Infectious Diarrhea: New Pathogens and New Challenges in Developed and Developing Areas

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(See the article by Nataro et al. on pages 402–7 and the article by Brooks et al. on pages 393–401)

Diarrhoeal illness remains one of the leading causes of morbidity and mortality worldwide, despite ongoing progress in our basic understanding of its epidemiology, pathogenesis, and treatment. In developing areas, where access to safe drinking water and sewage disposal are often limited or even absent, infectious diarrhoea is a major cause of childhood mortality, with an estimated 1.9 and 5.6 million deaths among children globally per year (i.e., >5000 and 15,000 children dying each day) because of diarrhoea and malnutrition, respectively [1]. Beyond this, however, are the underrecognised long-term effects of frequent early childhood diarrhoeal episodes, which include permanent shortfalls in physical and cognitive development, with decrements of up to 8 cm in growth, 10 intelligent quotient points, and 12 months of schooling attributable to early childhood diarrhoea and enteric parasitic infection [2–5].

In developed countries, where modern sanitation practices are commonplace, the burden of early childhood diarrhoea has been dramatically reduced. Nonetheless, recent large outbreaks of infectious diarrhoea due to Cryptosporidium species, enterohemorrhagic Escherichia coli, and Clostridium difficile underscore the fact that major intestinal infections lurk nearby even in the cleanest environments. Moreover, sporadic diarrhoeal illness remains important in developed countries, with 1–2 episodes per person per year, second only to the common cold as the most common infectious illness.

Two articles presented in this issue of Clinical Infectious Diseases underscore both the similarities and differences between diarrhoeal illnesses in developed and developing countries, with some surprising findings. The first is an article by Nataro et al. [6] that reports findings from prospective surveillance for causes of diarrhoeal illness in Baltimore, Maryland, and New Haven, Connecticut. The study population included all patients with a chief complaint of diarrhoea who presented to emergency departments or outpatient clinics at 2 large academic centers. Control subjects without diarrhoea were simultaneously recruited and included healthy volunteers and patients presenting to the same clinics with unrelated complaints. Patients were interviewed to identify symptoms of intestinal illness (including fever, vomiting, abdominal pain, and myalgias) and epidemiologic and historical data (including recent travel, antibiotic use, sick contacts, age, and immunodeficiency status). Stool samples were analyzed by PCR gene probes for all major pathogens, including viruses, Clostridium difficile, and diarrheagenic E. coli (including enterotoxigenic, enteropathogenic [either typical or atypical, depending on the presence of the EPEC adherence factor adherence plasmid], enteroaggregative [EAEC], and enterohemorrhagic E. coli [positive for both eae and Shiga toxin]), and non-E. coli bacterial pathogens. The prevalence of each pathogen in case patients versus control subjects was used to generate a pathogenicity index (the percentage of patients with the pathogen divided by the percentage of control subjects with the pathogen) that was critical for the establishment of a pathogenic role for emerging infectious agents. Consistent identification of an organism in significantly more patients than control subjects does not definitively prove it is a pathogen (it could be a commensal that coexists with the true pathogen, for example), but along with other studies (such as volunteer administration trials, therapy trials, and basic pathogenesis research), it helps to satisfy Koch’s postulates. Con-
versely, consistently finding a putative pathogen in healthy control subjects as frequently as in patients raises questions about its pathogenicity or about the ways in which it is detected and analyzed.

Several interesting findings emerged from the Baltimore and New Haven data [6]. First, the most prevalent pathogens identified were viruses (particularly, rotavirus and norovirus). In contrast, the “typical” pathogens Campylobacter and Salmonella species were only found in 2.9% and 2% of case patients, respectively (although, as expected, both were found in significantly more case patients than control subjects). Clostridium difficile toxins were only found in 1.9% of case patients, despite the fact that ~20% of patients had taken antibiotics within the last month. The major finding discussed in this article, however, was the identification of EAEC in 4.5% of case patients, making it the leading bacterial cause of diarrhea in this study. Moreover, the overall pathogenicity index for EAEC was 2.65, which was higher than for any of the other diarrheagenic E. coli pathotypes.

EAEC was first identified in 1987 on the basis of a unique pattern of aggregative adherence (AA) to mammalian cells in monolayer culture [7]. AA is associated with the expression of AA fimbriae, which are carried on the large AA virulence plasmid. Early studies of EAEC relied either on this single phenotype or on the demonstration of part of the AA plasmid that was not necessarily associated with pathogenicity, creating some difficulty in establishing the role of EAEC as a true pathogen. Nonetheless, repeated identification of EAEC in more case patients than control subjects in a majority of studies, the demonstration of several large outbreaks, and the development of diarrhea in human volunteers who received certain EAEC strains have combined to establish a strong case that EAEC causes human diarrhea illness.

The predominant burden of EAEC infection is in developing areas, where it is statistically associated with diarrheal illness in young children and has a prediction to cause persistent illness (lasting >2 weeks) [8]. EAEC has also been reported to cause chronic diarrhea in patients with AIDS [9]. In contrast, EAEC infection in developed countries was previously seen primarily in travelers to tropical areas, where it produced a self-limited illness indistinguishable from that caused by enterotoxigenic E. coli. One exception to this was a study by Tompkins et al. [10], which found EAEC as a common cause of sporadic diarrheal illness in the United Kingdom; another exception was a large outbreak of illness caused by strain 101-1 (OUT:H10) in Japan [11]. Interestingly, the incidence of EAEC infection in case patients and control subjects in the UK study was almost identical to that reported by Nataro et al [6], supporting the validity of both studies.

As in most previous studies, the studies by Brooks et al. [12] and Nataro et al. [6] find no clinical features that characterize EAEC infection; most patients presented with watery diarrhea without fever or blood. One interesting finding in persons with endemic childhood diarrhea and in travelers to Mexico was the presence of fecal lactoferrin in many cases of EAEC infection, as has been seen in children in Brazil, and a novel EAEC flagellin that induces IL-8 production in vitro, all suggesting that there is an inflammatory component to EAEC infection [13–15] that may distinguish it from enterotoxigenic E. coli infection or enteropathogenic E. coli infection. Indeed, only travelers with the proinflammatory allele in the IL-8 promoter region developed diarrhea due to their EAEC infections [13]. Unfortunately, fecal lactoferrin or cytokines were not measured in this study, so conclusions cannot be drawn regarding the degree of inflammation in endemic EAEC infection in the United States.

The second article, by Brooks et al. [12], presents a situation that is the extreme opposite of that presented in the article by Nataro et al. [6]. Brooks and colleagues analyzed a population living in some of the worst health conditions imaginable, with 88% lacking access to potable water and 26% lacking any sewage facilities whatsoever, as well as a 15% prevalence of HIV infection among young adults. The burden of diarrheal illness in this population is great, although the case incidence in this particular study was not reported. In this study, although Shigella species were more commonly isolated in older children and adults, Campylobacter species and diarrheagenic E. coli (predominantly EAEC) were the most frequently isolated pathogens in children <5 years old, and the incidence of infection with these pathogens decreased substantially thereafter, suggesting that common early childhood infections with these pathogens may provide some protective immunity. In contrast, this decrease in EAEC infection with age was not seen in the United States, possibly because fewer infections means less protective immunity.

The similar designs of the studies of Nataro et al. [6] and Brooks et al. [12] give them shared advantages, as well as potential sources of bias. The largest bias of concern is referral bias, because both studies relied on self-referred patients. Because people with mild or short-lived illness are less likely to present to clinics, the studies would be expected to preferentially target patients with unusual features, such as severe illness, dehydration, bloody diarrhea, or, perhaps, exposure to known sick contacts (because a second ill person in a family may feel more inclined to present for treatment because of concern about a family outbreak). The effects of this bias are discussed in detail in the article by Brooks et al. [12] as a possible reason why Shigella species (typically a childhood pathogen) were identified more commonly in adults in their study, whereas diarrheagenic E. coli and Campylobacter species were seen more commonly in children. They raise the reasonable hypothesis that watery, dehydrating illness (such as that commonly seen with diarrheagenic E. coli or Campylobacter species) is more likely to be considered...
serious when it occurs in children, who are then brought in for care by their parents or caregivers; whereas bloody diarrhea, such as that which occurs in shigellosis, is considered an indication for medical treatment in all age groups. This would tend to lead to overrepresentation of Shigella species in the group as a whole, which would explain its presence as the dominant pathogen (found in 16% of all illnesses). With regard to the US study [6], referral bias would also be likely to cause overrepresentation of illnesses with severe symptoms, which makes the overall incidence of EAEC infection all the more significant (because it still outranked infection due to infection all the more significant because of all illnesses). With regard to the US whole, which would explain its presence and monella and Campylobacter species).

The biggest shared advantage of the 2 studies was their careful design, with defined hypotheses, prospective surveillance, and established microbiological techniques. This strengthens the validity of the conclusions about what pathogens cause diarrhea among patients in the 2 populations who refer themselves for treatment with a complaint of diarrhea. The inclusion of a control group in the study by Nataro et al. [6] gives the added advantage of providing answers to questions about the relative association of different pathogens with diarrheal illness versus asymptomatic colonization. Short of a population-based prospective surveillance study (which would collect samples from a pre-defined group of subjects over time in times of health and illness), this is probably the best way to address these questions.

Although a surprising 20.5% of US patients with non-EAEC infection had taken antibiotics in the preceding month, and although 29% of persons with diarrhea had done so in Kenya, fully 67% of patients in Kenya used an antimicrobial to treat their diarrheal illness; however, in 53% of cases tested, the pathogen causing their infection was resistant to the particular antimicrobial. Furthermore, the frequency of antimicrobial resistance of Shigella and nontyphoidal Salmonella isolates (which has persisted since the earlier report by this group from 1997 [16]) directly correlated with the percentage of patients prescribed the drug. Therefore, most patients are receiving inappropriate antimicrobials that appear to drive antimicrobial resistance, a growing problem in areas where widespread, indiscriminate antimicrobial use is common.

Therefore, the tools to detect emerging pathogens, such as EAEC, as well as mechanisms of antimicrobial resistance, have evolved just in time to monitor the growing concerns they present. We now must apply these new tools where they are most needed, not only to drive improved water, sanitation, and hygiene standards here and abroad, but also to greatly improve carefully targeted therapy where it is most effective and to reduce the widespread, indiscriminate use of antimicrobials that appears to drive increasingly troublesome resistance.

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