Viruses, enteric bacteria and parasites can all produce similar syndromes of acute enteritis, although the pathophysiology and molecular pathogenesis may vary widely. The severity of acute enteritis varies greatly, and only a small fraction of cases undergo medical evaluation. There are over 200,000,000 episodes of acute enteritis annually in the USA, of which approximately 75,000,000 are foodborne. Fewer than 20% of estimated cases have a known etiology. Nearly half of the more than 4,000,000 cases of known foodborne bacterial enteritis are attributed to Campylobacter infections. The FoodNet active population-based surveillance system has demonstrated geographic variation in the incidence of Campylobacter infection, and generally declining incidence since 1996. Campylobacter jejuni infections vary in severity and duration. Antimicrobial therapy, especially if administered early, may hasten clinical resolution by 2–3 days. Therapy is generally restricted to individuals with moderate-to-severe disease and high-risk individuals (underlying immunodeficiency, chronic illness, extremes of age, etc.). Approximately 10–15% of C. jejuni isolates are fluoroquinolone resistant, although most strains are macrolide susceptible. Several acute intra-abdominal as well as extraintestinal complications can occur following C. jejuni enteritis, although bacteremia and metastatic infection are rare, except in high-risk patients. Post-infectious syndromes include post-dysenteric bowel dysfunction, the less frequent but more severe reactive arthritis (1%), and Guillain–Barre syndrome (0.1%). The recent demonstration that antibiotic administration for Escherichia coli O157:H7 hemorrhagic enteritis increases the risk of hemolytic–uremic syndrome 5–10-fold forces reconsideration of empirical broad-spectrum antibiotic therapy for acute hemorrhagic enteritis, and supports narrow-spectrum erythromycin therapy for acute enteritis.

In the USA, most episodes of gastroenteritis are attributable to viral infection, and produce only mild-to-moderate morbidity. Only a small fraction of episodes is evaluated by a physician, and only a subset of these ill individuals undergoes laboratory investigation. Routine diagnostic methodology is restricted to the detection of bacterial and parasitic diseases and only limited causes of viral gastroenteritis (e.g. rotavirus). In 1996, FoodNet (Foodborne Disease Active Surveillance Network) was established; this large-scale CDC-sponsored program monitors the incidence of foodborne enterobacterial disease in seven selected geographic areas which contain roughly 7.5% of the US population. In addition, FoodNet performs population and physician surveys to determine the frequency of physician visits for acute enteritis and the frequency of laboratory investigations to facilitate national incidence estimates. It is estimated that only 2.5–3% of non-dysenteric bacterial enteritides, and only 5% of episodes of bloody diarrhea, are captured by current active or passive surveillance systems in the USA.

EPIDEMIOLOGY OF FOODBORNE ENTERITIS

Despite the uncertainties introduced by such extrapolations, it is no surprise that gastrointestinal infections are exceedingly common. For the USA, 211 million episodes of acute gastroenteritis were estimated to have occurred in 1997, based on FoodNet data as reported by Mead et al. A global weighted estimate of foodborne transmission (36%) was created by pooling estimates of
foodborne transmission and incidence among known enteropathogens, yielding an estimated 76 million foodborne enteritis episodes annually. Among the nearly 39 million enteritis cases of known etiology, bacterial enteritis was responsible for 5.2 million cases (~14%); among these episodes of known etiology, 13.8 million (36%) were foodborne, and 4.2 million were due to bacterial pathogens. Almost half of the total episodes of bacterial enteritis (2.45 million, 47%) and foodborne bacterial episodes (1.96 million) were attributed to *Campylobacter* infections, making *Campylobacter* the most common cause of bacterial enteritis. *Campylobacter jejuni* accounted for nearly all of the specified *Campylobacter* isolates. It is important to note that routine antibiotic-containing selective media and incubation at 42°C are optimized to recover *C. jejuni*, and recovery of less thermophilic *Campylobacter* species is probably quite inefficient. *Salmonella*, *Shigella*, pathogenic *Escherichia coli*, *Yersinia* and *E. coli* O157:H7 accounted for most of the remaining episodes. The rates of severe illness as reflected by hospitalization differed among enteropathogens, so that *Salmonella* infections among hospitalized patients (16,430) exceeded those attributable to *Campylobacter* (13,174).

It is surprising, perhaps, that only 18% of the total gastroenteritis episodes (38.6 million) could be attributed to known pathogens. It is likely that many represented infections by known pathogens that were not recovered through laboratory evaluation, and that many others reflect presently unknown pathogens. Enteroviral infections may have been responsible for a portion of the unclassified cases, but were not tabulated separately.

Additional important epidemiologic aspects of bacterial enteritis have been provided by FoodNet. In 1999, *Campylobacter* was documented in 37% and *Salmonella* in 42% of bacterial enteritis episodes, but *Campylobacter* is considered the most common bacterial infection, due to different rates of investigation of symptomatic illnesses. The incidence of all causes of bacterial enteritis peaked during the summer months, and there was considerable variation in regional incidence observed among the different enteropathogens. There was a generally declining trend in the incidence of *Campylobacter* infections (23.5–17.5/100,000, a 25% decline) during 1996–99. The 2000 incidence increased to 20.1/100,000 among the original five sampling sites, although the incidence among all FoodNet sites was 15.7/100,000. Each enteropathogen possesses distinct epidemiologic features. For example, large outbreaks of *Campylobacter* enteritis are rare, and virtually all cases occur sporadically, even though the minimal infective inoculum for *C. jejuni* is approximately 1000 colony-forming units (CFUs). This inoculum is far smaller than that of the salmonellae, yet it is the latter which are commonly associated with outbreaks. There is very limited person-to-person spread of *Campylobacter* infection, and outbreaks of daycare center *Campylobacter* infections have not been reported in the USA.

**PATHOGENESIS**

*C. jejuni* produces local invasion of the small and large intestine and evokes a local acute inflammatory response. However, *C. jejuni* strains are generally susceptible to lysis by human serum, and, as a result, bacteremia and metastatic infections are quite rare in otherwise normal hosts. Bacteremia occurs in fewer than 1% of otherwise healthy patients with *C. jejuni* enteritis (although the blood culture rate in patients with acute enteritis is believed to be low). *Campylobacter* enteritis evokes a local and systemic antibody response. The humoral immune response is believed to be protective in individuals who are repetitively infected, such as individuals residing in underdeveloped regions with high endemic rates of *Campylobacter* infection. Both cellular and humoral immunity appear to be important host defense mechanisms, since patients with hypogammaglobulinemia and HIV-infected individuals with advanced immunodeficiency are at risk of developing severe refractory or chronic relapsing *Campylobacter* enteritis. Epidemiologic data obtained early in the AIDS era suggested that HIV-infected men had a 40-fold increased risk for *Campylobacter* infection, and a far greater rate of bacteremia (16%) in the setting of acute enteritis, but more recent data cast doubt on these early findings. Case reports of severe enteritis refractory to medical therapy, and even acute septic shock complicating *Campylobacter* enteritis in HIV-infected individuals, have been published, but the poor outcome seemed to correlate with advanced disease reflected by CD4+ lymphocyte depletion and marked immunosuppression, rather than with HIV infection per se. In such individuals, long-term antibiotic administration to control chronic symptoms has been associated with the appearance of antibiotic-resistant *C. jejuni*. Sequential courses of antibiotic therapy led to multiresistant strains and poor clinical outcomes. The use of macrolides or rifabutin as prophylaxis against *Mycobacterium avium-intracellulare* infections in individuals with advanced HIV disease may also offer protection against *Campylobacter* infection and reduce the severity or chronicity of enteritis in these patients. Hypogammaglobulinemic patients with refractory *Campylobacter* infection have benefited from immunoglobulin replacement therapy in addition to antibiotics.

**CLINICAL FEATURES**

The features of *C. jejuni* enteritis are largely indistinguishable from those of other forms of acute bacterial enteritis. After an incubation period of several days (usually 2–5 days, but may range from 1 to >7 days, perhaps inversely related to inoculum size), a brief prodrome with influenza-like symptoms of fever, myalgias and headache may appear, followed by prominent symptoms of gastroenteritis. Fever, cramping
abdominal pain and diarrhea supervene. The severity of diarrhea ranges from mild to severe (8–15 stools on the worst day), and may be accompanied by dysenteric symptoms of bloody diarrhea in nearly half of patients, and tenesmus in roughly one-quarter. Emesis is also seen in one-quarter of patients. Stool examination confirms fecal blood in the majority of patients, and demonstrates the presence of fecal leukocytes in over 75% of cases. Symptoms usually wane in less than a week, although symptoms may persist (usually for less than 2 weeks) in a fraction of patients. Fecal shedding of *C. jejuni* may persist for several weeks, despite uncomplicated clinical recovery. Although most infected individuals demonstrate classic manifestations of bacterial enteritis, asymptomatic infections have been documented in as many as 25% of individuals investigated during an outbreak. In occasional individuals, systemic complaints and abdominal pain are not accompanied by diarrhea, and patients may undergo laparotomy for possible appendicitis.

**ACUTE COMPLICATIONS**

Although the vast majority of *C. jejuni* enteritis episodes resolve with supportive care, complications are occasionally seen. These have been classified by Allos and Blaser as intra-abdominal (gastrointestinal hemorrhage, mesenteric lymphadenitis, appendicitis, cholecystitis, toxic megacolon, pseudomembranous colitis, pancreatitis, peritonitis, intestinal obstruction) and extraintestinal. The extraintestinal complications represent metastatic infections following *C. jejuni* bacteremia. There have been case reports describing a variety of parenchymal infections, including meningitis, septic arthritis, septic abortion, endocarditis, bursitis, and cellulitis. In many of these instances, the patient was immunocompromised or was chronically ill. In contrast to the predominantly local sequelae of *C. jejuni* infections, *C. fetus* resists the bactericidal activity of serum, and is associated with a higher rate of bacteremia complicating enteritis, and a higher rate of metastatic infections, especially in conjunction with underlying immunodeficiency.

**LATE COMPLICATIONS**

Persistent symptoms of abdominal discomfort and alterations in bowel pattern, including passage of mucus, bloating, urgency, and episodic diarrheal movements lasting 3 to >12 months, have been reported in up to 25% of patients with confirmed bacterial enteritis. This has been termed post-dysenteric irritable bowel syndrome, and has been studied in patients recovering from *Campylobacter* enteritis. Presumably, this is a sequela of more severe acute disease, since mildly ill individuals are unlikely to seek medical care or undergo stool culture. Rectal biopsies in patients with continued gastrointestinal complaints demonstrated a variety of histopathologic abnormalities, including increased enteroendocrine cells, increased intraepithelial and lamina propria CD3+ lymphocytes, and reduced macrophages; in addition, abnormal gut permeability was present. Symptoms wane in most patients, but on occasion can persist for extended intervals.

Noninfectious reactive arthritis is observed in approximately 1% of individuals recovering from *Campylobacter* enteritis; a similar syndrome of reactive arthritis follows enteritis caused by a variety of bacterial enteropathogens. Asymmetric oligoarticular or monoarticular arthritis, predominantly involving the lower extremities or the small joints of the hands, develops within 1–6 weeks following an episode of acute enteritis. The risk of this complication is increased among individuals bearing the HLA-B27 allele; up to 60% of individuals with post-dysentery reactive arthritis are HLA-B27 positive. The course of symptomatic arthritis is highly variable, and may be self-limited over a course of weeks to months, recurrent, or occasionally persistent, with a waxing and waning course. The severity of acute *C. jejuni* enteritis does not appear to predict the severity of reactive arthritis, and antibiotic therapy has not been shown to reduce the risk or severity of this complication. The long-term prognosis is favorable, despite the short-term disability.

Approximately 0.05–0.1% of patients recovering from *Campylobacter* enteritis are at risk of developing Guillain–Barre syndrome, an acute autoimmune polyradiculoneuropathy which presents with areflexic flaccid paralysis and variable sensory abnormalities. Different subtypes of the syndrome are associated with neuronal demyelination or axonal degeneration. *Campylobacter* infection is now recognized to be the most common precipitant of Guillain–Barre syndrome, accounting for roughly 25–40% of cases, and seems to be preferentially associated with the more severe axonal degenerative process. Ascending motor weakness is generally rapidly progressive, and is often severe, mandating assisted ventilation, although ultimately favorable recoveries are observed in 85% of patients. Selected serotypes of *C. jejuni* (e.g. O:19) appear to be particularly associated with the risk of subsequent Guillain–Barre syndrome. Specifc glycolipid moieties on the *Campylobacter* lipopolysaccharide closely resemble normal human gangliosides, and it is postulated that enteric infection triggers the production of cross-reactive antibodies which then attack neural structures.

**MANAGEMENT**

The foundation of management of acute enteritis is supportive care. Oral rehydration, using clear liquids for mild symptoms and oral rehydration solution for moderate-to-severe symptoms, if necessary, is usually successful in preventing or reversing evolving dehydration. Anti-motility agents are generally contraindicated if moderate or severe symptoms are present. The role of antibiotic therapy in the treatment of acute
enteritis remains controversial, since most patients with mild disease improve eventuantly. Consideration of antibiotic therapy in the empirical management of bacterial enteritis is complicated by the contrasting outcomes of such therapy, depending on the enteropathogen. The course of shigellosis is shortened by antibiotic therapy, the course of Campylobacter infection is probably shortened as well, but controversy exists in this area. However, antibiotic therapy is not believed to improve the course of Salmonella gastroenteritis. Rather, antibiotic therapy has been associated with prolonged stool carriage of Salmonella, and an increased risk of relapsing infection. In the case of Shiga toxin-producing E. coli, antibiotic therapy is believed to increase the risk of subsequent hemolytic-uremic syndrome. Empirical broad-spectrum antibiotic therapy for acute diarrhea became popular in the management of travelers’ diarrhea, where most infections are non-dysenteric in nature, and the majority of episodes are attributed to enterotoxigenic E. coli. Recent recommendations mention azithromycin for empirical therapy of travelers’ diarrhea in areas where there may be an increased risk of fluoroquinolone-resistant Campylobacter infection. However, empirical therapy for sporadic community-acquired enteritis, intended to treat a distinct panel of potential enteropathogens with differing likelihoods of response and definite potential therapy-associated risks, is more problematic. Empirical antibiotic therapy is considered for patients with moderate or severe disease, reflected by persistence of symptoms, presence of dysenteric symptoms and bloody diarrhea, and systemic features of severe illness. A lower threshold for therapy is appropriate for compromised individuals, particularly immunocompromised patients, debilitated and chronically ill individuals, and those at the extremes of age.

**TO TREAT OR NOT TO TREAT?**

Two strategies for antibiotic use may be considered: (1) early empirical antibiotic therapy administered at the time of initial presentation; or (2) specific therapy prescribed only after the recovery and identification (and susceptibility testing) of bacterial enteropathogens. Unfortunately, the time required for an etiologic diagnosis of acute enteritis is relatively long when compared to the natural history of most episodes. In the setting of mild or moderate illness, only a very small fraction of patients even undergo laboratory investigation. Such evaluation leads to specific antimicrobial therapy in an even smaller subset of patients, since many individuals have improved before etiologic information is available. Moreover, antibiotic susceptibility testing of isolated enteropathogens adds to this delay, and may not be routinely available, particularly for C. jejuni. Several clinical studies have suggested that empirical fluoroquinolone therapy administered to patients with sporadic enteritis shortens the duration of acute diarrhea by 2–3 days for all bacterial enteropathogens, including Campylobacter. However, some authors suggest that antibiotic therapy administered after 3 days of symptoms is not likely to alter the clinical course of resolution significantly. The presence of severe or prolonged symptoms or bloody diarrhea might suggest the need for early therapy even in normal hosts (see caveats below). It is reasonable to consider empirical erythromycin therapy directed against C. jejuni in the setting of moderate-to-severe or refractory non-hemorrhagic enteritis. This probably represents less than half of the patients who seek medical attention for acute enteritis, i.e. ≥1% of patients with C. jejuni infection based on FoodNet extrapolations. The logic behind such narrow-spectrum therapy is discussed below. Antibiotic therapy should be considered strongly in pregnant mothers (avoiding fluoroquinolones), and in debilitated and immunocompromised individuals (particularly those with hypogammaglobulinemia or HIV infection). In these high-risk individuals, initial combination therapy with a macrolide as well as a fluoroquinolone might be considered, with continued therapy guided by formal drug susceptibility testing. In immunocompromised individuals with bacteremia or metastatic infection, imipenem and/or aminoglycoside therapy may be considered in cases of macrolide or fluoroquinolone resistance or initial failure.

**BROAD-SPECTRUM OR NARROW-SPECTRUM THERAPY?**

Decisions to administer early empirical antibiotic therapy are confounded by the evolving resistance patterns of the commonly encountered bacterial enteropathogens. Over the past 15 years, fluoroquinolones have been popular for the empirical therapy of acute bacterial enteritis because of their broad efficacy against Salmonella, Shigella, Campylobacter and E. coli isolates. However, the demonstration that many enteropathogens, whether acquired domestically or imported, may possess fluoroquinolone resistance has complicated the situation. In the USA, 10–15% of domestically acquired C. jejuni isolates are fluoroquinolone resistant. Imported isolates often have far greater rates of resistance, and thus careful epidemiologic information regarding recent travel exposure or fluoroquinolone use should be explored before therapy is selected. Nevertheless, in the absence of risk factors associated with an increased resistance rate, fluoroquinolone therapy remains highly active against most enteropathogens in this country. In contrast to the trend toward increased fluoroquinolone resistance, the efficacy of macrolide therapy for C. jejuni infections has remained robust. Erythromycin, for example, remains an effective narrow-spectrum therapy against C. jejuni infections in severely ill or immunocompromised individuals, with erythromycin resistance rates generally below 5% in the USA. Historically, the narrow spectrum of action against C. jejuni and the
higher rate of gastrointestinal side effects associated with erythromycin have restricted its use in the empirical treatment of acute enteritis as well as for the specific therapy of mild or moderate C. jejuni enteritis. As will be discussed below, the very selectivity of erythromycin for C. jejuni infections may be considered an advantage rather than a limitation. Nevertheless, the availability of newer, broad-spectrum macrolides such as azithromycin, which are better tolerated and possess significant activity against a broad range of enteropathogens, has provided an alternative choice for initial broad-spectrum empirical therapy and for therapy of proven C. jejuni infections in erythromycin-intolerant individuals.

PRIMUM NON OCCERE: THE MANAGEMENT OF HEMORRHAGIC DYSENTERY

An additional dilemma confronts the clinician considering empirical antibiotic therapy for severe cases of enteritis which present as hemorrhagic dysentery. Both Campylobacter and enterohemorrhagic E. coli (O157:H7 as well as Shiga toxin-expressing non-O157 strains) may lead to hemorrhagic colitis, and cannot be readily distinguished on clinical grounds. Although early antibiotic therapy may hasten recovery from C. jejuni enteritis, antibiotic therapy is not thought to alter the course of hemorrhagic E. coli infections. E. coli O157:H7 infections in children are associated with a 10–15% risk of developing the hemolytic–uremic syndrome, in which hemolytic anemia, thrombocytopenia and renal failure develop shortly after the onset of diarrhea, and this risk is enhanced (5–10-fold) when antibiotic therapy is administered.3 The hemolytic–uremic syndrome is an important cause of acute renal failure, leading to death in 3–5% of patients and chronic renal failure among some survivors. The syndrome of thrombotic thrombocytopenic purpura, which resembles hemolytic–uremic syndrome but has more prominent neurologic findings, can occur in adult patients following E. coli O157:H7 infection.

These post-infectious syndromes are thought to occur following the systemic release of Shiga-like toxin expressed by an integrated bacteriophage during the course of hemorrhagic enteritis. The risk of developing these complications seems to correlate with the severity of the initial hemorrhagic enteritis. Paradoxically, antibiotic therapy appears to promote bacteriophage production and expression of the bacteriophage toxin. Trimethoprim, fluoroquinolones and possibly even broad-spectrum macrolide agents such as azithromycin are potential inducers of Shiga toxin production. Thus, individuals with more severe disease (e.g. with leukocytosis and earlier stool recovery of E. coli O157:H7), especially children and older adults, are at greatest risk for the development of hemolytic–uremic syndrome or thrombotic thrombocytopenic purpura. However, these are the same patients whose severe hemorrhagic colitis might prompt early empirical therapy, in the hope of ameliorating symptoms. These considerations are not merely theoretical concerns; the number of fatalities attributable to Shiga-toxin-expressing E. coli is comparable to that for Campylobacter. Current recommendations urge caution when considering empirical antibiotic therapy for acute enteritis. Shiga-like toxin is also associated with enterohemorrhagic E. coli infections in non-O157:H7 strains, and can produce hemolytic–uremic syndrome and thrombotic thrombocytopenic purpura. This creates additional diagnostic uncertainty, since routine screening for these strains is not undertaken. Thus, antibiotic therapy for the treatment of most hemorrhagic enteritis syndromes should be restricted to erythromycin to treat putative C. jejuni infection, or should be delayed until the positive isolation of C. jejuni, Shigella, or less commonly observed enteropathogens. This approach would specifically spare individuals with salmonellosis or E. coli O157:H7 infection, and perhaps all patients with hemorrhagic colitis whose stool cultures fail to yield identifiable enteropathogens, from broad-spectrum agents which might trigger hemolytic–uremic syndrome.

REFERENCES


**PANEL DISCUSSION**

O. Radostis: I am interested in the disease pyramid, and what it implies is that there are many cases that aren't very severe. I am also hearing that, when you get an infection, it will persist for a while, and you will be shedding organisms for some period after you have had the infection. I would submit that this might be, apart from anything else, a reasonable human reservoir. It might persist for long enough to jump from person to person, and it is probably still worth looking at.

M. Pasterнак: As was mentioned earlier, I can say that Campylobacter outbreaks are not common. The data on person-to-person spread have been hard to support. Usually, daycare centers answer that question for us, and there haven't been many daycare center cases. That there is a huge pyramid out there goes without saying. There are some remarkable FoodNet observations that I didn't mention. It is estimated that only 5% of patients with hemorrhagic enteritis ever seek medical care. Nineteen of 20 cases of bloody diarrhea at home are not reported to a physician. Of patients with suspected Campylobacter jejuni disease, only one in 38 sees a physician. We know there is a huge amount of disease that we are not detecting.

C. Hofacre: Do you know what percentage of your patients' stools may have mixed infection, say Shigella...
and *Campylobacter*, so that one ends up being cultured but is not necessarily the etiologic agent?

**M. Pasternack**: I think that there are situations where that has occurred. It is almost always in an outbreak situation, where dually contaminated food products have been available at a large gathering, and in returning travelers who were dually infected, having eaten food in another country. In terms of sporadic disease, I would say that it is quite rare to recover two bona fide enteropathogens from a single clinical illness. In a large series, usually a few per cent will turn out to be dually infected. Cases usually come from food outbreaks.

**C. Hofacre**: How often would anyone look?

**M. Pasternack**: Routine stool cultures should identify the vast majority of dual infections through the use of conventional selective media. Sporadic dually infected individuals would not be subjected to stool testing in most instances, since only a few per cent of individuals with enteritis seek medical evaluation and stool testing. In epidemic situations, dual infections can be identified more readily and investigated by the CDC.

**E. Gonder**: A number of times, you referred to waiting for a susceptibility test for *Campylobacter*, and my question is, how much do you rely on the laboratory report? I think that, probably, most clinical laboratories in the USA couldn’t do the right test unless they were using the E test. I always had the impression that even the E test might underestimate resistance. Unless a laboratory was using the E test, I wouldn’t have much confidence in their results.

**M. Pasternack**: This is a good point; I suppose that I am lucky to work in a tertiary care hospital where I trust the bacteriology laboratory. Their analytical skills are of very high quality, and they are very prompt in providing us with information. You are absolutely right that, in many clinical situations, a patient provides a stool sample, and at the end of the day the sample is sent to a regional clinical laboratory, making the turn-around time too long for the analysis to be clinically useful.

**C. Thornsberry**: I wouldn’t want to rely on a disk diffusion test.

**M. Pasternack**: I accept that point.