

FOODBORNE DISEASES

C C Lee, M S Lam

ABSTRACT

Foodborne diseases continue to cause significant morbidity and mortality both in developing and developed countries. Its spectrum has vastly expanded in recent years with the recognition of new foodborne pathogens and clinical syndromes. The increase in international travel and demand for exotic and raw food underscore the importance of traveller's diarrhoea. The emergence of day care centres and residential institutions predispose to an environment that enhances the transmission of foodborne pathogens. Last but not least, our greying population, the AIDS pandemic and increasing use of immunosuppressive chemotherapy have produced a special population that is easily susceptible to the microbial contamination of food. Diseases in these individuals are usually more chronic, severe or life-threatening. This article seeks to address the above issues as well as to present a practical approach to the diagnosis and management of foodborne diseases.

Keywords: foodborne, gastroenteritis, travellers, diarrhoea

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INTRODUCTION

The definition of foodborne diseases continues to be hotly debated. It embraces all diseases that result from the ingestion of food contaminated with chemicals, micro-organisms or its toxins. These micro-organisms may be bacteria, viruses, protozoa, fungi or algae.

The term 'foodborne' primarily refers to food as the vehicle via which the contaminating agent is transmitted to humans. It does not include illnesses that result from accidental ingestion of 'food' that contains its natural toxins; examples include the puffer fish and poisonous mushrooms. Food allergies are also excluded. The association with food is suggested when two or more persons experience similar symptoms after ingestion of a common meal. Pathogens which are largely waterborne are included in our discussion as water forms an integral part of our meals. Moreover, water that is contaminated may be used in the preparation of food.

The impact of foodborne diseases is enormous. World-wide, diarrhoeal disease is second only to cardiovascular disease as a cause of death. It is the leading cause of childhood deaths in Asia, South Africa and the Latin America⁽¹⁾. In the USA each year, estimated cases of foodborne illnesses range from 6.5 to 81 million cases with up to 7,000 deaths^(2,3).

In Singapore, outpatient attendances for diarrhoeal disease remain high throughout the year, averaging 500 to 1,000 cases per week⁽⁴⁾. This accounts for a significant loss of working hours. The incidence is also underreported. In 1993, we had 95 notifications involving 377 cases of food poisoning⁽⁴⁾. Seventy-eight of these were classified as outbreaks when two or more cases were traced to a common source. Most outbreaks occurred in restaurants and eating houses while some were from schools and institutions.

Department of Infectious Diseases
 Communicable Disease Centre
 Tan Tock Seng Hospital
 Moulmein Road
 Singapore 308433

M S Lam, M Med (Int Med), MRCP, FAMS
 Consultant

C C Lee, M Med (Int Med), MRCP, FAMS
 Registrar

Correspondence to: Dr C C Lee

The majority of foodborne diseases will present with acute gastrointestinal symptoms, most notably diarrhoea with or without vomiting and abdominal pain. Extra-intestinal manifestations are largely neurological, though systemic effects are also encountered.

EVALUATING FOODBORNE DISEASES

The approach to evaluating foodborne diseases entails the understanding of the epidemiologic and clinical settings as well as the selective use of laboratory tests for the varied aetiologic agents. From here, the physicians can then offer specific drug and supportive therapy. The specific diagnosis will enable us to offer the patient a more accurate prognosis of his illness and institute appropriate precautions for the control of outbreaks and contacts.

EPIDEMIOLOGY

Epidemiological clues include data on suspected vehicle of transmission, geographic locations and the time when the outbreak occurs.

VEHICLES OF TRANSMISSION

Certain food categories are associated with certain food pathogens.

Eggs

Traditionally, it is known that the shells of eggs may be contaminated with *Salmonella* from chicken faeces. The food is then contaminated during breaking of these shells. However, we now know that the contents may also be infected with *Salmonella* in eggs with intact shells. This is due to the transovarian contamination of these eggs from the infected egg-laying flocks. This route of contamination is responsible for the increasing incidence of egg-associated *Salmonella enteritidis* outbreaks in the USA^(3,5). The consumption of raw or partially cooked eggs is now considered unsafe⁽⁶⁾.

Milk and Dairy Products

Historically, drinking unpasteurised milk has been linked with brucellosis (*Brucella abortus*), tuberculosis (*Mycobacterium tuberculosis*), typhoid and paratyphoid fever (*Salmonella typhi* and *paratyphi*), dysentery (*Shigella* spp), diphtheria (*Corynebacterium diphtheria*), various streptococcal infections and Q fever (*Coxiella burnetii*)⁽⁷⁾. These have largely been

eliminated with proper milk sterilisation. However, up till today, milk-associated listeriosis (*Listeria monocytogenes*) and gastroenteritis from *E. coli*, *Campylobacter jejuni*, *Yersinia enterocolitica* and *Salmonella* (serovars other than *S. typhi* and *S. paratyphi*) continue to plague mankind⁽⁷⁾. Drinking raw milk is an unacceptable health hazard⁽⁸⁾. Dairy products like hard cheese, yogurt and butter are safe due to the low pH, but 5%-15% of soft cheese that is associated with higher pH is contaminated with *Listeria monocytogenes*⁽⁶⁾. This is irrespective of pre-heat treatment given to the original milk. Unripened cheese may contain *Brucella* organisms.

Meats

A wide variety of organisms are found here. *Clostridium perfringens*, *E. coli*, *Yersinia enterocolitica* and *L. monocytogenes* are part of the animal faecal flora. They can also be excreting *Salmonella* and *Campylobacter* spp. Meat may also be contaminated by other infected carcasses during the processing and packaging at the assembly line. Up to 100% of birds may contain *Campylobacter* and another 60% may harbour *L. monocytogenes* and *Salmonella*⁽⁶⁾. However, heat treatment of at least 70°C will eliminate the above organisms except for the sporeforming *Clostridium perfringens*.

Raw meat, especially in developing countries, are well-known vehicles of parasitic infections⁽⁷⁾. These include infections with tapeworms (beef-associated *Taenia saginata* and pork-associated *Taenia solium*), nematodes (*Trichinella spiralis*), liver flukes (*Fasciola hepatica*), protozoa (*Toxoplasma gondii*) and the sarcocystis (beef-associated *S. bovis* and pork-associated *S. suis*).

"Undercooked" hamburgers have recently caused a large outbreak of enterohaemorrhagic *E. coli* 0157⁽⁵⁾.

Fish and shellfish

These are often contaminated with pathogens from the environment where they were harvested. The increased popularity of "sushi" in recent years has led to an increased number of people infected with fish parasites like *Anisakis simplex*⁽⁷⁾. *Vibrio parahaemolyticus* is a well-known contaminant of raw fish and seafood. Shellfish are filter feeders and they concentrate *Salmonella*, *E. coli*, *Vibrio* spp and viruses viz hepatitis A and small round-structured viruses (SRSV) of the Norwalk group from the water.

In addition, fish may be found to be contaminated with toxins. Well-documented cases include the ciguatera, a poison synthesised by a specific dinoflagellate^(9,10). These algae gain entry into the fish as part of the food chain. Hence, the bigger the carnivorous fish, the more toxins it will contain.

Another toxin is the scombrototoxin, a poison produced as a result of the metabolism of marine bacteria in contaminated fish stored at improper temperatures. These marine bacteria viz. *Klebsiella pneumoniae* and *Morganella morganii* decarboxylate the histidine found in the fish to histamine, giving rise to histamine poisoning⁽¹¹⁾. Well-known scombroid fish are the yellow fin tuna, mackerel, bonito and skipjack.

Molluscs, like the fishes, may also be contaminated with toxin-containing dinoflagellates. Interestingly, such acquisition coincide with the blooming of the dinoflagellates that gives the sea a new colour. This is described as the "red tide"⁽¹²⁾. The toxins viz saxitoxin and domoic acid are heat stable and ingestion of these contaminated molluscs gives rise to serious shellfish poisoning which may be paralytic, neurotoxic or amnesic⁽¹³⁾. The chemical structure of domoic acid is related to the excitatory amino acid neurotransmitter glutamate⁽¹⁴⁾.

Fruits, vegetables, cereals

These are generally safe after they are washed or their skin removed. Contamination occurs from the organisms found in the soil or the polluted water used for irrigation. The pathogens are the enterics viz *Salmonella javiana* (tomatoes)⁽³⁾, *S. poona* (cantaloupes)⁽³⁾, *Shigella*, *V. cholera*, viruses and parasites. Apples were implicated in a recent outbreak due to *Cryptosporidium*, the fruits were picked from soil contaminated with the oocysts excreted by an infected calf⁽¹⁵⁾. *Cyclospora* has been isolated from the "heads" of lettuce⁽¹⁶⁾.

With the emphasis on more fresh fruits and vegetables against red meat in the promotion of a healthy diet and decreasing cardiovascular risks, there has been a corresponding increase of outbreaks involving shigellosis, salmonellosis and hepatitis A due to the ingestion of such fresh produce⁽³⁾.

Dried food

The predominant flora are the spore-forming organisms viz *Clostridium* and *Bacillus* spp. Herbs and spices can carry large loads of these microbes and therefore it is important that we should add such ingredients at the beginning of the cooking to ensure that they are properly cooked. Pepper is associated with transmission of the fungus *Aspergillus*.

Ready-to-eat foods

Organisms here include those that can survive the heating process like the *Clostridium* and *Bacillus* spp and those that can grow at refrigerative temperatures viz *Yersinia enterocolitica* and *Listeria monocytogenes*⁽⁶⁾. Airline food has been linked with *Shigella* outbreaks⁽¹⁷⁾. Fried rice is associated with *Bacillus cereus* food poisoning⁽¹⁸⁾. Foodborne *S. aureus* illness is associated with high-protein food like cooked meat⁽¹⁹⁾. The high protein content, especially with added salt, in these cooked dishes do not favour the growth of other organisms.

Waterborne pathogens and chemicals

This includes heavy metal poisoning found in acidic beverages that have been stored in metal containers or tubings which allow metallic ions to dissolve in the beverage, potential source being the vending machines.

Waterborne pathogens are also usually foodborne. The water is usually contaminated by the excreta of humans and animals. These are usually the parasites like *Giardia lamblia*, *Entamoeba histolytica* and the protozoa *Cryptosporidium* and *Cyclospora*. *Cryptosporidium* can be found in public drinking water and recreational waters. The oocyst is resistant to chlorine and can survive up to three months at low temperatures⁽²⁰⁾.

Enterotoxigenic *E. coli*, *Yersinia enterocolitica*, *C. jejuni*, *Salmonella* and *Shigella* spp have been implicated in waterborne outbreaks. Viruses like hepatitis A and E and Norwalk agents are also transmissible via water⁽²¹⁾.

Shigella, *Campylobacter*, *E. coli* 0157:H7 and the cysts of *Giardia* and *Cryptosporidium* are pathogens with low infective dose⁽²⁾. Ingestion of only 10-1,000 organisms causes infection and therefore it is not surprising that they are the main pathogens implicated in outbreaks involving commercial airlines⁽¹⁷⁾, day care centres⁽²²⁾, households⁽²³⁾, nursing homes⁽²⁴⁾ and hospitals⁽²⁵⁾.

Finally, it should not be forgotten that food may be contaminated by the vectors in the environment and the foodhandlers who can be asymptomatic excretors of the organisms. A good example is *Salmonella* (both typhi and nontyphi) asymptomatic carriers. Pathogens may also be on their hand lesions eg *S. aureus*. This route of infection is important in Singapore where consumption of commercial food is common.

In our country, all foodhandlers are screened and vaccinated against typhoid. The government takes a tough stand against unhygienic food preparation by food service establishments.

GEOGRAPHIC LOCATION AND TIME OF OUTBREAK

Some foodborne diseases have geographical predilections. Moreover, with the increase in international travel and migration, patients with suspected foodborne illness should always be asked for a history of travel. Time of outbreak is more relevant to countries with seasonal climate.

In Singapore, an island with a warm humid climate, infections with *S. aureus*, *Salmonella*, *Shigella* and *Vibrio* spp can be expected to be more common.

In the USA, Type A botulism is more common in the western United States, Type B from the eastern United States and Type C in the Great Lakes Region and in Alaska⁽¹³⁾. Cases are more common during winter due to the increased consumption of canned food.

Ciguatera outbreaks occur in countries between the 35 degrees north and 35 degrees south latitudes. In America, it is more common in the states of Hawaii and Florida. On the other hand, scombroid fish poisoning is more common in California and Hawaii⁽¹³⁾. Paralytic shellfish poisoning occurs in the New England coast, the West coast and in Alaska in association with the 'red tide'⁽¹²⁾.

Infection with *Vibrio* spp is more common in coastal areas. Fatal *Vibrio vulnificus* infections from oysters ingestion almost always occur during summer or early fall as this pathogen thrives in warm marine water of more than 20°C⁽²⁶⁾. This is despite the fact that there may be an increased harvesting of oysters in winter.

CLINICAL SETTINGS

This entails a knowledge on the different median incubation periods and specific signs and symptoms of the various suspected foodborne diseases.

THE MEDIAN INCUBATION PERIOD (MIP)

This provides the first and often the most important clue to the aetiology of an outbreak. This may be conveniently grouped into one of the following categories.

MIP less than one hour

Foodborne disease with very short MIP ie a few minutes to one hour, is almost certainly chemical. Examples are heavy metal poisoning, scombroid fish poisoning, shellfish poisoning and the Chinese restaurant syndrome. Ciguatoxin poisoning is probably the only exception that has a MIP of one to several hours.

The above can be differentiated from each other by their vehicles of transmission and striking extra-gastrointestinal symptoms besides vomiting and severe abdominal cramps. Symptoms due to histamines like flushing and headache are seen in scombroid poisoning⁽¹³⁾. Diagnosis is suggested by the clinical picture, identification of the scombroid fish and confirmed by finding an elevated level of histamines in the incriminated fish. Symptoms usually resolve within a few hours.

Paresthesia followed by paralysis and confusion progressing to coma is seen with ingestion of shellfish that contains a variety of poisons like saxitoxin and domoic acid produced by the dinoflagellates concentrated in shellfish⁽¹⁴⁾. Chinese restaurant syndrome victims suffer burning and tight sensation of the face and chest in addition to headache, lacrimation and abdominal cramps after a meal containing excessive monosodium L-glutamate⁽²⁷⁾.

MIP 1-7 hours

This is due to preformed toxins of pathogens like *Staphylococcus aureus* and *Bacillus cereus* of the short incubation type. They present with vomiting which is believed to be centrally mediated. There may also be diarrhoea but fever is rare and symptoms do not exceed 12 hours⁽¹³⁾.

Chemical poisoning may occasionally fall into this category but patients will have other symptoms like metallic taste, bloating (tin), myalgia (zinc) and salivation (cadmium).

Ciguatera fish poisoning presents with gastrointestinal symptoms and prominent neurological symptoms viz paresthesia, headache, photophobia, blurred vision, transient blindness, cranial nerves palsies, respiratory paralysis and characteristic sharp shooting pains in the legs that may run into years after the acute episode of gastroenteritis⁽²⁸⁾. In contrast to epidemiologically implicated scombroid fish, popular fish associated with ciguatera fish poisoning are barracuda, red snapper, amberjack, and grouper⁽¹³⁾.

MIP 8-14 hours

The illness here has predominant lower gastrointestinal symptoms, usually caused by toxins produced *in-vivo*. Both *Clostridium perfringens* and *Bacillus cereus* of the long incubation type characteristically cause moderate to severe abdominal cramps and watery diarrhoea. Fever is rare and symptoms usually resolve by 24 hours⁽²⁹⁾.

MIP more than 14 hours

The list of organisms here is lengthy. Major aetiological considerations here are those that cause inflammatory diarrhoea. These are the *Salmonella*, *Shigella*, *Campylobacter* spp, *Yersinia enterocolitica*, *Vibrio parahaemolyticus* and enteroinvasive *E. coli*. Illness is frequently accompanied by fever and occasionally by bloody stools. Viruses like the Norwalk agent also fall into this category; vomiting and headache are the prominent symptoms. Pathogens with longer MIP usually have longer duration of illness correspondingly. The gastroenteritis usually resolves by 2-7 days although they may be followed by various post-infectious syndromes which will be described later.

Other bacterial pathogens in this category are *Vibrio cholerae* and enterotoxigenic *E. coli*. In contrast to the above, they do not cause an inflammatory diarrhoea. The illness is non-febrile and examination of stools reveals no leucocytes. *Escherichia coli* 0157:H7 gastroenteritis is manifested by bloody diarrhoea without fever⁽³⁰⁾.

The MIPs of the above pathogens do not exceed two days with the exception of *V. cholerae* and *E. coli* 0157:H7. *V. cholerae* has an incubation period of 6 hours to 5 days⁽³⁰⁾. The incubation period of *E. coli* 0157:H7 range from 4-6 days⁽³¹⁾. The protozoa, *Cryptosporidium parvum*, has an incubation period of about 9 days⁽³²⁾.

The other subcategory of pathogens with a MIP of more than 14 hours are those that cause predominant extra-gastrointestinal symptoms. Nausea, vomiting and diarrhoea with descending weakness and paralysis within 18-36 hours suggest foodborne botulism due to germinating spores of *Clostridium botulinum* in inadequately processed canned food. Illness by hepatitis A and E is seen after a median period of 2-6 weeks. Other examples include toxoplasmosis (1-2 weeks), brucellosis (several days to several months) and anisakiasis (5-10 days).

Clinical Features and Post-Infectious Syndromes

The interesting features and syndromes of some selected pathogens will be discussed. Details for each pathogen are beyond

the scope of this paper and the interested reader may refer to the suggested list for further reading. Recent trends have shown an increase in *Salmonella* spp outbreaks⁽³⁾. *Campylobacter jejuni*, *Escherichia coli* 0157:H7 and *Listeria monocytogenes* have emerged as important foodborne pathogens during the last decade⁽³⁾. For these reasons, we have mainly chosen the above-named pathogens for discussion.

Pathogenic *E. coli*

E. coli are part of the intestinal flora in humans but they are harmless commensals. There are four main pathogenic strains that cause disease viz enteropathogenic *E. coli* (EPEC), enteroinvasive *E. coli* (EIEC), enterotoxigenic *E. coli* (ETEC) and enterohaemorrhagic *E. coli* (EHEC). Lately, two new ones were added, namely the enteroaggregative *E. coli* and the diffusely adherent *E. coli*⁽⁵⁾. They will not be described here.

EPEC causes infantile diarrhoea and had caused outbreaks in hospital nurseries. Infection is uncommon in developed countries. EIEC causes an invasive dysentery similar to that caused by *Shigella*. ETEC is the most common cause of traveller's diarrhoea⁽¹⁾. Infection is associated with poor hygiene seen in developing countries. It gives rise to secretory diarrhoea through the elaboration of either the heat labile cholera-like toxin or the heat stable enterotoxin. The initial presentation may mimic cholera.

EPEC, EIEC and ETEC are often present in the faeces of symptom-free human carriers in developing countries. Spread is often waterborne or faecal-oral through foodhandlers⁽³³⁾.

EHEC, with its ability to cause severe illness, is perhaps the most interesting of the four groups of pathogenic *E. coli*. In contrast to other *E. coli*, EHEC of the serotype 0157:H7 is the principal *E. coli* responsible for foodborne diseases in developed countries⁽³³⁾. It is a relatively new pathogen identified in 1983⁽³⁴⁾. This was soon followed by the recognition of the link between EHEC 0157:H7 infection and haemolytic-uraemic syndrome (HUS); a post-infectious syndrome⁽³⁵⁾. HUS had earlier been associated with *Shigella dysenteriae* infection⁽³⁶⁾.

EHEC is not invasive and commonly causes haemorrhagic colitis without fever. Only about 10% of the diarrhoea is not bloody⁽³¹⁾. It produces one or more toxins, one of which is very similar in structure and function to that produced by *Shigella dysenteriae*. It had caused many outbreaks in developed countries. Infection is particularly related to the consumption of ground beef⁽³⁾. This pathogen is also waterborne. As a first step toward prevention of this emerging pathogen, the Centre for Disease Control and Prevention (CDC) has recently addressed the urgent need for its improved surveillance⁽³⁷⁾.

The pathogenicity involved absorption of the toxins from the gut; these Shiga-like cytotoxins are lethal to the gut and kidney vascular endothelial cells. HUS occurs in about 10% of infected children less than 10 years old⁽³¹⁾. The course starts about 10 days after the onset of diarrhoea and is heralded by fever and leucocytosis. It presents with pallor, renal failure with proteinuria and oligo-anuria or a generalised haemorrhagic diathesis. Up to 75% of these patients need blood transfusions and 50% of the cases may need dialysis⁽³¹⁾. In adults, a rather similar syndrome is seen, known as thrombotic thrombocytopenic purpura. This condition is commonly accompanied by neurological manifestations. Other post-infections complications associated with this organism include biliary pigment stones and colonic strictures.

Stool culture request for *E. coli* 0157:H7 should therefore be obtained if initial culture is negative for *Salmonella*, *Shigella*, *Campylobacter* and *Yersinia* spp. This pathogen is routinely looked for in our laboratory in all cases of bloody diarrhoea. A serological test to 0157 lipopolysaccharide antigen is also

available. This test is useful in the diagnosis of *E. coli* 0157:H7-associated HUS because two-thirds of stool culture samples will be negative at the time HUS first presents⁽³¹⁾. *E. coli* 0157:H7 infection is rare here.

Antibiotics are not recommended as they have not been shown to decrease the severity or outcome of the infection⁽³¹⁾. Antibiotics may be associated with an increased risk of complications and a poorer outcome⁽²³⁾. Antimotility agents and narcotics are to be avoided as they delay clearance of the organisms and thus promote more toxin absorption. Rehydration is the mainstay of management especially if renal toxicity is to be avoided.

Campylobacter enteritis

Campylobacter spp, predominantly *Campylobacter jejuni*, is probably the most common foodborne bacterial pathogen in developed countries. In 1992, we had a total of 69 reported cases, all of which were sporadic⁽⁴⁾. In 1993, there was a total of 106 sporadic cases. The highest attack rate was seen in children less than four years old^(4,38).

Transmission is via the faecal-oral route and under-cooked chicken is the most frequent source of infection, others being contaminated water and raw milk. Infection generally causes a mild illness but can be severe with fever and watery, foul smelling diarrhoea which becomes bloody one to three days later. Abdominal pain may persist after the diarrhoea has subsided and may be severe enough to be confused with appendicitis, intussusception and acute peritonitis. Bacteraemia has been noted in AIDS patients^(2,3). Antibiotics like erythromycin can decrease the severity and duration of illness when given early. Antibiotics are indicated when there are systemic involvement viz meningitis, urinary tract infection and cholecystitis. Guillian-Barré syndrome may occur one to three weeks after a diarrhoeal illness from *C. jejuni*⁽³⁹⁾. Other post-infectious syndromes linked to this pathogen include reactive arthritis, Reiter's syndrome and erythema nodosum.

Yersinia enterocolitica

This was recognised as a foodborne pathogen in the mid 1970s. Pigs are the major reservoir. It is an organism that can grow at 0-2°C⁽³³⁾. Transmission is usually via ingestion of contaminated meat or milk. Person-to-person spread is rare; but infection has occurred through blood transfusion from asymptomatic donors⁽⁴⁰⁾. In two-third of the cases, there is fever, diarrhoea and abdominal pain lasting 1-3 weeks⁽⁴⁰⁾. It is an inflammatory diarrhoea and besides leucocytes, blood and mucus may also be seen in the stools. In older children and young adults, clinical presentation has been known to mimic acute appendicitis when there is mesenteric adenitis or terminal ileitis. The patient presents with fever, right iliac fossa pain and leucocytosis without diarrhoea. This had resulted in some unnecessary laparotomies.

Like *Campylobacter*, stool culture can still be positive for a few weeks after the symptoms have abated. Blood culture is occasionally positive when there is systemic infection involving hepatic and splenic abscesses, osteomyelitis, meningitis or endocarditis. Such presentations are mainly seen in those who are immunocompromised like the elderly, diabetics and notably those with liver disease where there is an associated iron overload; eg thalassaemia and haemochromatosis.

Post-infectious reactive arthritis including Reiter's syndrome occurs in 10%-30% of adults, especially in those with the HLA-B27 haplotype⁽⁴⁰⁾. Symptoms begin in a few days to one month after the onset of enteritis and usually resolve by one year. A minority may end up with a persistent backache. Erythema nodosum may also be seen 2-20 days after the enteritis. Antibiotics, usually an aminoglycoside plus a third generation

cephalosporin, should only be given to those with septicaemia.

Salmonella spp

Salmonella is the most frequently reported foodborne disease in many countries⁽⁴¹⁾. The incidence of non-typhoidal salmonellosis has increased in recent times, particularly that of *S. enteritidis* associated with intact eggs⁽³⁾.

S. typhi (serogroup D) and *S. paratyphi* (serogroup A, B, C1) cause enteritis of 2-5 days' duration in the acute stage; presenting with nausea, vomiting, abdominal cramps and watery diarrhoea. Infection may be followed by enteric fever 7-28 days later. This may present as pyrexia of unknown origin. The illness is characterised by prolonged fever, headache, malaise, sore throat, dry cough, splenomegaly, a relative bradycardia, rose spots and often constipation but sometimes diarrhoea.

In Singapore, there were 162 cases of enteric fever in 1992 and 144 cases in 1993⁽⁴⁾. The majority were typhoid fever, others being paratyphoid A or B fever. There were no deaths and most of the cases were imported from countries like Indonesia and India. A higher incidence was noted in the month of January, probably due to the locals travelling to endemic countries during the December school holidays.

Other salmonellae like *S. typhimurium* (serogroup B) and *S. enteritidis* (serogroup D) cause gastroenteritis too and like other salmonellae, they have a propensity for bacteraemia with a host of extra-intestinal manifestations like pneumonia, empyema, arthritis, osteomyelitis, endocarditis and pyelonephritis⁽⁴²⁾. These non-typhi salmonellae are not notifiable in Singapore. Immunocompromised patients are more prone to have bacteraemia. Recurrent *Salmonella* bacteraemia is an AIDS-defining illness.

Third generation cephalosporins (eg ceftriaxone 50m/kg/day) or the quinolones are the current drugs of choice due to presence of multi-drug resistant strains. One week of treatment is adequate for uncomplicated cases⁽¹³⁾. Therapy should be prolonged in those who are immunocompromised.

Listeria monocytogenes

This is an example of a foodborne pathogen which presents as an invasive disease without gastroenteritis. Human listeriosis has been known to be associated with contaminated food. Like *Yersinia enterocolitica*, it can multiply at low temperatures and isolation of these pathogens need cold enrichment technique of about 4°C. It is a rare disease with a high mortality. Immunocompromised patients including the elderly and pregnant females are at increased risk of this infection.

Illness can range from a mild influenza-like sickness to meningitis and meningoencephalitis. Infection in the pregnant patient varies from an influenza-like illness to abortion, stillbirth or delivery of an ill neonate. Meningitis is rare in pregnant females⁽⁴³⁾. In the non-pregnant immunocompromised host, bacteraemia with meningitis is the usual while infection in the healthy individual always present with meningitis⁽⁴³⁾. Ampicillin is the drug of choice in treatment of listeriosis.

Other foodborne diseases with primary symptoms outside the gastrointestinal tract are infections with *Vibrio vulnificus*, brucellosis and toxoplasmosis. *Vibrio vulnificus* infection presents as bacteraemia with hypotension and fulminant myonecrosis. Infection can be associated with ingestion of partially cooked seafood, especially oysters⁽²⁶⁾. Brucellosis presents with lymphadenopathy, arthralgia, malaise and weight loss. This is caused by ingestion of contaminated dairy products. Toxoplasmosis presents with malaise and lymphadenopathy in a normal host but with foetal congenital defects in the pregnant host and multiple ring-enhancing cerebral abscesses in HIV-infected patients. It is acquired by ingestion of contaminated

undercooked meat.

Rare but interesting foodborne diseases reported include an outbreak of thyrotoxicosis traced to ingestion of ground beef containing thyroid tissue, eosinophilia-myalgia syndrome through ingestion of yeast products containing excessive amount of L-tryptophan and chronic diarrhoea of up to one year (Brainerd's diarrhoea) related to consumption of raw milk and contaminated water⁽³⁾. An aetiological agent for Brainerd's diarrhoea has not been identified. These examples illustrate the importance of disease surveillance and epidemiological studies in recognising new foodborne diseases and its subsequent prevention. It is possible that other current or new diseases may actually be foodborne in nature.

LABORATORY TESTING

This usually serves to confirm the diagnosis of foodborne diseases. An aetiological agent can usually be suspected on the basis of the implicated food, median incubation period and clinical syndrome. The laboratory team should then be alerted to the possible pathogen as special media may be required.

On the other hand, the initial identification of a pathogen may provide a clue to the possible vehicle of transmission which may then lead to the discovery of an outbreak.

Stools, vomitus, blood and the implicated food should be sent for culture. If the pathogen is cultured, it should specifically be phaged (eg *S. aureus*) or serotyped (eg *Vibrio cholerae*) for correlation among multiple isolates to confirm an outbreak.

Chemicals (eg monosodium L-glutamate, histamine) and toxins (eg ciguatoxin, botulin toxin) may also be detected in the implicated food.

Serological tests are also available. This range from the well-known Widal test for *Salmonella typhi* and *paratyphi* infection (not a confirmatory test), hepatitis A and E serologies to the recently developed antibody assay to O157 lipopolysaccharide antigen of *E. coli* O157:H7⁽³⁰⁾.

A simple investigation is the examination of stools for leucocytes. Its presence signifies an inflammatory diarrhoea where the pathogens directly invade the intestinal epithelium. These pathogens include the *salmonellae*, *shigellae*, invasive *E. coli*, *C. jejuni*, *V. parahaemolyticus* or *Y. enterocolitica*.

Direct examination of stools are used to identify *Giardia lamblia* and *Entamoeba histolytica*. Acid fast stains, together with many other new stains are used to identify the other protozoa viz. *Cryptosporidium* and *Cyclospora*⁽²⁾.

MANAGEMENT OF FOODBORNE DISEASES

The approach to gastroenteritis from foodborne diseases in immunocompetent patients differs from that in immunocompromised patients to some extent. Immunocompromised patients, besides being at increased risk for similar pathogens, may also be infected with non-foodborne pathogens viz *Mycobacteria avium complex* and cytomegalovirus.

When a patient presents with diarrhoea, the physician should always exclude a foodborne aetiology. Food and travel history are routine questions. He should be aware that certain foods are more likely to transmit foodborne diseases than others. Conversely, some diseases are more likely to be foodborne. Together with epidemiological data and clinical clues as outlined above, one may be able to know the likely aetiological agent and therefore its possible implications. More effective treatment and advice can then be given to the patient. This is made more important if investigations are not easily available.

Generally, patients with acute bloody diarrhoea, painful diarrhoea, diarrhoea with fever or profuse watery diarrhoea should have a stool culture done. Threshold for hospital admission for the above categories should also be lower. They

should be admitted if there is accompanying dehydration with failure to retain fluids as a result of vomiting.

Non-inflammatory diarrhoea would only require symptomatic treatment and oral rehydration. Some chose to treat all cases with antibiotics as early treatment has been shown to decrease the duration of illness from 59-93 hours to 16-30 hours⁽⁴⁴⁾. This is exemplified by the experience with cholera. However, antibiotic treatment can prolong the carriage stage seen with *Salmonella* infections. It also encourages the emergence of resistant strains as seen in patients with Campylobacteriosis treated with quinolones⁽⁴⁴⁾.

Symptomatic treatment involves the use of loperamide or bismuth subsalicylate in infants and young children⁽⁴⁵⁾. They help to reduce abdominal cramps and stool frequency. Anticholinergic agents like propantheline are not useful. Almost any beverage, with the addition of salt or salted crackers can be used for rehydration. Oral rehydration salt (ORS) can easily be prepared as follows: 3/4 teaspoon of table salt, one teaspoon of baking soda, one cup of orange or two bananas and four tablespoons of sugar mixed into a litre of clear water. This oral therapy is also applicable in severe cases as absorption of glucose-coupled sodium remains intact in such cases⁽²⁾. Infections with *V. cholerae* and *cryptosporidium*, which can present with significant dehydration resulting from the explosive watery diarrhoea may require more aggressive hydration at a hospital setting.

Inflammatory diarrhoea is usually associated with fever, leucocytes and sometimes blood in the stools. This diarrhoea will require laboratory testing and may need specific therapy. Stool cultures should be sent and empirical antibiotics can be started to shorten the duration of illness. Choice of antibiotics include the cheaper trimethoprim-sulfamethoxazole or the quinolones which may be preferred due to resistance of some *E. coli* and *Shigella* to the former drug⁽⁴⁶⁾. Quinolones should also be used in areas where *C. jejuni* is commonly found⁽⁴⁶⁾. The antibiotic may be given as a single large dose or otherwise, eg ciprofloxacin 1 gm once or 500 mg bid for 3 days. Anti-motility agents should not be used here; they may cause dangerous paralytic ileus and abdominal distension in infants. Parasitic infections would require specific chemotherapy.

Finally, suspected foodborne diseases should be promptly reported to the relevant authorities as they can represent a threat to large numbers of people.

TRAVELLER'S DIARRHOEA

This refers to diarrhoeal diseases acquired when an individual goes from a developed to a developing area of the world. The disease is further defined as the passage of more than three episodes of loose stools in a day associated with one or more of the following viz nausea, vomiting, cramps, fever, faecal urgency, tenesmus and bloody mucoid stools.

Attack rate is as high as 50% in those who stay for more than two weeks⁽²⁾. For the military forces, the morbidity from diarrhoea may outnumber battle casualties; its incidence was noted to be 10 times that of heat-related disorders⁽²⁾. Those with increased risks include children (possibly related to increased oral-faecal contamination and decreased immunity), young adults with their more adventurous lifestyles, individuals with achlorhydria or gastrectomy, patients on histamine type 2 blockers and those who are immunocompromised for various reasons mentioned earlier.

Although traveller's diarrhoea may occasionally be related to stress or changes in the diet per se, most are caused by bacteria, viruses and parasites. Top on the list is the enterotoxigenic *E. coli* (ETEC) that produces either the heat labile or heat stable toxins⁽¹⁾. Infection is frequently polymicrobial. Other bacteria cited are the enteroadherent and enteroinvasive *E. coli*, *Shigella*

spp, *C. jejuni* and *Aeromonas* spp (especially in Thailand). *Salmonella* spp and the non-cholera *Vibrios* are especially seen in coastal areas. For viruses, rotavirus, Norwalk virus and hepatitis A are commonly implicated. The parasites implicated include the *Giardia* spp, *Entamoeba histolytica*, *Cryptosporidium* and *Cyclospora*. *Giardia* infections are commonly seen among mountain trekkers in North America. *Giardia* together with *Cryptosporidium* are seen in visitors to places in Russia like Saint Petersburg. *Cyclospora* is the latest aetiological agent identified, causing infections in visitors to South America, Nepal and Thailand⁽⁴⁴⁾.

Chemoprophylaxis

Prevention is largely through education of the individual regarding food and water hygiene. Chemoprophylaxis is not recommended as most cases are mild and it predisposes to development of resistance. Effective treatment to decrease the duration of illness is available. However, adverse reactions may occur from the antibiotics given. Nevertheless, chemoprophylaxis can be considered for the following groups viz the immunocompromised, individuals with achlorhydria, gastrectomy, or history of repeated episodes of traveller's diarrhoea, competitive athletes and military personnel.

Chemoprophylaxis includes the use of *Lactobacillus* preparations, bismuth subsalicylate liquid or tablets and antimicrobial agents. *Lactobacillus* is known to metabolise the carbohydrate in the gut to organic acids resulting in a low pH unfavourable for the growth of pathogens. Bismuth subsalicylate has antibacterial effect thereby reducing the dose of infective inoculum⁽⁴⁴⁾. Antimicrobial agents used are doxycycline, bactrim and the fluoroquinolones. Once a day dosing is sufficient and has been shown to have protective levels of 80%-90%. Quinolones are the preferred class of antibiotics for infections due to resistant strains but they should not be given to children because of the risk of cartilage damage and arthropathy.

EMERGING PATHOGENS

This can be a misnomer because newly recognised pathogens may not be truly new. In most cases, the organisms had existed for some time but have only recently been brought to medical attention because of a new susceptible population.

Cryptosporidium parvum has been known since 1907, but it was only in 1976 that human cryptosporidial infection was first described in an immunocompromised host⁽⁴⁷⁾. During the last decade, it has emerged as an important pathogen as a result of an increasing HIV-infected population. It is now recognised as a common cause of diarrhoea in the general population. In 1993, it was responsible for the largest waterborne outbreak in US history with over 400,000 individuals infected in the Milwaukee district⁽⁴⁸⁾.

There is also the problem of well-known pathogens with emerging new strains or clinical syndromes. A new toxigenic strain of *Vibrio cholerae* 0139, due to gene mutation of E1 Tor 0 antigen, is responsible for the current 8th pandemic. Known as Bengal cholera, the infection started in Madras, India, in October 1992. It is now spreading throughout South Asia, causing severe epidemic cholera⁽⁵⁾. There is no evidence of cross protection from previous EL Tor or classical cholera infections. In 1993, Singapore had a total of 24 cases of cholera, five of which were the new epidemic strain 0139; but all were imported cases from India⁽⁴⁹⁾.

One of the newly recognised syndromes is the haemolytic-uraemic syndrome linked to infection with *E. coli* 0157:H7. This has been described earlier. Perhaps the newest pathogen is the coccidian protozoa *Cyclospora*. This was incidentally found when investigators screening for *Cryptosporidium* in stool

samples found cysts that were bigger than that of *Cryptosporidium*.

Cryptosporidiosis (*Cryptosporidium parvum*)

Cryptosporidium is one of the most contagious enteric pathogen where ingestion of just 132 oocysts is sufficient to give clinical infection in healthy adults⁽³²⁾. This accounts for the high transmission rate in household contacts and day care centres. There is also risk of nosocomial outbreaks⁽²³⁾. The incubation period is about nine days⁽³²⁾. The oocysts may survive for as long as three months. It is resistant to chlorine and can be found in filtered water. It is killed by freezing or high temperatures.

People with increased risk of infection include those in contact with animals, infants in day-care centres, patients with HIV infection (3%-21% in USA and 50% in Africa and Haiti)⁽¹⁾, international travellers and persons living in developing tropical countries⁽⁴⁹⁾. It is an important cause of death in otherwise healthy children in developing countries.

The illness is often self-limited in immunocompetent hosts but usually causes dehydration that may last up to two weeks. In HIV positive patients, cryptosporidiosis is an AIDS-defining disease. HIV-associated cryptosporidiosis is a severe cholera-like illness that can last for months. There is overwhelming watery and foul-smelling diarrhoea resulting in severe dehydration and malnutrition culminating sometimes in death. However, the prognosis is not uniformly poor⁽⁵⁰⁾. Patients with CD4 counts of 180 cells per cubic millimeter or more have been found to have milder symptoms and shorter duration of illness with spontaneous remission⁽⁵¹⁾. This parasite also colonises the gallbladder and the biliary tree giving rise to sclerosing cholangitis⁽⁵⁰⁾. This occurs in about 10% of patients with AIDS⁽¹⁾. The liver function tests usually show a lone increase in alkaline phosphatase.

Diagnosis is best made by looking at multiple sets of stools for the acid-fast staining oocysts. Three or more samples of stools may be necessary as oocyst excretion varies from day-to-day. Three other acid fast organisms in HIV positive patients with diarrhoea are the protozoa *Isospora belli*, *Mycobacterium* spp (notably *M. avium* complex and *M. tuberculosis*) and *Cyclospora*. At present we are still searching for an effective specific therapy for cryptosporidiosis. Therapy includes fluid balance, nutritional support and symptomatic treatment. Paromomycin is effective in many cases but patients need to be on maintenance dose to prevent relapse⁽⁴⁷⁾.

Azithromycin may show promise in the future⁽⁴⁷⁾. Research is ongoing in the study of its epidemiology and virulence factors. Infection may have originated from animal (calves, dogs, cats) excreta which contaminate water supplies. Person-to-person spread through faecal-oral route is also important. Stringent control of water provision will prevent this parasite continuing as a public health hazard.

Cyclospora (*Cyclospora cayetanensis*)

Initially called by various names viz coccidian-like, cryptosporidium-like or cyanobacterium-like bodies, *Cyclospora* was first identified in 1870 in other mammals⁽⁵²⁾. The human isolate represents a new species that differ from the animal *Cyclospora* in size. First described in 1986⁽⁵³⁾, the emergence of *Cyclospora* is believed to be due to widespread use of quinolones replacing co-trimoxazole as the standard treatment for bacterial diarrhoea around the world⁽⁶⁴⁾. Quinolones, in contrast to co-trimoxazole, have no activity against *Cyclospora*.

It is now recognised as a new coccidian causing prolonged diarrhoea with anorexia, weight loss and fatigue both in immunocompetent and immunocompromised hosts. The illness may last from 1-15 weeks, averaging about six weeks. In the

immunocompromised host, however, it may be chronic and unremitting.

This pathogen has caused waterborne outbreaks in endemic areas like Peru and Nepal⁽⁵²⁾. It is also implicated in traveller's diarrhoea⁽²⁾. The cysts are bigger than cryptosporidium. They are about 7-9µm in diameter and contain granular substances. Like *Cryptosporidium*, they are acid-fast and appear pink to red with the Kinyoun stain. They also autofluoresce as intense blue spheres when viewed with 330-380nm ultraviolet filter⁽⁵⁵⁾. Currently, it is still unclear with regard to the true prevalence of this parasite, the reservoir of the infection and the optimal drug dosing. In a current study, co-trimoxazole taken twice daily for one week is shown to be highly effective in immunocompetent patients⁽⁵⁴⁾.

FOODBORNE DISEASES IN THE IMMUNOCOMPROMISED HOSTS

This forms a population at special risk for illness from contaminated food. Not only is the minimum infective dose of the organisms lower, the illness may run a serious, chronic or relapsing course.

As physicians, we should be aware of these predisposing conditions and recognise the potential for illness associated with consumption of 'high risk' food. This group includes the pregnant, elderly, patients with immune deficiencies (HIV, AIDS, malignancies, immunosuppressive drugs), diabetics and those with liver diseases. More than 50% of HIV-infected patients will eventually develop diarrhoea and more than 95% of patients with AIDS in Africa and Haiti present with diarrhoea initially⁽¹⁾. Non-immunocompromised hosts on anti-peptic ulcer medication are also at increased risk of foodborne diseases.

Pregnant females should specifically avoid soft cheese (Listeriosis) and uncooked meat (Toxoplasmosis). Individuals with liver diseases should abstain from uncooked or partially cooked seafood, especially oysters and clams, to avoid life threatening *Vibrio vulnificus* infections.

Generally, food classified as 'unsafe' include unpasteurized milk, raw seafood and moist food maintained at room temperatures in tropical regions. Food considered 'occasionally unsafe' are the salads, cheese, sandwiches, hamburgers, poultry, ice cubes and food on commercial airlines. Lastly, food that are rarely 'unsafe' will be the peeled or acidic citrus fruits, hyperosmolar items like jellies, irradiated milk, bottled carbonated drinks, food with high sugar content and food that are served steaming hot⁽⁶⁾. Immunocompromised hosts should abstain from 'unsafe' food as classified above.

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