before a vaccine became available. When such travel lasted less than 3 months, 0.02 mL/kg was given; for longer travel or residence in these areas, a dose of 0.06 mL/kg every 4 to 6 months was recommended. A formalin-inactivated vaccine made from a strain of HAV attenuated in tissue culture has been shown to be safe, immunogenic, and effective in preventing hepatitis A. It is approved for use in persons who are at least 2 years old and appears to provide adequate protection 4 weeks after a primary inoculation. If it can be given within 4 weeks of an expected exposure, such as by travel to an endemic area, hepatitis A vaccine is the preferred approach to preexposure immunoprophylaxis.

If travel is more imminent, IG (0.02 mL/kg) should be administered at a different injection site, along with the first dose of vaccine. Because vaccination

provides long-lasting protection (protective levels of anti-HAV should last 20 years after vaccination), persons whose risk will be sustained (e.g., frequent travelers or those remaining in endemic areas for prolonged periods) should be vaccinated, and vaccine should supplant the need for repeated IG injections. Other groups who are candidates for hepatitis A vaccination include military personnel, populations with cyclic outbreaks of hepatitis A (e.g., Alaskan natives), employees of day-care centers, primate handlers, laboratory workers exposed to hepatitis A or fecal specimens, and other populations whose recognized risk of hepatitis A is increased. For adults, a complete course of hepatitis A vaccine consists of two intramuscular injections (a 1-mL dose) given 6 to 12 months apart. For children, aged 2 to 18, three transmuscular injections (a 0.5-mL dose) are recommended, the first two a month apart and the third 6 to 12 months after the first. The role of hepatitis A vaccine in postexposure prophylaxis remains to be demonstrated.

Hepatitis B. Until 1982, prevention of hepatitis B was based on passive immunoprophylaxis either with standard IG, containing modest levels of anti-HBs, or hepatitis B immune globulin (HBIG), containing high-titer anti-HBs. The efficacy of standard IG has never been established and remains questionable; even the efficacy of HBIG, demonstrated in several clinical trials, has been challenged, and its contribution appears to be in reducing the frequency of clinical illness, not in preventing infection. The first vaccine for active immunization, introduced in 1982, was prepared from purified, noninfectious 22-nm spherical forms of HBsAq derived from the plasma of healthy HBsAg carriers. In 1987, the plasma-derived vaccine was supplanted by a genetically engineered vaccine derived from recombinant yeast. The latter vaccine consists of HBsAg particles that are nonglycosylated but are otherwise indistinguishable from natural HBsAg. Current recommendations can be divided into those for preexposure and postexposure prophylaxis.

For preexposure prophylaxis against hepatitis B in settings of frequent exposure (health workers exposed to blood, hemodialysis patients and staff, residents and staff of custodial institutions for the developmentally handicapped, intravenous drug abusers, inmates of long-term correctional facilities, promiscuous homosexual men as well as promiscuous heterosexuals, persons such as hemophiliacs who require long-term, high-volume therapy with blood derivatives, household and sexual contacts of HBsAg carriers, persons living in or traveling extensively in endemic areas, and unvaccinated children under the age of 11 who are Alaskan natives, Pacific Islanders, or residents in households of first-generation immigrants from endemic countries), three intramuscular (deltoid, not gluteal) injections of hepatitis B vaccine are recommended at 0, 1, and 6 months. Pregnancy is not a contraindication to vaccination. In areas of low HBV endemicity such as the United States, despite the availability of safe and effective hepatitis B vaccines, a strategy of vaccinating persons in high-risk groups has not been effective. The incidence of new hepatitis B

cases continued to increase in the United States after introduction of vaccines; fewer than 10 percent of all targeted persons in high-risk groups have actually been vaccinated, and approximately 30 percent of persons with sporadic acute hepatitis B do not fall into any high-risk-group category. Therefore, to have an impact on the frequency of HBV infection in an area of low endemicity such as the United States, universal hepatitis B vaccination in childhood has been recommended. For unvaccinated children born after the implementation of universal infant vaccination, vaccination during early adolescence, at age 11 to 12 years, has been recommended.

There are two comparable recombinant hepatitis B vaccines available, one containing 10 ug of HBsAq_(Recombivax-HB) and the other containing 20 ug of HBsAg (Engerix-B), and recommended doses for each injection vary between the two preparations. For Recombivax-HB, 2.5 ug is recommended for children <11 years of age of HBsAg-negative mothers, 5 ug for infants of HBsAg-positive mothers (see below) and for children and adolescents 11 to 19 years of age; 10 ug for immunocompetent adults; and 40 ug for dialysis patients and other immunosuppressed persons.

For Engerix-B, 10 ug is recommended for children aged 10 and under, 20 ug for immunocompetent children older than 10 years of age and adults, and 40 ug for dialysis patients and other immunocompromised persons. For unvaccinated persons sustaining an exposure to HBV, postexposure prophylaxis with a combination of HBIG (for rapid achievement of high-titer circulating anti-HBs) and hepatitis B vaccine (for achievement of long-lasting immunity as well as its apparent efficacy in attenuating clinical illness after exposure) is recommended. For perinatal exposure of infants born to HBsAg-positive mothers, a single dose of HBIG, 0.5 mL, should be administered intramuscularly in the thigh immediately after birth, followed by a complete course of three injections of recombinant hepatitis B vaccine (see doses above) to be started within the first 12 h of life. For those experiencing a direct percutaneous inoculation or transmucosal exposure to HBsAg-positive blood or body fluids (e.g., accidental needle stick, other mucosal penetration, or ingestion), a single intramuscular dose of HBIG, 0.06 mL/kg, administered as soon after exposure as possible, is followed by a complete course of hepatitis B vaccine to begin within the first week. For those exposed by sexual contact to a patient with acute hepatitis B, a single intramuscular dose of HBIG, 0.06 mL/kg, should be given within 14 days of exposure, to be followed by a complete course of hepatitis B vaccine. When both HBIG and hepatitis B vaccine are recommended, they may be given at the same time but at separate sites. The precise duration of protection afforded by hepatitis B vaccine is unknown; however, approximately 80 to 90 percent of immunocompetent vaccinees retain protective levels of anti-HBs for at least 5 years. Thereafter and even after anti-HBs becomes undetectable, protection persists against clinical hepatitis B, hepatitis B surface antigenemia, and chronic HBV infection. Currently, booster

immunizations are not recommended routinely, except in immunosuppressed persons who have lost detectable anti-HBs or immunocompetent persons who sustain percutaneous HBsAg-positive inoculations after losing detectable antibody. Specifically, for hemodialysis patients, annual anti-HBs testing is recommended after vaccination; booster doses are recommended when anti-HBs levels fall below 10 mlU/mL.

Hepatitis D. Infection with hepatitis D can be prevented by vaccinating susceptible persons with hepatitis B vaccine. No product is available for immunoprophylaxis to prevent HDV superinfection in HbsAg-carriers; for them, avoidance of percutaneous exposures and limitation of intimate contact with persons who have HDV infection are recommended.

Hepatitis C. Immunoglobulin has been shown to be ineffective in preventing hepatitis C and is no longer recommended for postexposure prophylaxis in cases of perinatal, needle stick, or sexual exposure. Although a prototype vaccine that induces antibodies to HCV envelope protein has been developed, currently, hepatitis C vaccination is not feasible practically. Genotype and quasispecies viral heterogeneity, as well as rapid evasion of neutralizing antibodies by this rapidly mutating virus, conspire to render HCV a difficult target for immunoprophylaxis with a vaccine. Prevention of transfusion-associated hepatitis C has been accomplished by the following successively introduced measures: Exclusion of commercial blood donors and reliance on a volunteer blood supply; screening donor blood with surrogate markers such as ALT (no longer recommended) and anti-HBc, markers that identify segments of the blood donor population with an increased risk of bloodborne infections; exclusion of blood donors in high-risk groups for AIDS and the introduction of anti-HIV screening tests; and progressively sensitive serologic screening tests for anti -HCV. Chemical and heat treatment of blood products used for large-pool and concentrated blood derivates are being pursued.

ABBREVIATION

ADP – adenosine diphosphate;
AMP – adenosine monophosphate;
CDC – Centers for Disease Control and Prevention in Atlanta;
CIEF – counterimmune electrophoresis;
CIN – Cefsulodin - Irgasan - Novobiocin;
CSF – cerebrospinal fluid;
DOC – drug of choice;
EIA – enzyme immunoassay;
ELISA – enzyme-linked immunoassays;
GBS – Guillain-Barre syndrome;
GI – gastrointestinal;
GMP – guanosine monophosphate;
HCC – hepatocellular carcinoma;
HUS – hemolytic-uremic syndrome;
IFAT – indirect fluorescent antibody test;
IM – intramuscular;
IFN – interferon;
IFN – interferon;
IV – intravenous;
LA – latex agglutination;
LT – heat-labile enterotoxin;
MIC – minimal inhibitory concentration;
O – oraly;
ORS – oral regidration solutions;
PCR – polymeroze chain reaction;
PEG-INF – pegylated interferon;
PHA – passive hacmagglutination;
RIA – radioimmunoassay;
RIAG – reaction of indirect agglutination;
ST – heat-stable enterotoxin.

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