may occur. Upon colonization of the small bowel, symptoms develop after a brief incubation period (1 or 2 days). Initial localized adherence via bundle-forming pili leads to a characteristic effacement of microvilli, with the formation of cuplike, actin-rich pedestals mediated by factors in the LEE. Diarrhea production is a complex and regulated process in which host cell modulation by a type III secretion system plays an important role. Strains lacking bundle-forming pili have been categorized as atypical EPEC (aEPEC); increasing data support a role for these strains as intestinal pathogens. Diarrheal stool often contains mucus but not blood. Although EPEC diarrhea is usually self-limited (lasting 5–15 days), it may persist for weeks.

ENTEROINVASIVE E. COLI EIEC, a relatively uncommon cause of diarrhea, is rarely identified in the United States, although a few food-related outbreaks have been described. In developing countries, sporadic disease is infrequently recognized in children and travelers. EIEC shares many genetic and clinical features with *Shigella*, both of which evolved from a common ancestor. However, unlike *Shigella*, EIEC produces disease only with a large inoculum (10^8–10^{10} CFU), with onset generally following an incubation period of 1–3 days. Initially, enterotoxins are believed to induce secretory small-bowel diarrhea. Subsequently, colonization and invasion of the colonic mucosa, followed by replication therein and cell-to-cell spread, result in the development of inflammatory colitis characterized by fever, abdominal pain, tenesmus, and scant stool containing mucus, blood, and inflammatory cells. Symptoms are usually self-limited (7–10 days).

ENTEROAGGREGATIVE AND DIFFUSELY ADHERENT E. COLI EAEC has been described primarily in developing countries and in young children. However, recent studies indicate that it may be a relatively common cause of diarrhea in all age groups in industrialized countries. EAEC has also been recognized increasingly as an important cause of traveler's diarrhea. It is highly adapted to humans, the probable reservoir. A large inoculum is required for infection, which usually manifests as watery and sometimes persistent diarrhea in healthy, malnourished, and HIV-infected hosts. In vitro, the organisms exhibit a diffuse or "stacked-brick" pattern of adherence to small-intestine epithelial cells. Virulence factors that probably are necessary for disease are regulated in part by the transcriptional activator AggR and include the aggregative adherence fimbriae (AAF/I-III); the Hda adhesin; the mucinase Pic; the enterotoxins Pet, EAST-1, ShET1, and HlyE; and dispersin, an antiaggregation protein that promotes mucosal spread. Some strains of DAEC are capable of causing diarrheal disease, primarily in children 2–6 years of age in some developing countries, and may perhaps cause traveler's diarrhea. The Afa/Dr adhesins may contribute to the pathogenesis of such infections.

Diagnosis A practical approach to the evaluation of diarrhea is to distinguish noninflammatory from inflammatory cases; the latter is suggested by grossly bloody or mucoid stool or a positive test for fecal leukocytes (Chap. 160). ETEC, EPEC, and DAEC cause noninflammatory diarrhea and are uncommon in the United States; in this country, the incidence of EAEC infection, which also causes noninflammatory diarrhea, may be underrecognized. The diagnosis of these infections requires specialized assays (e.g., polymerase chain reaction–based tests for pathotype-specific genes) that are not routinely available and are rarely needed because the diseases are self-limited. ETEC causes the majority and EAEC a minority of cases of noninflammatory traveler's diarrhea. Definitive diagnosis generally is not necessary. Empirical antimicrobial (or symptom-based) treatment, along with rehydration therapy, is a reasonable approach. If diarrhea persists for >10 days despite treatment, *Giardia* or *Cryptosporidium* (or, in immunocompromised hosts, certain other microbial agents) should be sought. The diagnosis of infection with EIEC, a rare cause of inflammatory diarrhea in the United States, also requires specialized assays. The CDC now recommends that all patients with community-acquired diarrhea, whether inflammatory or not, be evaluated for STEC/EHEC/STEAEC infection by simultaneous culture (which is important for outbreak detection and control) and assay for the detection of Shiga toxin or its associated genes. The reasons for this recommendation are that bloody stool is not always present and detection of fecal white blood cells is not optimally sensitive for the diagnosis of STEC/EHEC/STEAEC infection. The use of both tests increases the rate of identification of infection over rates obtained with either test alone. O157 STEC/EHEC may be identified via culture by screening for *E. coli* strains that do not ferment sorbitol, with subsequent serotyping and testing for Shiga toxin. Selective or screening media are not available for the culture of non-O157 strains. Detection of Shiga toxins or toxin genes via DNA-based, enzyme-linked immunosorbent, and cytotoxicity assays offers the advantages of rapidity plus detection of non-O157 STEC/EHEC/STEAEC strains. Specimens positive for toxin but culture-negative for O157 should be forwarded to the local or state public health laboratory.

TREATMENT INTESTINAL *E. COLI* INFECTIONS

(See also Chap. 128) The mainstay of treatment for all diarrheal syndromes is replacement of water and electrolytes. This measure is especially important for STEC/EHEC/STEAEC infection because appropriate volume expansion may decrease renal damage and improve outcome. The use of prophylactic antibiotics to prevent traveler's diarrhea generally should be discouraged, especially in light of high rates of antimicrobial resistance. However, in selected patients (e.g., those who cannot afford a brief illness or are predisposed to infection), the use of rifaximin, which is nonabsorbable and is well tolerated, is reasonable. When stools are free of mucus and blood, early patient-initiated treatment of traveler's diarrhea with a fluoroquinolone or azithromycin decreases the duration of illness, and the use of loperamide may halt symptoms within a few hours. Although dysentery caused by EIEC is self-limited, treatment hastens the resolution of symptoms, particularly in severe cases. In contrast, antimicrobial therapy for STEC/EHEC/STEAEC infection (the presence of which is suggested by grossly bloody diarrhea without fever) should be avoided because antibiotics may increase the incidence of HUS (possibly via increased production/release of Stx). The role of plasmapheresis and inhibition of C5 (eculizumab) in the treatment of HUS is unresolved.

KLEBSIELLA INFECTIONS

K. pneumoniae is the most important *Klebsiella* species from a medical standpoint, causing community-acquired, LTCF-acquired, and nosocomial infections. *K. oxytoca* is primarily a pathogen in LTCF and hospital settings. *Klebsiella* species are broadly prevalent in the environment and colonize mucosal surfaces of mammals. In healthy humans, the prevalence of *K. pneumoniae* colonization is 5–35% in the colon and 1–5% in the oropharynx; the skin is usually colonized only transiently. Person-to-person spread is the predominant mode of acquisition. Most *Klebsiella* infections in Western countries are caused by "classic" *K. pneumoniae* (cKP) and occur in hospitals and LTCFs. The most common clinical syndromes due to cKP are pneumonia, UTI, abdominal infection, intravascular device infection, surgical site infection, soft tissue infection, and subsequent bacteremia. cKP strains have gained notoriety because their propensity for acquiring antimicrobial resistance determinants makes treatment challenging. Clonal group ST258, many members of which produce the KPC carbapenemase, is undergoing international dissemination. The spread of NDM-1 carbapenemase-producing strains from India in association with medical tourism has captured the attention of physicians and the lay press.

cKP strains appear to be phenotypically and clinically distinct from hypervirulent *K. pneumoniae* (hvKP), an emerging variant that was first recognized in Taiwan in 1986. Although hvKP infections have occurred globally in all ethnic groups, the majority have been reported in the Asian Pacific Rim. This concentration of cases raises the question of whether a geo-specific distribution of the organism or increased susceptibility of Asian hosts is responsible. In contrast to the usual health care–associated venue for cKP infections in the West, hvKP causes serious life- and organ-threatening infections in younger, healthy individuals from the community and can spread metastatically