Bacterial Foodborne Pathogens

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Objectives

By the end of this educational encounter, the clinician will be able to:

1. Describe common modes of transmission of foodborne pathogens
2. Identify symptoms of common foodborne illness
3. Define treatment for foodborne pathogens

Purpose: The purpose of this course is to acquaint the clinician with foodborne illness and to impart familiarity with the signs and symptoms and treatment of foodborne pathogens.

Foodborne pathogens can cause a wide variety of clinical symptoms and can arise from a wide variety of sources.

Baccili

Bacillus species are rod-shaped, endospore forming aerobic or facultatively anaerobic, Gram-positive bacteria; in some species cultures may turn Gram-negative with age. The many species of the genus exhibit a wide range of physiologic abilities that allow them to live in every natural environment. Only one endospore is formed per cell. The spores are resistant to heat, cold, radiation, desiccation, and disinfectants. Bacillus anthracis needs oxygen to sporulate; this constraint has important consequences for epidemiology and control. Because the spores of many Bacillus species are resistant to heat, radiation, disinfectants, and desiccation, they are difficult to eliminate from medical and pharmaceutical materials and are a frequent cause of contamination. Bacillus species are well known in the food industries as troublesome spoilage organisms

Anthrax

Anthrax is primarily a disease of domesticated and wild animals, particularly plant eating animals, such as cattle, sheep, horses, mules and goats. Herbivorous

animals, the primary hosts of B anthracis, contract the infection by ingesting spores on forage plants; the spores are derived from soil or dust or are deposited on leaves by flies after feeding on an anthrax-infected carcass. Although the spores have been found naturally in soil samples from around the world, the organisms cannot be regularly cultivated from soils where there is an absence of endemic anthrax. In the United States, the incidence of naturally acquired anthrax is extremely rare (1-2 cases of cutaneous disease per year). There are recognized areas of infection in South Dakota, Nebraska, Arkansas, Texas, Louisiana, Mississippi, California and small areas that exist in other states. Even in endemic areas, anthrax occurs irregularly, often with many years between occurrences.

Worldwide, the incidence is unknown due to unreliable reporting, although B. anthracis is present in most of the world. Humans become infected incidentally when brought into contact with diseased animals, which includes their flesh, bones, hides, hair and excrement.

Gastrointestinal anthrax is analogous to cutaneous anthrax but occurs on the intestinal mucosa. As in cutaneous anthrax, the organisms probably invade the mucosa through a preexisting lesion. The bacteria spread from the mucosal lesion to the lymphatic system. Intestinal anthrax results from the ingestion of poorly cooked meat from infected animals. Gastrointestinal anthrax is rare but may occur as explosive outbreaks associated with ingestion of infected animals. Gastrointestinal infections can be treated but usually result in fatality rates of 25% to 60%, depending upon how soon treatment commences.

Gastrointestinal infection in humans is most often caused by eating anthrax-infected meat and is characterized by serious gastrointestinal difficulty, vomiting of blood, severe diarrhea, acute inflammation of the intestinal tract, and loss of appetite. Some lesions have been found in the intestines and in the mouth and throat. After the bacteria invade the bowel system, it spreads through the bloodstream throughout the body, making even more toxins on the way.

Generalized disease develops when the organisms spread from the mucosal lesion to the lymphatic system. In pulmonary anthrax, inhaled spores are transported to the mediastinal lymph nodes, where they germinate and multiply to initiate systemic disease. Gastrointestinal anthrax is more dangerous than the cutaneous form because it is usually identified too late for treatment to be effective. Meningitis due to B. anthracis is a very rare complication that may result from a primary infection elsewhere.

Symptoms prior to fulminant systemic anthrax may be absent or mild, consisting, for example, of malaise, low fever, and mild gastrointestinal symptoms in the case of gastrointestinal disease. During this phase, the organism is multiplying and producing toxin in the regional lymph nodes and spleen. Released toxin causes breakdown of these organs probably of the spleen in particular. This

causes the sudden onset of hyperacute illness with dyspnea, cyanosis, high fever, and disorientation, which progress in a few hours to shock, coma, and death. Although symptoms vary somewhat with the host species, this final acute phase is marked by a high-grade bacteremia. In humans, blood cultures are not always positive.

Gastrointestinal and pulmonary anthrax infections are difficult to identify before the fulminant phase and therefore carry a high mortality. In uncomplicated anthrax cases, adequate treatment consists of 500 mg of penicillin V taken orally every 6 hours for 5 days, or 600 mg (1 million units) of procaine penicillin administered intramuscularly every 12 to 24 hours for 5 days. In severe cases, 1,200 mg (2 million units) of penicillin G should be administered intravenously every 6 hours, reverting to the intramuscular regime of 600 mg every 12 to 24 hours once recovery starts. If pulmonary anthrax is suspected, continuous-drip administration is advisable. Tetracyclines (tests in animals indicate doxycycline is good), chloramphenicol, gentamicin, or erythromycin may be used if the patient has penicillin hypersensitivity. The fluoroquinolone, ciprofloxacin, has also been shown to be effective in monkeys and guinea pigs and would be expected to be effective in treatment of cases of human anthrax.

Several other Bacillus spp, in particular B cereus and to a lesser extent B subtilis and B licheniformis, are periodically associated with bacteremia/septicemia, endocarditis, meningitis, and infections of wounds, the ears, eyes, respiratory tract, urinary tract, and gastrointestinal tract.

Bacillus cereus is well known as an agent of food poisoning, and a number of other Bacillus species, particularly B subtilis and B licheniformis, are also incriminated periodically in this capacity. Bacillus cereus causes two distinct food poisoning syndromes: a rapid-onset emetic syndrome characterized by nausea and vomiting, and a slower-onset diarrheal syndrome. The diarrheal type is characterized by diarrhea and abdominal pain occurring 8 to 16 hours after consumption of the contaminated food. It is associated with a variety of foods, including meat and vegetable dishes, sauces, pastas, desserts, and dairy products. In emetic disease, on the other hand, nausea and vomiting begin 1 to 5 hours after the contaminated food is eaten. Boiled rice that is held for prolonged periods at ambient temperature and then quick-fried before serving is the usual offender, although dairy products or other foods are occasionally responsible. The principal virulence factors are a necrotizing enterotoxin and a potent hemolysin (cereolysin). Emetic food poisoning probably results from the release of emetic factors from specific foods by bacterial enzymes. The symptoms of food poisoning caused by other Bacillus species (B subtilis, B licheniformis, and others) are less well defined. Diarrhea and/or nausea occur 1 to 14 hours after consumption of the contaminated food. Wide varieties of food types have proved responsible in recorded instances.

Episodes of B cereus food poisoning occur sporadically worldwide and result from ingestion of contaminated food in which the bacteria have multiplied to high levels under conditions of improper storage after cooking. Food poisoning is controlled by adequate cooking, avoidance of recontamination of cooked food, and proper storage (efficient refrigeration) and by good hygiene.

Bacillus cereus infections are diagnosed by culture of the bacteria. Treatment is with non-ß-lactam antibiotics for Gram-positive bacteria. Bacillus cereus and its close relatives B thuringiensis and B mycoides produce potent ß-lactamases and thus are not responsive to penicillin, ampicillin, or the cephalosporins. They are mostly resistant to trimethoprim as well. These species are generally sensitive to standard empirical treatment with an aminoglycoside combined with vancomycin and to chloramphenicol, erythromycin, tetracycline, clindamycin, and sulfonamides.

Brucellosis

Brucellosis is the most common zoonotic infection; it is acquired from handling of infected animals or consuming contaminated milk or milk products. Brucellosis is not very common in the United States, where 100 to 200 cases occur each year. However, brucellosis can be very common in countries where animal disease control programs have not reduced the amount of disease among animals. Texas has the highest incidence of cases (1.38 per one million population). Nationally, the infection is due to two main sources: importation of disease (from infected food products or international travel) and cross-border spread (mostly B melitensis) from Mexico into neighboring states (mostly affecting Hispanics). Areas currently listed as high risk are the Mediterranean Basin (Portugal, Spain, Southern France, Italy, Greece, Turkey, North Africa), South and Central America, Eastern Europe, Asia, Africa, the Caribbean, and the Middle East. Unpasteurized cheeses, sometimes called "village cheeses," from these areas may represent a particular risk for tourists. Exposure is frequently occupational. Brucellosis is prevented by pasteurizing milk, eradicating infection from herds and flocks, and observing safety precautions (protective clothing and laboratory containment).

The disease is treated with doxycycline, streptomycin and rifampin. The presentation of brucellosis is characteristically variable. The incubation period is often difficult to determine but is usually from 2 to 4 weeks. The onset may be insidious or abrupt. Subclinical infection is common.

In the simplest case, the onset resembles influenza with fever reaching 38 to 40°C. Limb and back pains are unusually severe, however, and sweating and fatigue are marked. The leukocyte count tends to be normal or reduced, with a relative lymphocytosis. On physical examination, splenomegaly may be the only finding. If the disease is not treated, the symptoms may continue for 2 to 4

weeks. Many patients will then recover spontaneously but others may suffer a series of exacerbations. These may produce an undulant fever in which the intensity of fever and symptoms recur and recede at about 10 day intervals. Anemia is often a feature. True relapses may occur months after the initial episode, even after apparently successful treatment.

Most affected persons recover entirely within 3 to 12 months but some will develop complications marked by involvement of various organs, and a few may enter an ill-defined chronic syndrome. Complications include arthritis, often sacroiliitis, and spondylitis (in about 10 percent of cases), central nervous system effects including meningitis (in about 5%), uveitis and, occasionally, epididymoorchitis. In contrast to animals, abortion is not a feature of brucellosis in pregnant women. Hypersensitivity reactions, which may mimic the symptoms of an infection, may occur in individuals who are exposed to infective material after previous, even subclinical, infection. Mortality is low (<2%), and is usually associated with endocarditis. Brucellosis has been known by various names, including Mediterranean fever, Malta fever, gastric remittent fever, and undulant fever.

Campylobacter

Campylobacter, (meaning 'twisted bacteria') first discovered in 1963, describes Gram-negative, spiral, microaerophilic bacteria. Motile, with either uni- or bi-polar flagella, the organisms have a characteristic spiral/corkscrew appearance and are oxidase-positive, and grow optimally at 37° or 42°C. Campylobacter jejuni is now recognized as one of the main causes of bacterial foodborne disease in many developed countries; it causes up to 4 million human infections a year. Domestic and wild animals are the reservoirs for the organisms including food animals (cattle, sheep, poultry, swine, and goats). More than 50 percent of poultry sold in the United States is contaminated with C jejuni. Transmission from food sources accounts for most human infections. Rodents and pets including dogs, cats, and birds also may transmit infection to humans, and excreta from wild animals may contaminate water supplies. At least a dozen species of Campylobacter have been implicated in human disease, with C. jejuni and C. coli the most common. C. fetus is a cause of spontaneous abortions in cattle and sheep, as well as it is an opportunistic pathogen in humans.

The common routes of transmission are fecal-oral, person-to-person sexual contact, ingestion of contaminated food or water, and the eating of raw meat. It produces an inflammatory, sometimes bloody, diarrhea, periodontitis or dysentery syndrome, mostly including cramps, fever and pain. The symptoms and signs of Campylobacter enteritis are not distinctive enough to differentiate it from illness caused by many other enteric pathogens; the presence of neutrophils or blood in the feces of patients with acute diarrheal illnesses is an important clue to Campylobacter infection. Symptoms range from mild

gastrointestinal distress lasting 24 hours to a fulminating or relapsing colitis that mimics ulcerative colitis or Crohn's disease. The predominant symptoms experienced by individuals in developed countries are diarrhea, abdominal pain, fever, nausea, and vomiting. A history of grossly bloody stools is common, and many patients have at least one day with eight or more bowel movements; fecal leukocytes are usually present. Some strains of C jejuni produce a cholera-like enterotoxin, which is important in the watery diarrhea observed in infections.

Campylobacter enteritis usually is self-limiting with gradual improvement in symptoms over several days. Most patients recover within a week, but 10%–20% experience relapse or a prolonged severe illness. Toxic megacolon, pseudomembraneous colitis, and massive lower gastrointestinal hemorrhage also have been described. Mesenteric adenitis and appendicitis have been reported in children and young adults. Bacteremia is uncommon (<1%) in immunocompetent patients with C jejuni infection. C jejuni and C coli infections are endemic worldwide and hyperendemic in developing countries. Infants and young adults are most often infected. Disease incidence peaks in the summer. Outbreaks are associated with contaminated animal products or water. Among populations in developing countries, infection by C jejuni and closely related organisms is associated with much milder illness, without bloody diarrhea, fever or fecal leukocytes. Asymptomatic infection is much more common than in the developed countries, especially in older children and adults. However, when travelers from developed countries acquire C jejuni infections in developing countries, the symptoms are those associated with an inflammatory process. This indicates that organisms in the developing countries are fully pathogenic. Campylobacter infections have been identified as the most common antecedent to an acute neurological disease, the Guillain-Barré syndrome. Guillain-Barré syndrome is an uncommon consequence of C jejuni infection that is present 2–3 weeks after the diarrheal illness. However, because of the high incidence of Campylobacter infection, it has been estimated to be the trigger of 20 to 40 percent of all cases of Guillain-Barré syndrome. One cause of the effects of campylobacteriosis is tissue injury in the gut including the jejunum, the ileum, and the colon. C jejuni appears to achieve this by invading and destroying epithelial cells; the lesions show an acute exudative and hemorrhagic inflammation. Patients frequently have colonic involvement consisting of inflammation of the lamina propria with neutrophils, eosinophils, and mononuclear cells. Destruction of epithelial glands with crypt abscess formation occurs in severe cases. The pathologic lesions seen in Campylobacter colitis are difficult to distinguish from those in ulcerative colitis. Therefore, before ulcerative colitis can be diagnosed, infection by Campylobacter and related organisms should be ruled out. In a small number of cases, the infection may be associated with hemolytic uremic syndrome and thrombotic thrombocytopenic purpura through a poorly understood mechanism. Complications are relatively rare, but infections have been associated with reactive arthritis, and following septicemia, infections of nearly any organ. The estimated case/fatality ratio for all C. jejuni infections is 0.1, meaning one death per 1,000 cases. Fatalities are rare in healthy individuals

and usually occur in cancer patients or in the otherwise debilitated. Only 20 reported cases of septic abortion induced by C. jejuni have been recorded in the literature. Meningitis, recurrent colitis, and acute cholecystitis are very rare complications.

The infection is usually self-limiting and in most cases, fluid and electrolyte replacement are the cornerstones for treatment. Specific treatment with antimicrobial agents indicated for persons with severe or prolonged symptoms. However, for mild infections, the efficacy of treatment with antimicrobial agents has not yet been demonstrated. When treatment is required, erythromycin or ciprofloxacin appear to be the agents of choice.

Nonspecific defenses such, as gastric acidity and intestinal transit time are important. Specific immunity, involving intestinal immunoglobulin (IgA) and systemic antibodies, develops. Persons deficient in humoral immunity develop severe and prolonged illnesses. Campylobacter jejuni can be killed by hydrochloric acid, suggesting that normal gastric acidity may be an important barrier against infection. Acutely infected persons frequently develop elevated specific serum Immunoglobulin A (IgA), IgG, and IgM titers, which may persist for several weeks. Experimentally infected animals and humans manifest specific intestinal IgA production. Whether the antibody response eliminates the infection or protects against reinfection is not known. However, upon challenge with C jejuni, human volunteers with elevated specific serum IgA levels were likely to develop asymptomatic infection with only a brief duration of pathogen excretion. In contrast, hypogammaglobulinemic persons and those with acquired immune deficiency syndrome (AIDS) are at increased risk for severe, recurrent or bacteremic infections. Regardless of the exact host defense mechanisms involved, most C jejuni infections resolve spontaneously.

Observation of darting motility in fresh fecal specimens or of vibrio forms on Gram stain permit presumptive diagnosis; definitive diagnosis is established by stool culture, and occasionally by blood culture.

As with other enteric pathogens, the attack rate of C jejuni varies with the ingested dose. In outbreaks of Campylobacter enteritis, the incubation period has ranged from 1–7 days, with most illness developing 2–4 days after infection. Infection leads to multiplication of organisms in the intestines. Patients shed 10^6 to 10^9Campylobacter per gram of feces, concentrations similar to those shed in Salmonella and Shigella enteric infections. The minimal infection-causing dose of C jejuni is not known, although volunteers who have ingested as few as 800 organisms have become ill.

Between 3 and 14 percent of patients with diarrhea who seek medical attention are infected with C jejuni. Prolonged asymptomatic carriage is rare. The attack rate is highest in children less than 1 year old, and gradually decreases throughout childhood. A second peak occurs in young adults (18 to 29 years

old). In contrast, up to 40 percent of healthy children in developing countries may carry the organism at any time. This is an age-related phenomenon, with the highest excretion rates in very young children. Case-to-infection ratios decline with age, which probably is indicative of acquisition of immunity due to recurrent exposure.

Control of Campylobacter enteritis depends largely on interrupting the transmission of the organism to humans from farm and domestic animals, food of animal origin, or contaminated water. Individuals can reduce the risk of Campylobacter infection by properly cooking and storing meat and dairy products, avoiding contaminated drinking water and unpasteurized milk, and washing their hands after contact with animals or animal products.

Clostridium botulinum is a Gram-positive, rod shaped bacterium that produces the neurotoxin botulin, this neurotoxin characteristically causes a symmetrical, descending paralysis seen in botulism. It is also the main paralytic agent in botox. Seven types (A, B, C, D, E, F and G) of botulism are recognized, based on the antigenic specificity of the toxin produced by each strain. Types A, B, E and F cause human botulism. Types C and D cause most cases of botulism in animals. Although type G has been isolated from soil in Argentina, no outbreaks involving it have been recognized.

C botulinum spores are found worldwide in both cultivated and forest soils, bottom sediments of streams, lakes, and coastal waters, and in low numbers in the gastrointestinal tracts of some birds, fish, and mammals, and in the gills and viscera of crabs and other shellfish. All adults have likely ingested these spores with no ill effects. In the United States, the most frequent isolate is type A, followed by B and E, with an occasional isolate of type F. In Europe, B is the most frequent isolate, whereas A is comparatively rare.

It is an anaerobic spore-former, which produces oval, subterminal endospores. It is an obligate anaerobe, meaning that oxygen is poisonous to the cells. However, they tolerate very small traces of oxygen due to an enzyme called superoxide dismutase (SOD), which is an important antioxidant defense in nearly all cells exposed to oxygen. Under unfavorable circumstances, they are able to form endospores that allow them to survive in a dormant state until exposed to conditions that can support their growth. The spores can survive in most environments and are very hard to kill.

Four types of botulism are recognized: foodborne, infant, wound, and a form of botulism whose classification is yet undetermined. Certain foods have been reported as sources of spores in cases of infant botulism and the undetermined category; wound botulism is not related to foods.

Foodborne botulism is the name of the disease (actually a foodborne intoxication) caused by the consumption of foods containing the neurotoxin

produced by C. botulinum. Botulism accounts for less than one of every 400 cases of food poisoning in the U.S., but two factors make it very important. First, it has caused death in approximately 30 percent of the cases; and secondly, it occurs mostly in home-canned foods. Originally, botulism food poisoning was thought to be associated only with contaminated meat, especially sausage; however, it is now known that C botulinum can grow equally well in many types of food including vegetables, fish, fruits, and condiments. They can survive the temperature of boiling water at sea level, thus many foods are canned with a pressurized boil that achieves an even higher temperature, sufficient to kill the spores. Growth of the bacterium can be prevented by high acidity, high ratio of dissolved sugar, high levels of oxygen, very low levels of moisture, or storage at temperatures below 38°F (type A). For example in a low acid, canned vegetable such as green beans that are not heated hot enough to kill the spores (i.e., a pressurized environment) may provide an oxygen free medium for the spores to grow and produce the toxin. Home canning using inadequate sterilization techniques has been responsible for most cases of botulism during this century. The spores are heat resistant and can survive 100° C for hours, but the toxin is relatively heat labile. An affected food may show signs of spoilage such as a bulging can or an off-odor. This is not true in all cases, so canned foods should not be tasted before heating. The botulinum toxin is destroyed by boiling the food for 10 minutes. The toxin is usually produced at pH 4.8–8.5. However, even acid foods such as canned tomatoes have been responsible for several recent cases of botulism food poisoning. On the other hand, pickles are sufficiently acidic to prevent growth; even if the spores are present, they pose no danger to the consumer. Honey, corn syrup, and other sweeteners may contain spores but the spores cannot grow in a highly concentrated sugar solution; however, when a sweetener is diluted in the low oxygen, low acid digestive system of an infant, the spores can grow and produce toxin. As soon as infants begin eating solid food, the digestive juices become too acidic for the bacterium to grow.

In addition, certain culture conditions have been shown to cause toxin production at pH values lower than 4.6. In general, germination of botulinum spores is favored in food kept at warm temperatures under anaerobic conditions for a long period.

Onset of symptoms in foodborne botulism is usually 18 to 36 hours after ingestion of the food containing the toxin, although cases have varied from 4 hours to 8 days. Early signs of intoxication consist of marked lassitude, weakness and vertigo, usually followed by double vision and progressive difficulty in speaking and swallowing. Difficulty in breathing, weakness of other muscles, abdominal distention, and constipation may also be common symptoms.

Diagnosis is from the clinical symptoms, especially gastrointestinal and neurological symptoms, coupled with laboratory confirmation. A finding of normal

spinal fluid helps to eliminate the possible diagnosis of numerous other central nervous system disorders. The best means of control is to eliminate the toxin source via proper food handling. Once the food poisoning is diagnosed, treatment measures should include an attempt to neutralize unbound toxin. Supportive care is of primary importance. They are involved in a variety of human diseases, the most important of which are gas gangrene, tetanus, botulism, pseudomembraneous colitis and food poisoning. The symptoms of botulism can occur in both the nervous system and the alimentary tract of the patient. Therefore, many diseases enter into the differential diagnosis, including pharyngitis, gastroenteritis, sepsis, intestinal obstruction, myasthenia gravis, encephalitis, muscular dystrophy, electrolyte imbalance, meningitis, poliomyelitis, cerebrovascular accident, Guillain-Barré syndrome, chemical food poisoning, tick paralysis, Reye syndrome, hypothyroidism, heavy metal ingestion, carbon monoxide poisoning, and snake bite. For infant botulism, additional syndromes enter into the differential diagnosis: failure to thrive, acute infantile polyneuropathy, dehydration, and various hereditary and metabolic disorders. Infant botulism often is missed by physicians, but it always should be considered if any of the typical symptoms are present.

Type A toxin is the most potent poison known; ingestion of only 10^{-8} grams of this toxin can kill a human. Put another way, the amount of toxin that could be held on the tip of a dissecting probe could kill 40 medical students. The pathogenicity of C botulinum depends entirely on neurotoxin production.

From its site of entry into the body, the toxin travels through the blood and lymphatic systems (and possibly the nervous system). It then becomes fixed to cranial and peripheral nerves, but exerts almost all of its action on the peripheral nervous system. The toxin appears to bind to receptor sites at the neuromuscular junctions of parasympathetic nerves, and inhibits the release of acetylcholine at peripheral cholinergic synapses.

The cranial nerves are affected first, followed by a descending, symmetric paralysis of motor nerves. The early involvement of cranial nerves causes problems with eyesight, hearing, and speech. Double or blurred vision, dilated pupils, and slurred speech are common symptoms. Decreased saliva production causes a dryness of the mouth and throat, and swallowing may be painful. An overall weakness ensues, followed by descending paralysis with critical involvement of the respiratory tree. Death usually is caused by respiratory failure, but cardiac failure also can be the primary cause. Mortality is highest for type A, followed by type E, and then type B, possibly reflecting the affinities of the toxins for neural tissue: type A binds most firmly, followed by type E, then type B. Fatality rates are directly proportional to the infectious dose and inversely proportional to the incubation time of the disease.

Type A toxin is used therapeutically to treat a variety of conditions involving involuntary muscle spasms, including strabismus and certain focal dystonias.

This therapy takes advantage the effect of the toxin as a specific muscle relaxant. The therapeutic toxin is a neurotoxin-hemagglutinin complex isolated from C botulinum cultures. The extreme potency of type A botulinum toxin requires extreme caution in using this compound as a therapeutic agent.

Food poisoning.

In botulism food poisoning, the toxin is produced by the vegetative cells of C botulinum in contaminated food, and preformed toxin then is ingested with the contaminated food. The incubation time can vary from a few hours to 10 days, but most commonly is 18–36 hours. Only a small, but effective, percentage of the ingested toxin is absorbed through the intestinal mucosa, the remainder being eliminated in the feces. Gastrointestinal disturbances are early symptoms of the disease in about one-third of the patients with toxin types A or B, and in almost all of the cases involving type E toxin. These symptoms include nausea, vomiting, and abdominal pain. Diarrhea often is present, but constipation also may occur. Symptoms of toxemia then become apparent. No fever occurs in the absence of complicating infections.

In contrast to food poisoning with toxemia caused by ingestion of preformed toxin, infant botulism results from germination of spores in the gastrointestinal tract. Because spores can cause poisoning in infants, obvious sources should be eliminated from the infant's environment and especially the infant's diet. In the intestines, vegetative cells replicate and release the botulinum toxin. It is unclear as to why spores can germinate and bacteria replicate in the infant intestine, but phenomenon appears to be related to the composition of the intestinal flora of infants. Almost all reported cases have occurred in infants between 2 weeks and 6 months of age, with the median age of onset being 2 to 4 months. Toxins A or B are most frequently implicated. Honey is the only dietary ingredient that has been implicated, and honey is no longer recommended for infants under 1 year of age. Most cases are not caused by ingesting honey, however, so this will not eliminate the disease. The other more common environmental sources of spores, such as soil and dust, are not so easily controlled. In infant botulism, the usual first indication of illness, constipation, is often overlooked. Constipation may precede the illness by several weeks. The infant with botulism is typically afebrile with generalized weakness, a weak cry, pooling of oral secretions, and poor sucking ability. The infant then becomes lethargic and sleeps more than normally. Later, head control may be lost, and the infant becomes flaccid. In the most severely affected babies, respiratory arrest can occur. The infant should be kept under close supervision, with facilities for respiratory support immediately available. Infant botulism can be lethal and is the likely etiologic agent in 4 to 15% of the cases of sudden infant death. The fatality rate for infant botulism is surprisingly less than 5%. The most important aspect of treatment of infant botulism is meticulous supportive care. Oral antibiotic therapy is not indicated because it may unpredictably alter the intestinal microecology and allow accidental overgrowth of C botulinum.

Cathartics and enemas are also potentially dangerous. The value of human botulinum antitoxin is disputed, and there is not firm evidence to support its efficacy.

There are scattered reports that C botulinum can occasionally multiply and secrete toxin in the intestinal tracts of adults with an altered intestinal flora due to antibiotic therapy. Host defenses against C botulinum are undefined. Some people can tolerate ingestion of botulinum toxin better than others can. The reason for this phenomenon is obscure, but could be due to differences in the efficiency of uptake of the toxin from the intestine or in transporting the toxin to neural tissue. An attack of botulism does not produce effective immunity. The small amount of toxin in the circulation and its affinity for neural tissue probably prevent adequate amounts of toxin from interacting with the immune system.

Although all forms of botulism are difficult to diagnose, prompt diagnosis and treatment are crucial to patient survival. Laboratory tests offer little in establishing an initial diagnosis of botulism, and accordingly, the finding of a normal cerebrospinal fluid can help to eliminate many of the diseases concerned with central nervous system disorders. Differential diagnoses are myriad and include neurological as well as gastrointestinal disorders.

Confirmation of the initial diagnosis rests on demonstrating toxin in the patient's feces, serum, or vomitus. In adult botulism, serum samples rarely yield type A toxin because of the strong affinity of this toxin for neural tissue. In infant botulism, circulating toxin can occasionally be found in the serum. Fecal samples are the best specimens for detecting toxin in botulism food poisoning or infant botulism because only a small percentage of ingested or in situ formed toxin is absorbed through the intestinal mucosa. Toxin may be excreted for days or even weeks following botulism food poisoning. In infants, the organism can usually be cultured from the stool.

Once a case of food poisoning has been diagnosed, therapy has four objectives: to eliminate the source of the toxin, to eliminate any unabsorbed toxin, to neutralize any unbound toxin with specific antitoxin, and to provide general supportive care.

Food Poisoning in Adults

In food poisoning, the unabsorbed toxin may be eliminated by stomach lavage and high enemas. Although cathartics may be used to eliminate residual toxin, they may have adverse effects in patients with bowel paralysis. Antibiotic therapy is of questionable value in food poisoning, but is advocated by those who believe the organism can replicate in the intestinal tract of adults.

For both food poisoning and wound botulism, antitoxin therapy is most effective if administered early; however, clear-cut evidence for the efficacy of antitoxin therapy exists for only type E toxin. Antitoxin is available from the Centers for Disease Control (Atlanta, GA) through State Health Departments; trivalent ABE botulinum antitoxin is currently recommended. Unfortunately, all antitoxins are equine preparations, so a significant percentage of patients experience reactions typical of anaphylaxis and serum sickness. Thus, before they receive antitoxin, all patients should be tested for sensitivity to horse serum. The most important aspect of treatment in botulism is close observation of the patient and availability of adequate facilities for immediate respiratory support. Respiratory failure may occur within minutes, and immediate respiratory assistance often saves the lives of patients with botulism toxemia. Due to improvements in supportive care, the mortality rate for botulism has been dramatically reduced from approximately 60% (in the 1940s) to 10%.

All cases of botulism food poisoning should be reported immediately to local, state, or federal authorities, who will then take steps to minimize the chance of an outbreak. All persons suspected of ingesting contaminated food should be closely observed. Antitoxin should be administered both to those with overt symptoms and to those who have definitely ingested contaminated food

Undetermined category of botulism involves adult cases in which a specific food or wound source cannot be identified. It has been suggested that some cases of botulism assigned to this category might result from intestinal colonization in adults, with in vivo production of toxin. Reports in the medical literature suggest the existence of a form of botulism similar to infant botulism, but occurring in adults. In these cases, the patients had surgical alterations of the gastrointestinal tract and/or antibiotic therapy. It is proposed that these procedures may have altered the normal gut flora and allowed C. botulinum to colonize the intestinal tract.

Clostridium perfringens (formerly known as Clostridium welchii) is a Gram-positive, rod-shaped, anaerobic, spore-forming bacterium of the genus Clostridium. C. perfringens is abundant in nature and can be found as a normal component of decaying vegetation, marine sediment, the intestinal tract of humans and other vertebrates, insects, and soil. Virtually every soil sample ever examined, with the exception of the sands of the Sahara, has contained C. perfringens.

Infections due to C. perfringens show evidence of tissue necrosis, bacteremia, emphysematous cholecystitis, and gas gangrene, which is also known as clostridial myonecrosis. The toxin involved in gas gangrene is known as α-toxin, which inserts into the plasma membrane of cells, producing gaps in the membrane, which disrupt normal cellular function. The location of C perfringens enterotoxin within the bacterial cell is controversial; some investigators claim that the enterotoxin is localized in the bacterial cytoplasm and others claim that it is

associated with the spore coat. The enterotoxin directly affects the permeability of the plasma membrane of mammalian cells. Some strains of C. perfringens produce toxins, which cause food poisoning if ingested. In the United Kingdom and United States, they are the third most common cause of food-borne illness, with poorly prepared meat and poultry the main culprits in harboring the bacterium. The clostridial enterotoxin mediating the disease is often heat-resistant and can be detected in contaminated food and feces.

C perfringens type A is the usual causative agent, and serotyping is necessary and available for epidemiologic studies. Incubation time is between 8 and 16 hours after ingestion of contaminated food. Manifestations typically include abdominal cramping and diarrhea; vomiting and fever are unusual. The whole course usually resolves within 24 hours but elderly and immunologically compromised patients should be closely supervised. Very rare, fatal cases of clostridial necrotizing enteritis have been known to involve "Type C" strains of the organism, which produce a potently ulcerative β-toxin. The short incubation period, short duration, and absence of fever in most patients differentiates C perfringens foodborne disease from shigellosis and salmonellosis, and the infrequency of vomiting and longer incubation period contrast with the clinical features of foodborne disease associated with heavy metals, Staphylococcus aureus enterotoxins, and fish and shellfish toxins. Diarrheal illness caused by Bacillus cereus enterotoxin may be indistinguishable from that caused by C perfringens

It is likely that many cases of C. perfringens food poisoning remain sub clinical, as antibodies to the toxin are common amongst the population. This has led to the conclusion that most, if not all, of the population has experienced food poisoning due to C. perfringens. The disease results from ingestion of a large number of organisms in contaminated food, usually meat or meat products. Food poisoning usually does not occur unless the food contains at least 10^6–10^7 organisms per gram. Perfringens poisoning is one of the most commonly reported foodborne illnesses in the U.S. There were 1,162 cases in 1981, in 28 separate outbreaks. At least 10-20 outbreaks have been reported annually in the U.S. for the past 2 decades. Typically, dozens or even hundreds of person are affected. It is probable that many outbreaks go unreported because the implicated foods or patient feces are not tested routinely for C. perfringens or its toxin. The CDC estimates that about 10,000 actual cases occur annually in the U.S.

The spores, if present in food, can be triggered to germinate when the food is heated. Some heat-sensitive strains do not need heating to germinate. After germination, the number of organisms quickly increases in warm food because the generation time can be extremely short (minutes) and bacterial multiplication occurs over a wide temperature range. Regardless, food poisoning results from the ingestion food contaminated with enterotoxin-producing C perfringens. Meats, meat products, and gravy are the foods most frequently implicated.

Institutional feeding (such as school cafeterias, hospitals, nursing homes, prisons, etc.) where large quantities of food are prepared several hours before serving is the most common circumstance in which perfringens poisoning occurs. Hot foods should be served immediately or held above 140 degrees F. When refrigerating large volumes of gravies, meat dishes, etc., divide them into small portions so they will cool rapidly. The food should be reheated to 165^{o} F. prior to serving.

Necrotic enteritis, or pig-bel disease, in humans has not been well documented. In adults, the disease appears to result from ingesting large amounts of food contaminated with C perfringens, usually type C. The latter illness is known as enteritis necroticans. It generally follows ingestion of a large meal, implicating bowel distention and bacterial stasis as contributing factors. The intestinal pathology varies considerably, and may include sloughing of intestinal mucosa, submucosa, and mesenteric lymph nodes. Intestinal perforations occur frequently. The best-documented cases of this disease involve the natives of New Guinea, who develop necrotic enteritis after eating large quantities of improperly cooked pork that has been contaminated with the bowel contents of the animal. The course of the disease is fulminate, and the mortality rate is high. Scattered cases of necrotizing enteritis with C perfringens as the prominent bacterial isolate have been reported in Western countries. In these cases, controversy exists concerning whether C perfringens is a primary invader, an accidental contaminant, or an opportunistic pathogen.

Some evidence suggests that acute necrotizing enterocolitis of infants may be caused by a clostridium, but definitive evidence is lacking. The theory is supported by the fact that pneumatosis cystoides intestinalis, a syndrome that can be caused by C perfringens, often is present in cases of acute necrotizing enterocolitis of infants. In addition, C perfringens, C butyricum, C difficile and other clostridial species are often isolated in cases of neonatal necrotizing enterocolitis, but a clear pathogenic role for clostridia is yet to be elucidated.

Perfringens poisoning is diagnosed by its symptoms and the typical delayed onset of illness. Diagnosis is confirmed by detecting the toxin in the feces of patients. Bacteriological confirmation can also be done by finding exceptionally large numbers of the causative bacteria in implicated foods or in the feces of patients. Serological assays are used for detecting enterotoxin in the feces of patients and for testing the ability of strains to produce toxin. The procedures take 1-3 days.