Foodborne Infections of the Gastrointestinal Tract

Medical Grand Rounds

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Introduction

Foodborne illness is a major public health concern in all nations. Foodborne diarrheal disease is much less common in this country than in less developed countries; nevertheless, estimates of the incidence of foodborne enteric infections in the U.S. range from 7 to 81 million cases with 9000 fatalities and a cost of 4-17 billion annually(1-3).

Foodborne enteric infections are transmitted by the fecal-oral route with the feces being derived either from other humans (person-to-person) or from the intestines of domestic animals used for food(Figure 1). In the later case, animal-to-person transmission of enteric pathogens may be followed secondarily by person-to-person spread. In this country, person-to-person spread of enteric pathogens, which is an enormous problem in less developed countries (and in Americans traveling to these countries), has remained relatively stable for several decades.

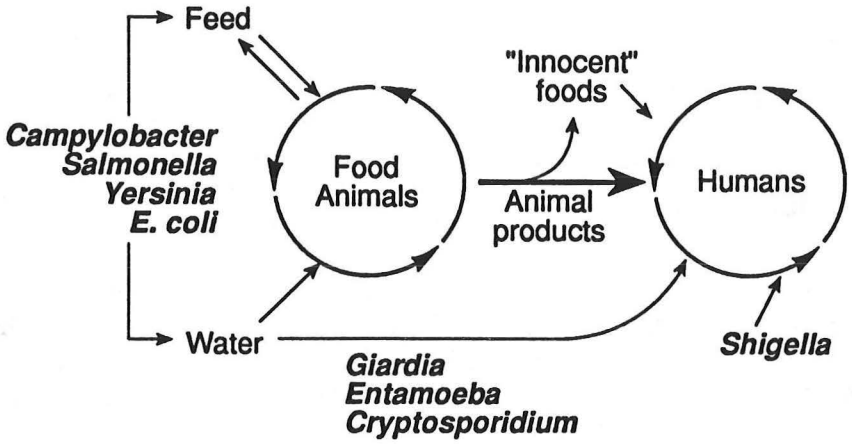

Figure 1. Sources of enteric pathogens.

Thus, as illustrated in Figure 2, the incidence of *Shigella* (which has no domestic animal reservoir and is transmitted predominantly from person to person) has remained relatively constant since the mid 1950s(4). In contrast, enteric infections derived from food animals appears to be increasing. Indeed, during the past two decades, the incidence of *Salmonella* (which is primarily a meat/poultry-borne pathogen) has increased approximately 3-fold and a number of other organisms that colonize the GI tracts of cattle and poultry have emerged as important enteric pathogens. For example, *Campylobacter*, which was first recognized as a human enteric pathogen in the early 1970s, is now the leading cause of bacterial enteritis in the U.S.(5) and at least 4 categories of *E. coli*, which is the predominant gram negative aerobe in normal gut flora, are now known to produce serious human disease, one of which may lead to hemolytic uremic syndrome, a sometimes fatal disorder(6-8). In addition, the increasing popularity of seafood, and in particular raw or undercooked seafood, has resulted in a substantial increase in seafood-borne bacterial, viral and parasitic infections. Thus, although meat/poultry/seafood-borne enteric disease is not a new problem, the incidence appears to be significantly increasing and previously unrecognized pathogens are emerging, some of which have the potential for serious systemic complications.

The increase in meat/poultry-borne enteric diseases is probably accounted for both by changes in the food production industry and by changes in the population at risk. Recent consolidation of food production in the hands of large corporations and mass production

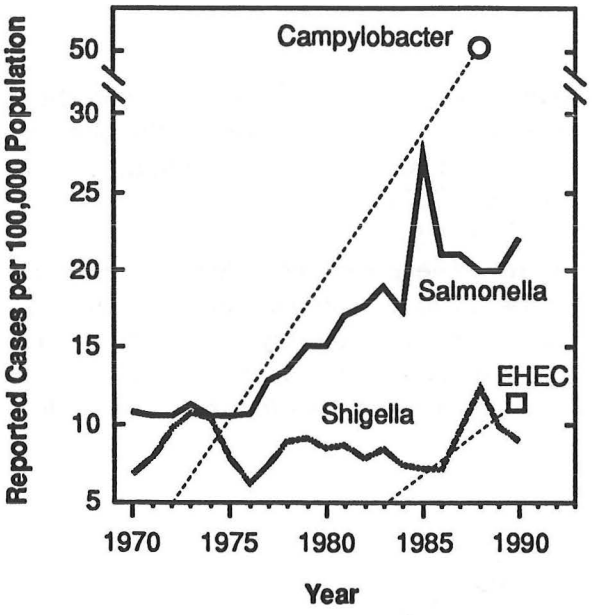

Figure 2. Isolation rates of major enteric pathogens (1970-1990).

practices provide economic and technical advantages but increases the risk of cross contamination and tend to promote large dispersed outbreaks that are difficult to detect and trace(9-11). Animals are now raised in large numbers in close quartered-conditions and fed contaminated feed often supplemented with low levels of antibiotics. Animals from all over the country are co-mingled in feedlots and in slaughterhouse holding pens as well as during transportation to these sites, greatly increasing animal to animal transmission of enteric pathogens. It is estimated that approximately 50% of animals arriving in slaughterhouses are subclinically infected with human enteric pathogens(9-11). Fecal contamination of the carcass may occur during evisceration, which for poultry is performed mechanically, and cross-contamination is common, especially during cutting, grinding and mixing that is customary in the production of retail products. If levels of contamination are low and products are widely dispersed, the resulting illnesses can fade into the background of sporadic disease and the source may never be determined. The majority of retail meat/poultry is positive for at least one enteric pathogen and their presence, especially in low numbers, should be expected (and considered natural and unavoidable) unless terminal destructive processes have been applied, such as thorough cooking or pasteurization.

The consuming public is also changing with a growing population of elderly, immunocompromised and generally debilitated persons who are at increased risk of developing foodborne infections and complications attributable to these infections.

Bacterial Enteric Pathogens

Epidemiology

Bacterial enteropathogens are responsible for the vast majority of foodborne enteric infections in cases where a specific etiologic agent is identifie(10, 11). The major enteric bacterial pathogens include *Campylobacter*, *Salmonella*, *Shigella*, *Yersinia* and pathogenic *E. Coli*. While identification of a particular enteric pathogen is adequate for many purposes, this provides insufficient discrimination for epidemiological purposes. A variety of typing schemes have been developed to differentiate among a single species including serotyping, phage typing, plasmid profiling and restriction endonuclease analysis. Serotyping is the most widely used form of typing and is based on the immunological analysis of the surface structures of the cell. These include the polysaccharide component of the lipopolysaccharides in the outer membrane of the cell (O antigen), capsular polysaccharides (K antigen) and flagellar protein (H antigen). In the case of *E. coli*, approximately 175 O and 60 H serogroups are currently recognized.

Nontyphoid *Salmonella*. Salmonellosis refers to disease caused by any serotype of the genus *Salmonella*, with the exception of *Salmonella typhi* and *Salmonella paratyphi*, the etiologic agents of typoid fever. Although ~2000 different serotypes of *Salmonella* exist, many have a narrow host range and the vast majority of human infections are caused by less than 20

serotypes, with *S. typhimurium* and *S. enteritidis* being most common. As noted above, nontyphoid *Salmonella* infections have been steadily increasing and transmission has been closely linked to commercially produced foods of animal origin. *Salmonella* are ubiquitous in the environment and tend to colonize the GI tracts of domestic animals, usually producing asymptomatic or subclinical infections. In recent years major outbreaks of salmonellosis have been traced to milk, beef, poultry and eggs(12-18). The use of subtherapeutic levels of antibiotics in feeds for growth-promoting purposes or for prophylaxis of stress has led to the emergence of multiple-drug resistant *salmonella*(16, 17, 19, 20). The most important consequence is that the number of drug-resistant organisms necessary to produce symptomatic infection is greatly reduced in individuals treated with antibiotics. Much of the recent increase in Salmonellosis has been associated with contaminated eggs. Carriage of *Salmonella* is very high in poultry and it is now apparent that vertical transmission may occur intermittently via the transovarian route(14, 15). Such intrauterine transmission may persist for generations in chickens that are asymptomatic and do not excrete *Salmonella* in the stool.

Campylobacter. *Campylobacter* is the most frequently identified agent of acute infectious diarrhea in this country. *Campylobacter* infections are not reported to the CDC by all states. Nevertheless, when looked for in patients with diarrhea, *Campylobacter* is isolated more frequently than *Salmonella* by ratios ranging from 2.5:1 to 50:1. *Campylobacter* is present in almost all surface water and colonizes birds, domestic animals and food animals(5, 21). Poultry is the major vehicle of transmission to humans with ~90% of raw poultry being contaminated with *Campylobacter*. Unpasteurized milk is also a frequent vehicle of transmission. Person-to-person spread of the organism is uncommon.

Yersinia enterocolitica. *Yersinia enterocolitica* is a common cause of enterocolitis in certain European countries and Canada but is relatively uncommon in the U.S. In some European countries, >80% of pigs carry *Yersinia enterocolitica* and raw or undercooked pork appears to be a likely vehicle. Most cases in this country are associated with outbreaks involving contaminated milk. Person-to-person spread is uncommon.

Shigella. As noted above, humans and higher apes are the only natural reservoirs of *Shigella*. *Shigella* are unique among enteric pathogens in the small infectious inoculum needed to transmit disease, with as few as ten organisms causing illness in human volunteers. For this reason, person-to-person contact is the most important mode of transmission, especially in countries where sanitation standards are low. Foodborne transmission can occur from infected food handlers, as was the case a few years ago for ~one-third of the Minnesota Vikings football team, who acquired Shigellosis from sandwiches served on a flight home from a loss to the Miami Dolphins(22).

***E. Coli* that cause diarrhea.** As the most common aerobic organism in the gastrointestinal tract *E. coli* plays an important role in normal intestinal physiology. Within this species, however, there are fully pathogenic strains that cause distinct syndromes of diarrheal disease. The five main categories of diarrheagenic *E. coli* are:

1) Enteropathogenic *E. coli* (EPEC)
2) Enteroadherent *E. coli* (EAEC)
3) Enterotoxigenic *E. coli* (ETEC)
4) Enteroinvasive *E. coli* (EIEC)
5) Enterohemorrhagic *E. coli* (EHEC)

These categories are based on distinct virulence properties, different interactions with the intestinal mucosa, distinct clinical syndromes, differences in epidemiology and distinct O:H serotypes(23).

Enteropathogenic *E. coli*. The first association of *E. coli* and diarrhea was made in the 1940s and 1950s when certain serotypes of *E. coli* were linked epidemiologically to outbreaks of infantile summer diarrhea and epidemic diarrhea in nurseries(23, 24). The most frequently incriminated serotypes were termed enteropathogenic *E. coli*. EPEC is now an uncommon cause of neonatal diarrhea in this country but is a major cause of infant diarrhea in less developed countries and in travelers from the U.S. to these countries.

Enteroadherent *E. coli*. EAEC include nonclassical EPEC serotypes that can be identified by their pattern of adherence to cultured epithelial cells (Hep-2 or HeLa cells). Some of these strains are associated with infant diarrhea in less developed countries and with diarrhea in travelers to these countries and at least one strain caused diarrhea without blood or fecal leukocytes in adult volunteers. The overall importance of EAEC as an enteric pathogen continues to be investigated(24).

Enterotoxigenic *E. coli*. ETEC is one of the most common causes of diarrheal diseases among children in less-developed countries and is the most common cause of diarrhea among traveler's to those countries(23). Sporadic cases of ETEC diarrhea are rarely detected in this country; however, a number of large foodborne outbreaks have occurred. The bacteria colonize the proximal small intestine where they elaborate heat-labile and/or heat-stable enterotoxins that alter fluid absorption and secretion(25, 26). The clinical features of ETEC infection are watery diarrhea, nausea, abdominal cramps and low-grade fever.

Enteroinvasive *E. coli*. Certain strains of *E. coli* are capable of penetrating cells of the intestinal epithelium, producing a disease spectrum virtually identical to that of *Shigella*(23, 26, 27). EIEC appears to be a relatively infrequent cause of sporadic diarrhea in this country. EIEC are recognized enteric pathogens in pediatric populations of some less developed countries and have been detected in travelers with diarrhea.

Enterohemorrhagic *E. coli*. In 1982, a previously unrecognized enteric pathogen, *E. coli* O157:H7, was associated with outbreaks of bloody diarrhea in persons eating hamburgers contaminated with the organism(28). The illness, subsequently called hemorrhagic colitis, was characterized by abdominal cramps and watery diarrhea that after a few days became streaked with blood or grossly bloody. In addition, the hemolytic uremic syndrome was found to be a complication of EHEC infection in ~2-10% of cases (up to 40% of cases in some series) as discussed by Dr. Sandra Hofmann in her recent Grand Rounds. Indeed, evidence for infection with EHEC can be found in 75-95% of patients with hemolytic uremic syndrome(7, 29).

A retrospective study by the CDC of 3,000 *E. coli* strains obtained from clinical isolates during the preceding 10 years revealed only a single O157:H7 isolate suggesting that *E. coli* O157:H7 represented a new pathogen. Genetic analysis indicates that *E. coli* O157:H7 isolates from throughout north America are essentially identical suggesting that these isolates are members of a single clone that has become widely distributed(30). In addition to many well-described outbreaks(7, 29, 31), *E. coli* O157:H7 appears to be a common cause of sporadic infectious diarrhea, especially in the northern states and Canada, where isolation rates are similar to those of *Salmonella* and *Shigella*(7, 29, 32, 33). Ground beef and unpasteurized milk are the major vehicles of infection(7, 29, 34) although unpasteurized apple cider (made from apples on the ground presumably contaminated with bovine feces) has also been implicated(35). *E. coli* O157:H7 has been isolated in up to 6% of fecal samples from cattle and in up to 29% of raw ground beef(7). Isolation rates tend to be highest in areas where the incidence of EHEC infections are the highest. Secondary person-to-person spread by direct fecal-oral transmission can occur, especially in day care centers(36) or nursing homes(37), and at least

one health care worker appears to have acquired *E. coli* O157:H7 from a patient, resulting in hemorrhagic colitis complicated by hemolytic uremic syndrome(38).

Virulence factors

Bacterial enteric pathogens express a variety of virulence factors that contribute to infection and disease and enable them to circumvent host defense mechanisms. These virulence factors generally fall into one of the following major categories: (1) enterotoxins that cause fluid and electrolyte secretion by activating intracellular enzymes without damaging the intestinal epithelium, (2) various adherence factors that allow bacteria to colonize the GI tract and stick to enterocytes, (3) factors that allow bacteria to penetrate and replicate within cells and (4) cytotoxins that destroy or damage intestinal epithelial cells. Although a particular virulence factor may predominate, successful enteric pathogens generally possess multiple virulence properties that are expressed coordinately or sequentially in response to environmental signals.

The structural genes encoding virulence factors may be located on the bacterial chromosome or may be carried on mobile genetic elements such as plasmids or bacteriophages (viruses that infect bacteria). Plasmids are circular duplex DNA molecules that carry genes for antibiotic resistance as well as genes encoding toxins and various virulence factors. Plasmids contain their own origin of replication and hence can replicate autonomously. Some plasmids also carry genes that enable bacteria to transfer genetic material to each other by forming direct cell-cell contacts—a process called conjugation. Bacteriophages can also mediate the exchange of genetic material between bacteria. In addition, within a given cell, plasmids and bacteriophages can exchange blocks of genes with bacterial chromosomes and can recombine with each other. Thus, genes encoding antibiotic resistance and virulence factors are highly mobile and can be transmitted in mixed cultures even among different bacterial species.

The majority of virulence factors expressed by enteric pathogens are encoded by plasmids although chromosomal genes and phage-encoded genes also play a role(39, 40). Examples of the most common virulence factors are discussed briefly below.

Enterotoxins that cause secretion of fluid and electrolytes without causing mucosal damage. In general, these enterotoxins are polypeptides that induce intestinal secretion by activating cyclic AMP- or GMP-dependent transport pathways(25, 41). The genes that encode most, but not all, of these peptide toxins are located on plasmids. The prototype for toxins that affect cyclic AMP-dependent pathways is cholera toxin. Certain strains of enterotoxigenic *E. coli* elaborate "heat-labile toxin", which is remarkably similar to cholera toxin both structurally and functionally(Figure 3). Heat-labile toxin is actually a family of high molecular weight proteins that, like cholera toxin, consist of a single "A" subunit surrounded by five "B" subunits. The B subunits of these toxins bind to the brush border membranes of enterocytes via interaction with ganglioside G_{M1}(42, 43)(Figure 8). *E. coli* heat-labile toxin binds to an additional glycoprotein receptor on brush border membranes(42, 44, 45). The A subunit of both toxins is translo-

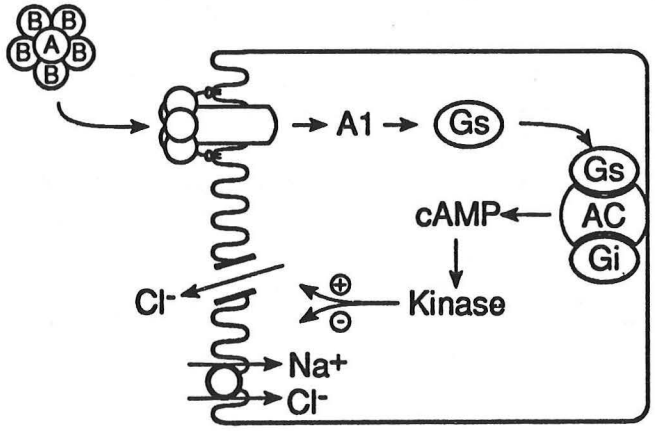

Figure 3. Mechanism of action of *E. coli* heat-labile enterotoxin.

cated into the cytoplasm where it catalyzes ADP-ribosylation of $G_{s\alpha}$ thereby stimulating adenylate cyclase located on the basolateral membranes of the enterocyte and raising cyclic AMP levels(46-48). This leads to the activation of cyclic AMP-dependent protein kinases and ultimately to stimulation of Cl^- secretion in crypt cells and inhibition of neutral NaCl absorption in villus cells. The overall effect is net fluid and electrolyte secretion and watery diarrhea. A number of other enteric pathogens elaborate labile toxins that are homologous to varying degrees to cholera toxin including *Salmonella*, *Campylobacter*, *Aeromonas hydrophila* and *Plesiomonas shigelloides*. Labile toxin can be detected by bioassay (fluid secretion into ligated loops of rabbit intestine) or by serological methods using monoclonal antibodies or GM1 ganglioside as a ligand for the toxin. DNA probes can be used to detect the gene.

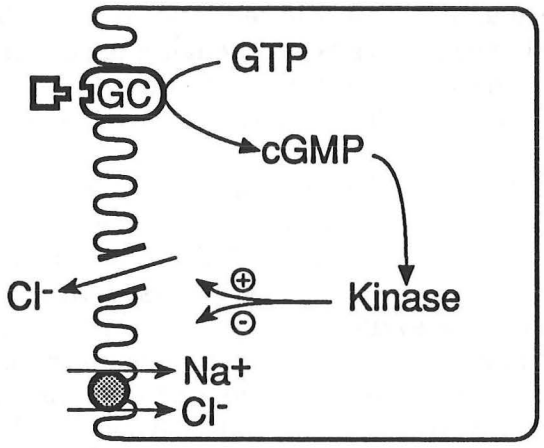

Figure 4. Mechanism of action of heat-stable enterotoxin.

The prototype for toxins that affect cyclic GMP-dependent pathways is the *E. coli* heat-stable enterotoxin(25, 41). Heat stable toxins are a family of low molecular weight peptides that are elaborated by a variety of bacteria including *Yersinia enterocolitica* and non-O1 cholera. As illustrated in Figure 4, heat-stable toxin appears to bind directly to guanylate cyclase itself (or to a guanylate cyclase-linked receptor) in the brush border membranes of enterocytes resulting in an increase in cyclic GMP(49, 50). This leads in turn to the activation of a cyclic GMP-dependent protein kinase and ultimately to stimulation of Cl- secretion in crypt cells and inhibition of neutral NaCl absorption in villus cells(Figure 4). As with heat labile toxin, the overall effect is net fluid and electrolyte secretion.

Heat stable toxin can be detected by bioassay (fluid secretion into the intestines of infant mice) or by serological methods using monoclonal antibodies. DNA probes can be used to detect the gene.

Adherence factors. Numerous enteropathogens, including enterotoxigenic *E. coli*, enteropathogenic *E. coli*, *Vibrio cholerae*, *Yersinia enterocolitica*, *Shigella* and *Salmonella* produce adhesive fimbriae (or pili) that extend from the bacterial cell surface as thin filamentous structures and mediate attachment to gut epithelial cells(51, 52). For example, enterotoxigenic *E. coli* possess hair-like fimbriae that mediate attachment to enterocytes in the proximal small bowel and are essential for virulence. These fimbrial colonization factors are encoded by plasmids that also encode the heat labile and/or heat stable toxins discussed above. Little is known regarding host cell receptor sites for fimbriae but sialic acid containing glycoproteins, collagen and fibronectin have been implicated. It is likely that all successful enteric pathogens express adhesion molecules on the tips of fimbriae or on the cell surface that allow them to initially associate with and subsequently adhere to gut epithelial cells. Such attachment to gut epithelial cells is presumed to be essential if these bacteria are to avoid host clearance mechanisms and compete with normal flora for appropriate niches.

A second genetically independent form of bacterial interaction with brush border membranes has been termed attachment-effacement(Figure 5). Attachment-effacement is the characteristic way in which entero-pathogenic *E. coli* (EPEC) associate with the intestinal mucosa, as observed in human intestinal biopsies and experimental animals(53-55). The affected enterocytes exhibit a dramatic loss of microvilli and rearrangement of cytoskeletal elements, with a proliferation of filamentous actin beneath areas of intimate bacterial

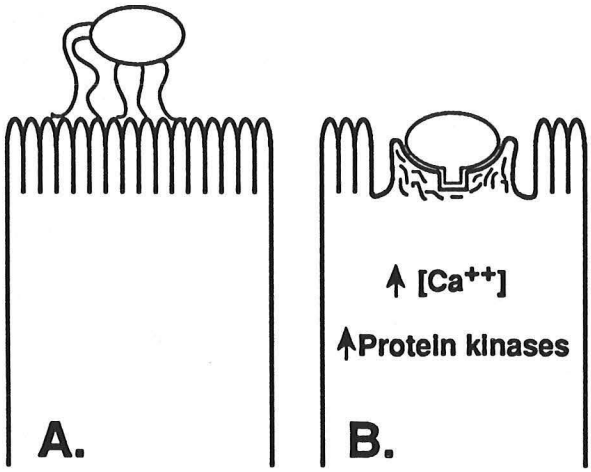

Figure 5. Attachment-effacement lesion characteristic of enteropathogenic and enterohemorrhagic *E. coli*.

attachment(24, 56). These cellular changes, the mucosal response to them and to the adhering bacteria—namely, inflammation—and their effects on digestion and absorption are presumably key to EPEC-induced diarrhea. However, malabsorption alone does not explain the very short incubation period and massive secretion of fluid and electrolytes that is seen in many patients. Recently EPEC have been shown to induce elevations of intra-cellular calcium and to stimulate protein phosphorylation(24, 56). It seems likely that effects on fluid and electrolyte secretion as well as effects on the host cell cytoskeleton may be mediated, at least in part, by the ability of EPEC to subvert eukaryotic second messenger systems. The attaching and effacing pattern of histopathology characteristic of EPEC is also observed with EHEC (see below) and in both cases, a recently cloned cell surface adhesion protein appears to mediate intimate adhesion and attachment-effacement activity(57).

Invasive factors. *Shigella* and enteroinvasive *E. coli* (EIEC) cause dysentery by invading colonic epithelial cells(Figure 6). The full expression of virulence of these organisms requires both chromosomal and plasmid encoded proteins. The ability to penetrate epithelial cells is essential for virulence and is associated with cell surface proteins that are encoded on large 120-140 Mdal plasmids(58). Transfer of these plasmids into avirulent *E. coli* enables them to invade epithelial cells in culture(59). Additional chromosomal loci are required for full pathogenicity which includes replication within enterocytes, spread to adjacent cells, induction of an inflammatory response in the lamina propria and the killing of these inflammatory cells by programmed cell death (apoptosis) resulting in crypt abscesses(60).

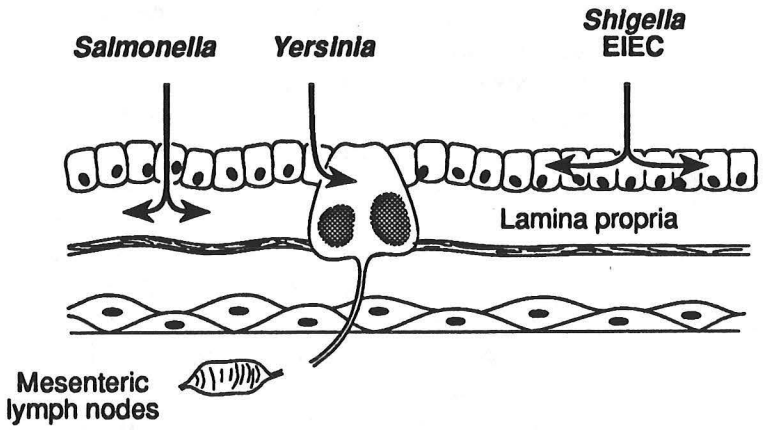

Figure 6. Typical location of pathology produced by various invasive enteropathogens.

Salmonella and *Yersinia* also possess the ability to invade intestinal epithelial cells; however, these organisms tend to pass rapidly through the enterocytes into underlying reticulendothelial cells and regional lymph nodes. The invasive determinants of *Salmonella* and *Yersinia* appear to be genetically distinct from those of *Shigella* and EIEC described above(56, 61, 62).

Cytotoxic factors. Shortly after *E. coli* O157:H7 was linked to outbreaks of hemorrhagic colitis, it was shown that this strain produced cytotoxins that destroyed cultured vero cells (African green monkey kidney cells)(7, 8, 29). The

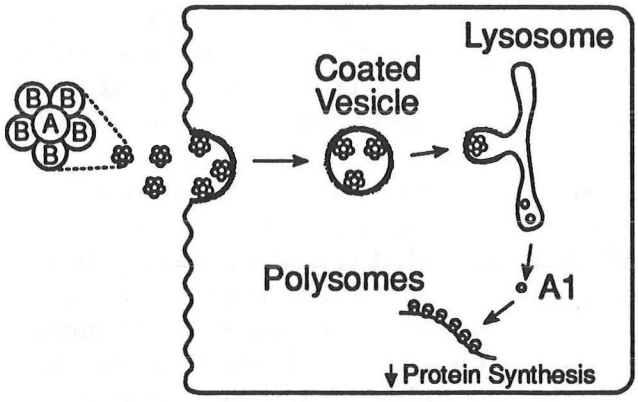

Figure 7. Mechanism of action of Shiga and Shiga-like toxins.

toxins were therefore called verotoxins (VT) and strains of *E. coli* producing these toxins are sometimes referred to as verotoxigenic *E. coli* (VTEC). Since the toxins are similar to Shiga toxin, a cytotoxin produced by *Shigella dysenteriae* type 1; they are also referred to as Shiga-like toxins (SLT)(63). On further analysis of O157:H7 organisms it became apparent that there were at least two families of cytotoxins that were designated SLT1 and SLT2.

The structure of SLT1 is essentially identical to Shiga toxin (differs by only a single amino acid) whereas SLT2, which probably represents a family of closely related toxins, shares only 50-60% amino acid homology with Shiga toxin. Both possess biologic activity that is indistinguishable from Shiga toxin. Shiga toxin and the SLTs are composed of an "A" subunit, which is the active component, surrounded by multiple "B" subunits, which attach to neutral glycolipids on mammalian cells(Figures 7 and 8). The usual receptor is a galactose-α-1,4-galactose-containing glycolipid designated Gb_3(64). After the toxin binds, it is internalized by receptor-mediated endocytosis. The catalytically active A subunit gains access to the cytoplasmic compartment where it removes a single adenine residue from a specific site of 28S ribosomal RNA that is critical to attachment of elongation factor-1-dependent amino acyl tRNA to the ribosome thereby resulting in irreversible inhibition of protein synthesis and cell death(65).

The exact role of SLTs in the pathogenesis of hemorrhagic colitis is not entirely clear. Diarrhea associated with EHEC infections may result from a local effect of SLTs on intestinal epithelial cells (with death and premature sloughing of mature villus tip enterocytes), from the attachment-effacement effects of EHEC (as described above), or from the systemic effects of SLTs on intestinal vasculature. SLTs are probably responsible for the systemic effects of EHEC(29, 34, 66). Enterohemorrhagic *E. coli* (EHEC) are thought to release SLTs in the bowel, from where they are absorbed into the blood. Here the toxins are thought to cause endothelial damage of small blood vessels, leading in turn to local intravascular coagulation and fibrin deposition in the brain, gut and kidney. These events variably lead to microangiopathic hemolytic anemia, thrombotic thrombocytopenic purpura and bowel ischemia and necrosis.

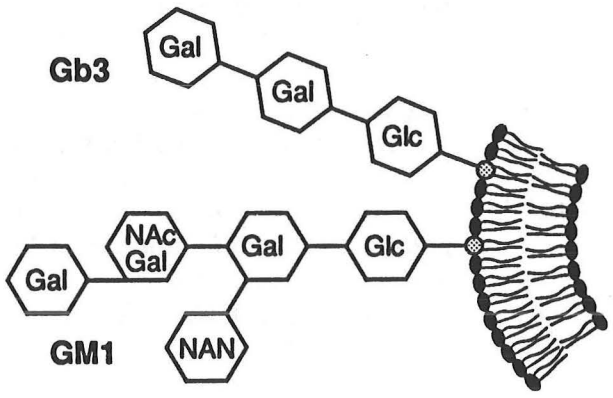

Figure 8. Glycolipid receptors for *E. coli* Shiga-like (Gb3) and heat-labile toxins (GM1).

The structural gene for Shiga toxin in *Shigella dysenteriae* type 1 is chromosomal whereas the SLT genes of EHEC are located on bacteriophages. It would appear that a bacteriophage acquired the gene from *Shigella dysenteriae* type 1 and that this toxin-producing bacteriophage subsequently infected certain strains of *E. coli*(39).

Table I. Major clinical syndromes caused by enteropathogens

Syndrome	Location of infection	Clinical features	Fecal leukocytes	Organism	Major Pathogenic mechanism
Secretory diarrhea	Proximal SB	Watery diarrhea	None	ETEC Cholera	Enterotoxin
Terminal ileitis	Distal SB	Fever, pain, diarrhea, bacteremia, extra-intestinal infection	Few to none	Salmonella Yersinia	Invasion, translocation, lymphoid inflamation, dissemination
Dysentery	Colon	Fever, pain, bloody mucopurulent diarrhea	Many	Shigella EIEC Campylobacter Salmonella Yersinia	Invasion, local spread
Hemorrhagic colitis	Colon	Pain, diarrhea, grossly bloody stools, HUS	Few to none	EHEC	Shiga-like toxin

Although *E. coli* O157:H7 remains the most commonly recognized EHEC there are other EHEC serotypes and, in addition, many strains of *E. coli* that are not associated with hemorrhagic colitis are low level producers of SLTs.

Host resistance factors

The conditions inside the GI tract are generally hostile to enteric pathogens. Gastric acid suppresses or inactivates most bacteria(67). The infective dose of many enteric pathogens is quite dependent on gastric pH—being several orders of magnitude lower at a pH of 7 compared to a pH of 4. Food is an important factor in buffering gastric acid; nevertheless, hypochlorhydria is a significant risk factor for most foodborne infections. As discussed above, successful enteric pathogens must be able to adhere to the epethelial surface, and gut motility and mucus present problems to enteric pathogens in this regard. The presence of specific sIgA antibodies within the mucus layer appears to be particularly effective in blocking the attachment of pathogens to the epethelial surface. Finally, the indigenous bowel flora appears to be one of the most important barriers to enteric pathogens and recent exposure to antibiotics has been one of the most consistent and important risk factors in terms of susceptibility to bacterial enteric infections.

Clinical syndromes

Enteric pathogens produce acute GI symptoms that vary in severity from a few loose stools to fulminant enterocolitis(26, 27). In general it is not possible to predict the enteric pathogen responsible for a particular illness since, as discussed above, different serotypes of *E. coli* can produce the entire spectrum of symptoms depending on the particular virulence factors it has acquired. Moreover, epidemiological studies of foodborne outbreaks have shown that individuals infected with the exact same organism can experience a clinical course ranging from asymptomatic to desperately ill apparently depending on the size of the inoculum and host defense mechanisms. Nevertheless, although there is much overlap, illness caused by enteric pathogens can generally be divided into four clinical syndromes that are based on the region of bowel that is involved and whether or not the organism is invasive(Table I). These clinical syndromes include: (1) secretory diarrhea, (2) terminal ileitis, (3) dysentery with fever and blood-tinged mucopurulent diarrhea and (4) hemorrhagic colits.

Secretory diarrhea is produced by organisms such as *Vibrio cholera* and ETEC. These organisms colonize the proximal small bowel and elaborate enterotoxins that stimulate fluid and electrolyte secretion resulting in watery diarrhea that can be voluminous. There is no evidence of tissue invasion or cellular destruction and the fecal effluent contains no RBCs or leukocytes.

Terminal ileitis is most commonly associated with *Salmonella* and *Yersinia*. These organisms penetrate the surface epithelium of the distal small bowel and quickly make their way to deeper tissues including the regional lymphatics. Clinical features include diarrhea and prominent RLQ pain. The stool generally contains few if any leukocytes. The clinical spectrum of these organisms includes mesenteric adenitis mimicking acute appendicitis (especially with *Yersinia*) and bacteremia with hematogenous spread (especially with *Salmonella*).

Dysentery with fever, abdominal cramps and bloody mucopurulent diarrhea is produced by invasive organisms that target the colon. Enteric pathogens in this group include *Shigella*, *Salmonella*, *Campylobacter*, *Yersinia* and invasive *E. coli* (EIEC). The initial lesions are confined to the epithelial layer; however, as the disease progresses, the lamina propria becomes involved extensively with an inflammatory response and crypt abscesses are prominent. Frank dysentery is frequently preceded by a day or two of watery diarrhea—the mechanism of which is not fully understood but is probably due to the elaboration of

enterotoxins or to local effects on prostaglandin synthesis.

Hemorrhagic colitis due to enterohemorrhagic *E. coli* typically presents with severe abdominal cramping followed by grossly bloody stools. Fever occurs in the minority of patients and fecal leukocytes are uncommon. Gross and microscopic examination of the colon shows a pattern of injury similar to that seen with ischemic colitis, infectious colitis, *C. difficile*-associated colitis or all three(68, 69). The right colon is often most severely affected. As discussed by Dr. Sandra Hofmann in her recent Grand Rounds, the hemolytic uremic syndrome and thrombotic thrombocytopenic purpura are the most serious complications of EHEC and occur overall in about 5% of cases, usually in the very young or very old.

Extraintestinal complications of bacterial enteropathogens

In addition to the diarrheal syndromes outlined above, an extensive list of extraintestinal complications has been associated with various bacterial enteric pathogens. Reactive arthritis follows infections with with *Campylobacter*, *Salmonella*, *Shigella* or *Yersinia* in 2-3% of cases, usually in persons with the HLA-B27 major histocompatibility antigen. Bacteremia with hematogenous spread occurs most commonly with *Salmonella*; seeding of almost any site in the body may occur although a particular tropism for infrarenal aortic aneurysms has been noted(26). (Septicemia due to *Vibrio Vulnificus* is discussed below.) *Yersinia* is associated with a variety of autoimmune phenomena including rheumatoid arthritis, Sjogren's syndrome, polyarteritis and Graves' disease while *Campylobacter* appears to be a common initiator of the Guillain-Barre syndrome(70).

Evaluation and Treatment of Acute Diarrhea

Evaluation

The incidence of acute diarrhea in this country is in the range of 1-2 episodes per person per year. Most of these episodes are self-limiting with mild to moderate symptoms and require no specific evaluation or treatment. Individuals presenting to a physician can usually be placed into one of the four major clinical syndromes described above based on history and physical examination. In addition, the severity of the illness in terms of fluid and electrolyte status and systemic toxicity should be assessed. Microscopic examination of the stool for RBCs and leukocytes using a counterstain such as methylene blue is a very useful technique for presumptively differentiating invasive bacterial pathogens from noninvasive pathogens, viruses and protozoa. In some cases sigmoidoscopy may be helpful in documenting the presence or absence of colitis. Decisions regarding stool cultures, treatment and need for hospitalization can then be made based on this information.

A specific etiologic diagnosis can be useful therapeutically and epidemiologically and studies of the stool, the putative infected excretion, are key in this regard. Most episodes of acute diarrhea (especially foodborne diarrheal disease) with a confirmed etiology are due to bacterial enteric pathogens. Nevertheless, the yield from routine stool cultures is notoriously low, with only 2-3% of stool cultures being positive in most clinical microbiology labs. Furthermore, even when stool cultures are positive they may not alter therapy since the patient often is improving or has been treated empirically by the time the results become available. Thus, with the current interest in cost-containment it is important to consider those circumstances where stool cultures are useful and indicated as opposed to the vast majority of situations where stool cultures are unlikely to be helpful and should probably not be obtained. Although opinions vary, Table II presents a list of the situations in which stool cultures are generally indicated. Most clinical labs routinely culture stool for *Salmonella*, *Shigella* and *Yersinia*; cultures for other organisms must be specifically requested as indicated by the clinical presentation and the presence or absence of fecal leukocytes.

Table II. Indications for stool cultures in the evaluation of acute diarrhea.

- **Dysentary**
- **Hemorrhagic colitis, HUS/TTP**
- **Immunocompromised**
- **Food handlers**
- **Common source outbreak**
- **Severe or protracted (> 1 week)**

Dysentery with blood-tinged, mucopurulent stools is probably the most common indication for stool cultures. Dysentery or the finding of numerous fecal leukocytes suggests infection with *Salmonella*, *Shigella* or *Campylobacter* and the stool should be cultured for these organisms. *Campylobacter* is somewhat more fastidious than *Salmonella* and *Shigella* and requires immediate refrigeration of the stool sample and different culture techniques. Stool should also be examined for Ova and parasites since "amebic dysentery" is fairly common in this area. Interestingly, fecal leukocytes are usually absent in patients with amebic colitis.

Other microbiological studies of stool may be useful under certain circumstances. For example, grossly bloody stools or the hemolytic uremic syndrome suggest infection with enterohemorrhagic *E. coli*. *E. coli* O157:H7, which is by far the most common serotype associated with hemorrhagic colitis and HUS in this country, is distinctive in that it, unlike most fecal *E. coli*, fails to ferment sorbitol within 24 hours. Thus, sorbitol-MacConkey (smac) agar can be used to screen for *E. coli* O157:H7 and the diagnosis confirmed by serotyping those organisms that do not ferment sorbitol. Assays to detect shiga-like toxins (cytopathic effect on vero or HeLa cells, ELISAs using monoclonal antibodies or toxin receptor analogs) or the genes encoding the shiga-like toxins or specific fimbrial adhesion molecules have recently been developed but are not yet widely used in clinical labs.

Yersinia is a major cause of enterocolitis in some countries but is uncommon in most regions of the U.S. Nevertheless, cultures for *Yersinia* should be requested (if not performed routinely by the lab) for individuals who present with symptoms of terminal ileitis or who have an underlying predisposition such as cirrhosis and/or iron overload. *Yersinia* will grow on most selective enteric media but is readily overgrown by common gut flora. For this reason, isolation schemes usually employ cold enrichment in liquid media at 4-10°C, which retards the growth of commensal enteric organisms and exploits the ability of *Yersinia* to grow at these temperatures.

C. difficile toxin should be obtained for individuals with recent exposure to antibiotics (preceding 6 weeks).

In addition to the usual enteric pathogens, patients with AIDS may have diarrhea due to a variety of opportunistic organisms such as *isospora*, *cryptosporidia*, *microsporidia* and CMV.

Finally, as discussed below, acute diarrhea associated with recent raw or undercooked shellfish ingestion raises the possibility of enteric infection with *Vibrio* spp., *Aeromonas hydrophyla* or *Plesiomonas shigelloides*. Although these organisms usually cause a mild gastroenteritis, immunocompromised or debilitated hosts may experience protracted or severe symptoms.

Treatment

In most adults with acute diarrhea, fluid and electrolyte replacement can be accomplished orally. Milk, caffeine and alcohol should probably be avoided since they may increase

stool volume. Regular diet can usually be continued as tolerated. Loperamide is very helpful in controlling mild to moderate diarrhea but probably should not be used in cases of severe dysentery.

Indications for antibiotic therapy are generally the same as the indications for obtaining stool cultures(listed in Table II). Individuals with febrile dysenteric syndromes (passage of bloody mucopurulent stools) should be treated empirically while awaiting the results of stool cultures. The quinolone drugs are highly active against all bacterial enteric pathogens (except *C. difficile*) and are the agents of choice for empiric therapy(71-73). The quinolones are not recommended for use in children or during pregnancy because of possible effects on cartilage formation(74). Very ill patients should probably also receive Metronidazole to cover for *C. difficile* and *Entamoeba histolytica*. For most of the other groups listed in Table II, it is probably reasonable to await the results of the stool cultures before beginning specific therapy. At present there is no convincing evidence that antibiotics improve symptoms or shorten the duration of illness with *E. coli* O157:H7(66) although the fluoroquinolones may eventually prove to be beneficial.

Although antibiotics are generally reserved for individuals with severe or protracted disease, recent studies indicate that early empiric therapy with a quinolone modestly shortens the duration of acute diarrhea (by ~ 50%) regardless of the severity of the illness, whether or not fecal leukocytes are present or whether stool cultures ultimately show *Salmonella*, *Shigella*, *Campylobacter* or no bacterial pathogen(71, 72)(Figure 9). Nevertheless, the benefit of empiric antibiotics in individuals with mild to moderate diarrhea was quite modest and, at the present time, routine empiric antibiotic therapy for mild to moderate diarrhea is not recommended.

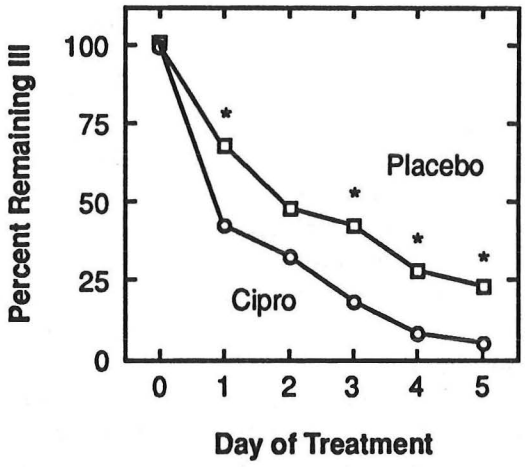

Figure 9. Empiric antibiotic therapy for domestically acquired acute diarrhea in adults (ref. 72).

Enteric Infections Associated with Seafood

The incidence of illness related to seafood is increasing in this country, probably owing to the increased consumption of seafood and, more importantly, to the increasing popularity of raw fish and shellfish. Major hazards associated with the consumption of seafood include exposure to bacterial, parasitic and viral pathogens (mainly a hazard of raw seafood) and exposure to various algal-derived neurotoxins that concentrate up the food chain(75-77).

Enteric Infections Associated with Raw or Undercooked Shellfish

Among consumers of seafood, individuals at greatest risk of enteric infection appear to be those who ingest raw or undercooked shellfish. Shellfish feed by sieving large volumes of water thereby concentrating pathogenic organisms, particularly if the water from which they are harvested is contaminated with human sewage. Norwalk virus is by far the most common infectious cause of acute diarrhea associated with eating raw shell fish. The illness lasts 1-2 days and treatment is supportive.

Marine *Vibrios* are native to warm coastal waters and are the most important bacterial pathogens. In the Gulf Coast states, *Vibrio parahaemolyticus* and *Vibrio cholera* non-O1 are the most common bacterial causes of diarrhea associated with the ingestion of raw or undercooked shellfish(78-80). Symptoms include abdominal cramps and watery diarrhea

although ~one-third of individuals with *vibrio parahaemolyticus* will experience a febrile dysenteric illness with visibly bloody stools containing many leukocytes. Although symptoms are usually self-limited, the majority of recognized cases require hospitalization to maintain fluid balance(78). Doxycycline or a quinolone should be used for severe or protracted symptoms. Other bacterial enteric infections that are less frequently associated with consumption of shellfish include *Salmonella*, *Campylobacter*, *Shigella*, *Aeromonas hydrophila* and *Plesiomonas shigelloides*.

Of the marine *Vibrios*, *Vibrio vulnificus* is the organism that poses the greatest threat to individuals ingesting raw or undercooked shellfish(78, 81). *Vibrio vulnificus* colonizes the GI tract after the consumption of raw shellfish, particularly oysters. Although the organism rarely causes gastroenteritis, it is extremely invasive and frequently causes septicemia and shock with a mortality rate of ~50%. A necrotyzing vasculitis, distinct hemorrhagic bullae that rapidly progress to necrotic ulcers, and DIC are common. Persons most prone to the development of disseminated disease—and who should be strongly encouraged to avoid raw oysters—are those with chronic liver disease and iron overload. *Vibrio vulnificus* is unusual in that it is unable to acquire iron from unsaturated transferrin. Normal human blood or plasma is strongly bactericidal against *Vibrio vulnificus* whereas rapid growth of the bacteria occurs in blood from patients with hemochromatosis, or in normal blood supplemented with iron to increase the saturation of transferrin into the 50-90% range(82, 83)(Figure 10). Other modest risk factors for *Vibrio vulnificus* septicemia are hypochlorhydria (from surgery or medication), cancer, and immunodeficiency states. Treatment is supportive care and antibiotics. The organism is sensitive to most antibiotics that would be used empirically in septic shock; however, doxycycline and an aminoglycoside probably represents the optimal regimen.

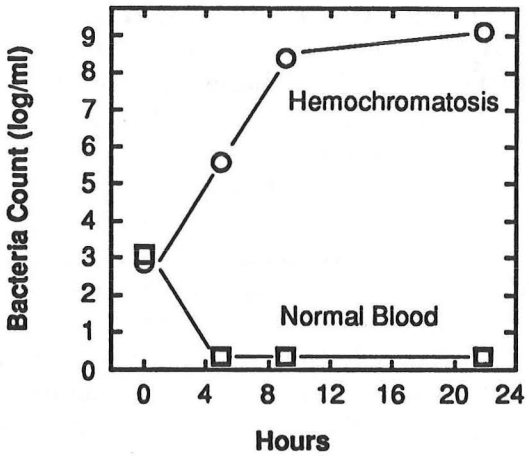

Figure 10. Effect of transferrin saturation on the growth of *Vibrio Vulnificus* in blood (ref. 83).

A second less common syndrome associated with *Vibrio vulnificus* is wound infection. The majority of these have direct contamination of an open wound with seawater.

Enteric Infections Associated with Sushi

Eating raw or inadequately cooked fish carries the potential risk of several types of worm infections. Anisakiasis is the parasitic disease most frequently associated with the ingestion of raw seafood(84). The causative agents are marine nematodes (round worms) belonging to the subfamily Anisakidae which commonly infect commercial fish taken off both coasts of the U.S. There are two forms of anisikiasis: noninvasive (or luminal) and invasive. The noninvasive form gives rise to the "tingling throat syndrome," which occurs when worms migrate back up the esophagus into the oropharynx. These worms are often coughed up or are felt wiggling around in the mouth between the gums and cheek during the week or two following ingestion. Invasive anisakiasis occurs when larvae attach to, embed in, or penetrate host tissues. Worms are most often found in the mucosa or submucosa of the stomach and intestine but may migrate to other tissues such as the omentum, pancreas, liver or lung(85). Most cases present with severe abdominal pain within one to two days of ingesting the infected meal and many undergo surgical exploration for acute abdomen—the most common preoperative diagnoses being appendicitis, perforated peptic ulcer, Crohn's disease, diverticulitis or cancer.

Symptoms may become chronic with intermittent symptoms lasting from weeks to years. Eosinophilia is unusual and stool studies are not helpful since eggs are not produced. Endoscopic visualization and removal of the worms is the most useful method of diagnosis and treatment(86, 87). Abdominal pain resolves immediately after endoscopic extraction of the worms. Antihelmintics are ineffective. Fish to be eaten raw should be frozen at -30° for 15 h or -10° for a week, either of which kills worms.

Toxic syndromes

Approximately one-fourth of all cases of food poisoning reported to the CDC result from toxic seafood ingestion. Several syndromes are caused by neurotoxins of algal origin that become more concentrated as they pass up the food chain(76). These include Ciguatera, Neurotoxic shellfish poisoning, paralytic shellfish poisoning and amnesic shellfish poisoning. Symptoms include abdominal pain, nausea, vomiting and diarrhea followed by various neurologic symptoms that may persist for months. These toxins are heat-stable and unaffected by cooking.

Scombroid fish poisoning results from eating fish that contain high levels of histamine, which is formed when bacteria on the surface of the flesh are allowed to proliferate due to improper refrigeration(88, 89). Free histidine, present in increased quantities in dark meat fish, is degraded to histamine by bacterial action. The histamine-like reaction begins minutes to hours after ingestion of the toxic fish and is preventable by proper refrigeration during all stages of handling.

Puffer fish poisoning is notorious in Japan where it is associated with a mortality rate of ~60%(90). Puffer fish is considered a gourmet delicacy despite its toxicity and requires special training and a license to prepare. The causative toxin is tetrodotoxin, a heat-stable, nonprotein neurotoxin that acts by inhibiting sodium channels in excitable membranes, thereby blocking the propagation of nerve and muscle action potentials. A restaurant in New York now offers puffer fish and if other restaurants follow, tetrodotoxication could become more common in this country.

Traveler's Diarrhea

Diarrhea is by far the most frequent health problem of travelers to developing countries. Approximately 20 million persons from industrialized countries, including ~10 million residents of the U.S., will travel this year to a developing country. The most important determinant of risk is the destination of the traveler. Although relatively little recent data exist regarding country-specific attack rates, the best available estimates indicate a high risk in most of the developing countries of Latin America, Africa, the Middle East and Asia with 40-60% of travelers to these areas experiencing diarrhea(91, 92).

Traveler's diarrhea is acquired through ingestion of fecally contaminated food and/or beverages. Traveler's diarrhea typically results in four to five loose or watery bowel movements per day usually accompanied by abdominal cramps, nausea and vomiting. The median duration of diarrhea is three to five days with 10% lasting > 1 week and 2% lasting > 1 month. Up to 10% will develop dysentery

Table III. Etiology of traveler's diarrhea.

Pathogen	Average (%)
Enterotoxigenic *E. coli*	40-60
Shigella	10
Campylobacter	5
Salmonella	5
Invasive *E. Coli*	<5 each
Vibrio spp.	<5 each
Giardia	<5 each
Amoeba	<5 each
Cryptosporidium	<5 each
Viral	<5 each
No pathogen identified	10-25

with fever and bloody mucoid stool.

The important agents that cause travelers diarrhea are similar to those that cause diarrhea in children of developing countries. As summarized in Table III, bacterial enteric pathogens are responsible for the overwhelming majority of cases with enterotoxigenic *E. coli* being the most commonly identified pathogen in all studies(91-94). Recovery of multiple potential pathogens is not uncommon. All travelers to developing countries quickly develop a dramatic change in their intestinal flora with the acquisition of antibiotic-resistant *E. coli* and a variety of potential enteric pathogens(95).

Prevention and treatment of traveler's diarrhea

Since the organisms that cause traveler's diarrhea are acquired through the ingestion of fecally contaminated food and beverage, it might be anticipated that precautions aimed at reducing or eliminating the ingestion of microorganisms would also reduce the incidence of diarrhea. Unfortunately this has been difficult to demonstrate and in some studies, stricter adherence to dietary precautions was associated with a higher incidence of diarrhea(93). Nevertheless, assuming that there is a link between inoculum size (and frequency) and the incidence of diarrhea, all traveler's should receive instructions regarding the careful selection of food and beverages while in high-risk areas(96).

Given the high attack rate of travelers diarrhea in high-risk areas and the difficulty of maintaining dietary precautions, it is not surprising that a large number of agents have been assessed for efficacy in the prophylaxis and treatment of diarrhea. From a practical point of view, the two options that can be discussed with the traveler are empiric self-therapy of diarrhea and chemoprophylaxis(91, 94). To date, no vaccines have been developed that are clinically useful in preventing traveler's diarrhea(97).

Empiric self-therapy

Most individuals with traveler's diarrhea do not develop serious dehydration and fluid and electrolyte balance can usually be maintained with caffeine-free soft drinks and salted crackers. Individuals with moderate to severe diarrhea, especially if accompanied by vomiting, abdominal cramps, fever or blood in the stools may benefit from antibiotics. Under these conditions, a 3 day course of trimethoprim-sulfamethoxazole (1 DS bid) or a fluoroquinolone (Norfloxacin 400 mg bid or Ciprofloxacin 500 mg bid have been most extensively studied) reduces mean duration of diarrhea from ~4 days to ~1 day and the addition of loperamide further reduces mean duration of diarrhea to ~12 hours(94, 98-102)(Figure 11). Since these studies were carried out, resistance to trimethoprim-sulfamethoxazole has been reported in most high-risk areas limiting its usefulness unless susceptibility data are available(95, 103-105). In contrast, clinically important resistance to the fluorquinolones has been rare although an occasional *Campylobacter* may develop resistance

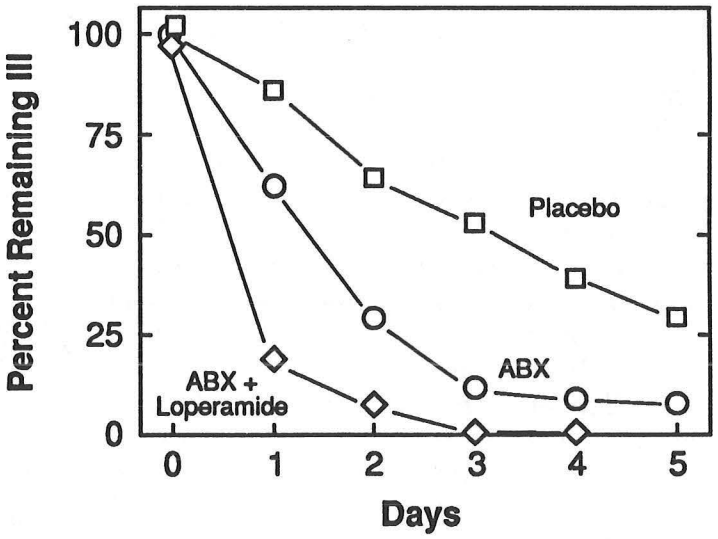

Figure 11. Effect of empiric self-therapy on the duration of traveler's diarrhea (refs. 94, 98-102).

during therapy(72). Thus, the combination of loperamide (2 mg after each loose stool not to exceed 16 mg/d) and a 3 day course of a fluoroquinolone is probably the optimal treatment for moderate to severe traveler's diarrhea. One to three percent of individuals taking a 3 day course of a quinolone may develop a rash or vaginitis while the risk of anaphylaxis or Stevens-Johnson syndrome is 1 in 10,000 to 1,000,000(74). Loperamide should not be taken by individuals who develop frankly bloody diarrhea because of the possibility of exacerbating colitis caused by invasive organisms. Fluorquinolones are not recommended for use in children or during pregnancy due to potential effects on cartilage formation(74).

Chemoprophylaxis

Of the many agents assessed, bismuth subsalicylate and antibiotics have proven efficacy for the prevention of traveler's diarrhea. Bismuth subsalicylate (60 ml or 2 tablets qid) is modestly effective in preventing diarrhea (reduces risk by ~50%)(106). Lower levels of protection occur with smaller or less frequent doses. Overall, bismuth is safe and effective for prophylaxis but the degree of protection is very modest and for most people the inconvenience of taking medication four times a day and the loss of luggage space may not be worth the partial protection.

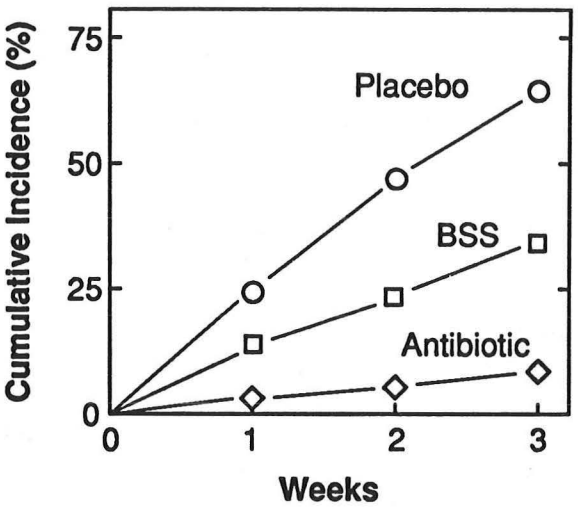

Figure 12. Effect of chemoprophylaxis on the incidence of traveler's diarrhea by week of exposure (refs. 93, 108-110).

Antibiotics have been known to protect travelers from diarrhea for several decades. In the 1970s doxycycline (100 mg/d) was shown to prevent 80-90% of the diarrhea that would occur without prophylaxis in travelers to various high-risk areas of Latin America, Africa and Asia(94, 107). Resistance is now common in most of these areas limiting the usefulness of the drug. In the 1980s, trimethoprim-sulfamethoxazole (1 DS/day) was shown to be 80-90% effective and still is in certain areas(93, 108). Again, however, resistance has developed in many high-risk areas(103-105). At the present time, the fluoroquinolones (Ciprofloxacin 500 mg/d, Norfloxacin 400 mg/d or Ofloxacin 200 mg/d) provide the greatest protective efficacy (85-95%) and as yet, no important level of resistance to these drugs has developed(74, 109, 110)(Figure 12). As noted above, the quinolones are not recommended for use in children or during pregnancy.

While chemoprophylaxis (especially with a quinolone) is clearly effective, the indications for antibiotic prophylaxis are controversial. An NIH-sponsored Consensus Development Conference did not endorse routine antibiotic prophylaxis for travelers to high-risk areas for several reasons(91). First, although life-threatening side effects of TMP-SMZ or the quinolones are extremely rare; nevertheless, travelers taking antibiotic prophylaxis risk a potentially fatal reaction to prevent a generally self-limiting disease. Second, promotion of drug resistance by travelers taking prophylactic antibiotics is a theoretical concern, although the impact is likely to be negligible in most developing countries where poor regulation and misuse of antibiotics is a major problem. Finally, and most importantly, empiric therapy begun early in the course of diarrhea can reduce the duration of symptoms to less than 12 h making prophylaxis difficult to justify in most individuals.

Thus, antibiotic prophylaxis should be recommended only for those individual taking a short trip (2 weeks or less) to a high-risk area who cannot afford to be disabled for even a single

day. These individuals, who should represent a small minority of all travelers, should begin the antibiotic on the day of arrival in the high-risk area and continue it for a day or two after leaving the area. Other groups where antibiotic prophylaxis might be considered include the immunocompromised and others debilitated by chronic medical diseases or age in whom travelers diarrhea might be poorly tolerated; however, here again, prompt empiric treatment would seem preferable. For most travelers to high risk areas, advise regarding the selection and preparation of foods and beverages and a filled prescription for loperamide and a fluoroquinolone to be used for empiric therapy of moderate to severe symptoms as described above probably represents the best overall approach at the present time.

New and Emerging Enteropathogens

Campylobacter was first recognized as a cause of diarrhea in the 1970s and is now the most frequently isolated enteropathogen. In the 1980s, *E. coli* O157:H7 emerged as an important enteropathogen, causing both hemorrhagic colitis and hemolytic uremic syndrome, and several protozoans were recognized as common causes of diarrhea in normal and immunocompromised hosts.

The recently described protozoan, cyclospora appears to be a new human pathogen, capable of causing prolonged diarrhea in immunocompetent as well as immunocompromised persons. Since 1986, reports have described the detection of large numbers of "cyanobacteria-like bodies" in the stools of persons with the acute onset of prolonged intermittent watery diarrhea associated with anorexia, fatigue and weight loss(111-113). More recently the organism was identified as a coccidian protozoan (named Cyclospora) that is closely related to Isospora(113). Symptoms usually resolve within a month in immunocompetent persons whereas the organism is associated with intractable diarrhea in persons with AIDS. The organism can be identified on the same modified acid-fast stain used to detect cryptosporidium. A contaminated hospital water supply was the source of infection for several physicians in Chicago(111). Many affected persons have recently traveled to tropical countries or to Eastern Europe.

Several outbreaks of chronic diarrhea associated with raw milk or untreated water have also occurred over the past few years for which no etiologic agent has been identified as yet(114, 115, 116). The first outbreak, which was associated with raw milk consumption, occurred in Brainerd, Minn and produced chronic watery diarrhea, that was acute in onset and associated with urgency and incontinence(114). Symptoms continued for at least 18 months in the majority of affected persons(Figure 14). Presumably, an as yet unidentified infectious agent present in raw milk or contaminated water is capable of causing diarrhea that may persist for years.

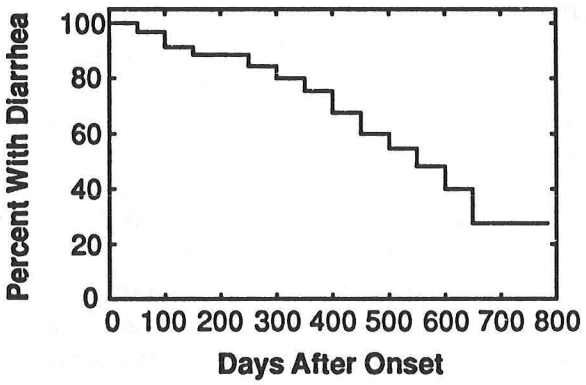

Figure 13. Brainerd diarrhea: percent of patients with diarrhea by day after onset (ref. 114).

Summary and Conclusions

Enteric infections have steadily increased over the last 2-3 decades and transmission is increasingly linked to organisms that colonize the GI tracts of healthy animals and enter the food chain during the slaughter and manufacture of food products of animal origin. Moreover, several previously unrecognized pathogens have emerged, some of which have the potential for serious systemic complications. Enteric infections derived from animal products can be prevented by adequate cooking. Thus, persons at increased risk of acquiring enteric infections or of developing complications attributable to these infections, ie., persons who are immunocompromised or debilitated because of age or chronic medical problems, should not ingest foods from animal sources that have not been adequately cooked. Finally, in evaluating patients with acute GI symptoms, a careful history regarding the ingestion of unpasteurized milk, or raw or undercooked seafood/meat/poultry/eggs may provide important clues to the cause of the illness and, in some cases, could prevent unecessary surgery.

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