Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

HHS Public Access

Author manuscript

Discov Med. Author manuscript; available in PMC 2016 February 02.

Published in final edited form as:

Discov Med. 2012 August ; 14(75): 105–113.

Clostridium difficile: An Emerging Pathogen in Children

Natalia Khalaf[1,†], **Jonathan Crews**[1,†], **Herbert L. DuPont**[1,2,3,4], and **Hoonmo L. Koo**[1,2]

[1]Baylor College of Medicine, Houston, Texas

[2]University of Texas – Houston School of Public Health, Houston, Texas

[3]University of Texas – Houston Medical School, Houston, Texas

[4]St. Luke's Episcopal Hospital, Houston, Texas

Abstract

Clostridium difficile is emerging as an important enteric pathogen in children. Historically considered as an asymptomatic colonizer of the gastrointestinal tract, *C. difficile* infection (CDI) has not been well-studied in pediatric populations. While asymptomatic carriage remains high among infants, recent epidemiological surveillance has demonstrated a rise in the prevalence of CDI in both healthcare and community settings, particularly in children 1-5 years of age. The pathogenesis of pediatric CDI, including the factors underlying the absence of toxin-mediated effects among colonized infants, remains ill-defined. Studies suggest that traditional adult CDI risk factors such as antibiotic and healthcare exposure may not be as important for children who acquire CDI in the community. As recognition of the significant impact of CDI in children increases, the pressing need for deepening our understanding of this disease and identifying optimal therapeutic and preventative strategies is becoming apparent.

Introduction

Clostridium difficile is emerging as an important cause of healthcare- and community-associated diarrhea in children. *C. difficile* infection (CDI) is estimated to cost the United States health care system between 1.1 (Kyne et al., 2002) to 3.2 billion dollars annually (O'Brien et al., 2007). Originally described as a commensal organism in infants (<1 year of age) (Hall & O'Toole, 1935), *C. difficile* is considered primarily a diarrheal agent of the elderly (>64 years of age). Past epidemiologic studies have demonstrated that up to 71% of children are asymptomatically colonized with *C. difficile* (Al-Jumaili et al., 1984). However, a paradigm shift has occurred over the past decade, and *C. difficile* is increasingly being recognized as an important pediatric enteric pathogen. More recent surveillance has revealed that CDI incidence is increasing in children, including those without traditional risk factors (Sandora et al., 2011; Benson et al., 2007).

Communication: Dr. H L Koo, Baylor College of Medicine, One Baylor Plaza, Houston, TX 77030, Phone 713/798-2900, Fax 713/798-0171, koo@bcm.edu.

†These authors contributed equally to the composition of this manuscript.

Potential Financial Conflicts of Interest: None

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

In this review, we will discuss the dynamic epidemiology of *C. difficile* infection in the pediatric population. We will also review the literature regarding the pathogenesis, host immune response, risk factors for infection, spectrum of clinical manifestations, and the diagnosis and treatment of CDI in children.

Epidemiology

C. difficile can be recovered from newborns as early as the first week of life. Between 14% to 71% of children <12 months of age are colonized with this organism (Table 1) (Al-Jumaili et al., 1984; Larson et al., 1982), most commonly with non-toxigenic strains (Larson et al., 1982; Kato et al., 1984). Greater prevalence of *C. difficile* colonization has been reported in sicker children requiring admission to the neonatal intensive care unit (Al-Jumaili et al., 1984; Kato et al., 1984). By 12-18 months, *C. difficile* colonization frequency decreases to ~4%, similar to colonization in non-hospitalized adults (Table 2) (Vernacchio et al., 2006; Merida et al., 1986).

Recent studies based on large, pediatric databases have demonstrated that CDI prevalence in US children is increasing. A retrospective analysis of the Pediatric Health Information System (PHIS) records, which included data from 4,895 children with CDI from 22 tertiary-care pediatric hospitals, revealed a 53% increase in the annual incidence density from 2001-2006, from 2.6 to 4.0 cases/1,000 admissions (p=0.04) (Kim et al., 2008). The national rate of CDI-related pediatric hospitalizations increased from 1997-2006, from 7.24 to 12.80/10,000 hospital admissions in the Kids' Inpatient Database (KID), which was derived from >3,700 hospitals from 38 states (Zilberberg et al., 2010).

CDI rates appear to be increasing particularly in young children aged 1-5 years. In the PHIS study, CDI incidence increased 85% in this age group from 2001-2006, from 0.7 to 1.3 cases/1,000 admissions (p=0.04) and 50% in children 5-17 years of age, from 1.2 to 1.8 cases/1,000 admissions (p=0.03) (Kim et al., 2008). In the KID study, CDI-related hospitalizations were most common in children aged 1-4 years (44.87 hospitalizations/10,000 admissions), followed by children 5-9 years of age (35.27 hospitalizations/10,000 admissions) (Zilberberg et al., 2010).

Whether CDI prevalence is increasing in infants <1 year of age is less clear. No significant change in CDI rates among hospitalized infants, including newborns <28 days, from 2001-2006 was demonstrated in the PHIS study (Kim et al., 2008). In contrast, the incidence of CDI-related hospitalizations in infants increased 80% from 2000-2005, with an 18.5% annual increase, in the National Inpatient Sample database (Zilberberg et al., 2008). High colonization rates and different institutional testing policies complicate interpretation of CDI trends in infants. Collectively, these large epidemiologic studies have demonstrated that *C. difficile* is an important pediatric enteropathogen in the hospital setting, especially in children 1-5 years of age.

Community-acquired CDI in children is also becoming more common. A significant proportion of children who acquire *C. difficile* in the community lack traditional CDI risk factors, including recent antibiotic use and health-care exposure. The incidence of community-acquired CDI increased from 0.841 to 2.036 cases per 1,000 emergency room

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

visits at the Children's National Medical Center in Washington, D.C., between 2001—2006. Forty-three percent of these children had no history of recent antibiotic use (Benson et al., 2007). Similarly, from January-August 2008, 25% of 134 pediatric CDI cases at Boston Children's Hospital were community-acquired, 65% of whom reported no recent antibiotic exposure (Sandora et al., 2011).

Recognition of epidemic, restriction endonuclease analysis group BI, North American pulsed field gel electrophoresis type 1, ribotype 027 (BI/NAP1/027) *C. difficile* strains has been associated with increasing CDI prevalence and mortality in adults (McDonald et al., 2005). The BI/NAP1/027 *C. difficile* strains are characterized by fluoroquinolone resistance, production of *C. difficile* transferase (CDT) or binary toxin, and *tcdC* gene deletions (Loo et al., 2005). These strains are endemic throughout the US, Canada, and Europe (Warny et al., 2005) and may be contributing to increasing pediatric CDI rates as well. In some pediatric hospitals, NAP1 strains constitute 20% of *C. difficile* isolates (Toltzis et al., 2009).

Pathogenesis

Commensal colonization of the neonatal gastrointestinal tract begins with passage through the birth canal and the first meal. During the first 6 months, considerable infant intestinal microbial diversity is present. However, the infant's intestinal microbiota evolves to resemble adult colonic microflora by 12 months, consisting primarily of *Bacteroides* and Firmicutes anaerobes (Palmer et al., 2007). Adult commensal organisms are believed to provide "colonization resistance," limiting overgrowth of enteric pathogens such as *C. difficile*. Antibiotic disruption of the indigenous microbiota plays a key role in *C. difficile* pathogenesis. Decreased gut microbiota diversity and numbers of *Bacteroides* and Firmicutes bacteria have been associated with recurrent CDI (Chang et al., 2008).

Frequent asymptomatic *C. difficile* carriage among infants is not well understood. Although the majority of colonizing *C. difficile* strains are non-toxigenic (Larson et al., 1982; Kato et al., 1994), toxigenic strains are often isolated as well (Al-Jumaili et al., 1984; Bolton et al., 1984). Fecal *C. difficile* levels in asymptomatic infants are similar to adults with pseudomembranous colitis (Stark et al., 1982). Infantile fecal microbiota composition has been hypothesized to protect against disease (Naaber et al., 1997; Kleesen et al., 1995). Resistance to *C. difficile* toxins due to lack of toxin receptor expression on gastrointestinal epithelial cells in infancy has also been hypothesized, based upon a rabbit model. Minimal toxin binding in the newborn rabbit ileum was associated with intestinal toxin A receptor absence; increased ileal toxin binding was observed with increasing age (Eglow et al., 1992).

C. difficile toxins A and B, encoded by the *tcdA* and *tcdB* genes in the pathogenic gene locus (PaLoc), mediate CDI pathogenesis. *C. difficile* strains producing only toxin B (A-B+) may cause disease, while toxin A only (A+B-) strains and non-toxigenic isolates lacking the PaLoc virulence genes are non-pathogenic (Alfa et al., 2000).

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Host Immune Response to CDI

The human immune response to CDI is not well characterized. Elevated toxin A serum immunoglobulin levels have been reported to be protective against symptomatic infection (Kyne et al., 2000) and recurrence (Kyne et al., 2001) among hospitalized adult patients. However, other adult studies have described serum anti-toxin B antibody's essential role (Leav et al., 2010) or no protection with humoral immunity against CDI (Loo et al., 2011). Pediatric literature regarding host immunity to CDI is scant. Six children with multiple CDI recurrences were reported to have lower anti-toxin A IgG levels compared to healthy children and adults (Leung et al., 1991).

Risk Factors for CDI

Several CDI risk factors have been well-established, including intestinal microbiome alteration with medications such as antibiotics, exposure to *C. difficile* in healthcare settings, and significant, chronic underlying conditions. However, with increasing community-acquired CDI in children, many of whom did not receive antibiotics, further evaluation of the importance of these risk factors in children is necessary.

Virtually all antibiotics have been shown to increase susceptibility to CDI in adults, and extensive literature supports CDI development with clindamycin, cephalosporin, and penicillin use (Thomas et al., 2003). Similar findings regarding the impact of antimicrobials on CDI susceptibility have been reported in pediatric studies. A nested case-control analysis of a retrospective pediatric cohort demonstrated that antibiotics in the past four weeks was a significant predictor of CDI (Sandora et al., 2011).

C. difficile acquisition is primarily related to healthcare exposure. Increased neonatal colonization has been associated with greater healthcare environmental contamination (Larson et al., 1982) and longer hospitalization stays (Delmee et al., 1988).

Chronic pediatric co-morbidities such as immunosuppression (Wolfhagen et al., 1994), inflammatory bowel disease (Pascarella et al., 2009), Hirschsprung's disease (Hardy et al., 1993), hematologic and oncologic diseases (Castagnola et al., 2009), solid organ transplantation (Sandora et al., 2011), and cystic fibrosis (Pohl et al., 2011) have been shown to predispose to CDI. The presence of a gastrostomy (G tube) or jejunostomy (J tube) has also been significantly associated with CDI (Sandora et al., 2011). In the PHIS study, 67% of pediatric cases had chronic medical conditions including neuromuscular, cardiovascular, respiratory, renal, gastrointestinal, hematologic, immunologic, metabolic, malignancy, or congenital disorders (Kim et al., 2008).

Other proposed factors related to pediatric CDI include delivery method, feeding pattern, and use of acid suppressive agents. Maternal-infant transmission appears unlikely, with infrequent vaginal colonization with *C. difficile* (Larson et al., 1982; Matsuki et al., 2005) and no difference in neonatal colonization irrespective of delivery mode, whether vaginal or caesarean section (Bolton et al., 1984).

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

C. difficile colonization is influenced by infant feeding behavior. Exclusively breast-fed infants are significantly less frequently colonized (14-16%) than breast-fed infants who also receive formula or solids (35%) and formula-fed only infants (30-62%) (Cooperstock et al., 1983; Penders et al., 2005). Breast milk's protective effect may be related to the distinct intestinal microbiome composition of breast-fed children compared to formula-fed infants (Stark and Lee, 1982). In addition, secretory IgA in breast milk has been shown to block toxin A binding to purified hamster-toxin receptors in *in vitro* studies (Rolfe and Song, 1995).

A recent meta-analysis of 23 studies involving 288,000 patients, mostly adults, reported a 65% increase in CDI incidence among patients receiving proton-pump inhibitors (PPIs) (Janarthanan et al., 2012). However, pediatric study results regarding the role of gastric acid suppressive therapy in CDI are conflicting (Sandora et al., 2011; Turco et al., 2010).

Transmission

CDI is transmitted fecal-orally, through person-to-person contact or contaminated environmental surfaces. Resistance of *C. difficile* spores to heat, acidity, and many disinfectants enables environmental persistence for prolonged time periods (Wilcox et al., 2003). Upon ingestion, spores survive gastric acidity and germinate into the vegetative form in the colon. Up to 1×10^4 to 1×10^7 *C. difficile* spores/gram of stool may be excreted (Mulligan et al., 1984). Spore aerosolization may also lead to CDI dissemination (Best et al., 2010).

Asymptomatic carriers of toxigenic strains, including a significant proportion of colonized infants, may serve as a reservoir and contribute to *C. difficile* transmission. Toxigenic isolates from asymptomatically infected children <2 years of age have been shown to correspond with infectious strains in adults residing in the same geographic region of France (Rousseau et al., 2011). Close contact with children ≤2 years of age was significantly associated with community-associated CDI in a case-control study of adults in the United Kingdom (Wilcox et al., 2008). In addition, genetically identical strains have been detected in post-partum women with recurrent CDI and their colonized infants in published case series (McFarland et al., 1999).

Clinical Manifestations

C. difficile infection causes a spectrum of symptoms, including asymptomatic colonization; mild, watery diarrhea; and severe pseudomembranous colitis. Infants are usually asymptomatically colonized. Most symptomatic children experience mild-moderate watery diarrhea, associated with fever, anorexia, or abdominal pain. Among 200 Canadian children with CDI, 79% presented with watery diarrhea and 12.5% with bloody diarrhea (Morinville and McDonald, 2005). Fever (84%), moderate diarrhea (passage of 7-10 stools/day; 60%), abdominal pain (40%), and bloody diarrhea (24%) were relatively frequent CDI manifestations among 45 Indian children (Gogate et al., 2005). Similar to adults, 20-30% of children will experience ≥1 recurrence following their initial episode (Morinville and McDonald, 2005). Chronic diarrhea may lead to growth retardation (Sutphen et al., 1983).

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Stratification of *C. difficile* disease severity is not well-defined, and no validated scoring system for severe CDI is available. A recent pediatric study classified severe CDI based upon the presence of CDI-related complications (pseudomembranous colitis, toxic megacolon, gastrointestinal perforation, pneumatosis intestinalis, intensive care unit admission, or surgical intervention), abnormal laboratory markers (leukocytosis, leukopenia, hypoalbuminemia, or elevated creatinine), and clinical parameters (fever or bloody diarrhea). Forty-eight of 82 (59%) CDI children developed severe disease, including 8 children who experienced complications. However, no differences in clinical outcomes were noted between children with severe versus non-severe CDI (Kim et al., 2012).

Other pediatric CDI studies have reported a lower frequency of CDI complications. Among the 200 Canadian children with CDI, 2% developed severe morbidity or mortality. Three children required intensive care unit admission; one required exploratory laparotomy; two died (Morinville and McDonald, 2005). One percent of children required colectomy, and 4% expired among CDI cases in the PHIS study (Kim et al., 2008). No CDI complications were reported among pediatric cases at Boston Children's Hospital (Sandora et al., 2011).

Diagnosis of CDI

Diagnostic methods are evolving, as use of molecular techniques is becoming widespread. Once considered the reference standard with its relatively high sensitivity (75%-90%) and high specificity (97%-100%) (Peterson et al., 2007), cell culture cytotoxicity neutralization assay (CCNA) has been abandoned by many laboratories because of its slow turnaround time and the labor requirements. The rapid turn-around time, ease of testing, and high specificity of the enzyme immunoassay (EIA) for toxins A and B led to its use by the majority of clinical laboratories. However, alternative diagnostic approaches have been developed because of EIA insensitivity (Planche et al., 2008). Detection of glutamate dehydrogenase (GDH), an antigen present on toxigenic and non-toxigenic *C. difficile*, is associated with a high negative predictive value and is often incorporated in a multi-step algorithm with an EIA or molecular test. Most recently, polymerase chain reaction (PCR) tests with high sensitivity and specificity for toxins A and B genes have been developed. A comparison of the toxin EIA and PCR assay at Texas Children's Hospital demonstrated sensitivities of 35% and 95%, respectively. Subsequent change from EIA to PCR as the routine CDI diagnostic test at this hospital was associated with the frequency of positive *C. difficile* tests increasing from 8% to 16% (Luna et al., 2011). Similar increases in *C. difficile* prevalence have been noted at other institutions utilizing the PCR assay (Fong et al., 2011). Although the PCR assay may be more expensive than other laboratory tests, the rapid turnaround time and the high sensitivity and specificity of these assays have been reported to lead to overall lower costs with more rapid discontinuation of contact isolation, decreased hospitalization stays, and discontinuation of inappropriate antibiotics (Tenover et al., 2011).

Evaluation for CDI should be reserved for children with diarrheal symptoms, defined as passage of ≥3 loose stools within a 24-hour period. Only unformed stools should be tested. Given the high rates of asymptomatic *C. difficile* colonization in children <1 year of age, routine testing of infants and neonates is not recommended (Dubberke et al., 2008). Evaluation for alternative enteropathogens should be considered as well, particularly in

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

younger children; approximately 10% of CDI cases may have a concomitant pathogen detected (Sandora et al., 2011). With the rising incidence of CDI in children who lack traditional risk factors, further studies are needed to help define children at greatest risk for CDI and most appropriate for testing.

Treatment

The management of *Clostridium difficile* infection involves three basic principles: 1) supportive care; 2) discontinuing the precipitating antibiotic(s); and 3) the initiation of effective anti-*C. difficile* therapy. Symptomatic support is critical for children, who may require aggressive intravenous hydration for diarrheal diseases. Adjunctive anti-motility agents (e.g., loperamide, diphenoxylate and atropine) have traditionally been discouraged due to concerns of increased intestinal contact time with toxins, although supporting evidence is limited. Discontinuation of the offending antibiotic may be sufficient for the resolution of mild symptoms (Gogate et al., 2005) and facilitates reconstitution of the normal enteric flora, which has been shown to decrease recurrence in adults (Fekety et al, 1997).

No prospective clinical trials for CDI treatment in children have been conducted, and treatment recommendations are based on adult CDI studies. However, it is unclear whether adult CDI study results are appropriate for children. For primary mild-moderate CDI in children, oral metronidazole is considered the drug of choice (American Academy of Pediatrics, 2012) and is currently the most widely used agent by pediatricians in the US and Canada (Kim et al., 2008; Morinville and McDonald, 2005). This recommendation is based on similar efficacy between metronidazole and vancomycin for mild-moderate disease in adult studies, similar tolerability for oral administration of the two drugs in children, metronidazole's lower cost, and concern for promotion of resistant pathogens including vancomycin-resistant enterococci (Zar et al., 2007). Decreased oral absorption related to rapid diarrheal transit and drug diffusion across inflamed colonic mucosa are believed to lead to intra-colonic metronidazole concentration; however fecal metronidazole concentration decreases as colonic inflammation resolves (Bolton and Culshaw, 1986). Peripheral neuropathy may develop with prolonged use.

Oral vancomycin with intravenous metronidazole is recommended for severe CDI in children (American Academy of Pediatrics, 2012). This recommendation is based on significantly improved outcomes in severe adult CDI patients who received vancomycin compared to metronidazole (Zar et al., 2007). However, most pediatricians continue to treat severe CDI in children with metronidazole alone. Kim et al. described 64% of mild-moderate and severe pediatric CDI cases treated with only oral or intravenous metronidazole. No difference in the frequency of clinical treatment failure or recurrence was observed between patients with severe or non-severe CDI (Kim et al., 2012). Future pediatric studies are needed to evaluate whether oral vancomycin, which is poorly absorbed leading to high intestinal drug levels and has a favorable side effect profile, is more effective for severe CDI in children.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Fidaxomicin, a macrocyclic antibiotic, was approved in the U.S. in May 2011 for adults with CDI. Despite its high cost, its minimal systemic absorption with excellent safety profile, limited activity against normal gut flora, and potent activity against *C. difficile* make it a promising future therapeutic candidate for children. Randomized double-blind clinical trials have demonstrated similar clinical cure rates with fidaxomicin and vancomycin, but significantly lower recurrence with fidaxomicin (Louie et al., 2011). Children were excluded in these studies; however, pediatric studies evaluating fidaxomicin are currently in development.

Treatment strategies similar to adults are often used in children with recurrent CDI. A second course of the initially successful antibiotic is used with the first recurrence. If this treatment fails, then tapered or pulsed vancomycin regimens can be used (American Academy of Pediatrics, 2012).

Reconstitution of “colonization resistance” may also be effective for *C. difficile* recurrence treatment. Fecal transplantation or probiotics have been successfully used in case reports of children with recurrent CDI. A 2 year-old child who relapsed despite several different therapeutic regimens for recurrent CDI was successfully treated with fecal transplantation from a parent donor (Russell et al., 2010). A second child with surgically-corrected Hirschsprung’s disease and recurrent CDI was given *Saccharomyces boulardii*, which led to fewer episodes and eventual symptom resolution (Ooi et al., 2009). Non-toxigenic *C. difficile* colonization may also be beneficial. Two adult patients with recurrent CDI given oral doses of non-toxigenic strains experienced no further recurrence or adverse events (Seal et al., 1987).

Prevention

Monoclonal antibodies to toxins A and B may be helpful as an adjunct to traditional CDI therapy for secondary prophylaxis. A randomized, double-blind trial demonstrated significantly decreased CDI recurrence in adults with a combination of monoclonal antibodies to toxins A and B compared to placebo (Lowy et al., 2010).

Additionally, candidate vaccines for CDI are in the early stages of development. A formalin-inactivated toxoid vaccine against toxins A and B, currently undergoing phase II evaluation, successfully interrupted multiple episodes of recurrent CDI in three adult patients (Foglia et al., 2012).

Limiting inappropriate antibiotic usage, contact isolation, decontamination of contaminated surfaces with sporicidal cleaning agents, and handwashing are critical components of nosocomial prevention of *C. difficile* dissemination. Alcohol-based hand sanitizers may not be as effective as handwashing with soap and water because of spore resistance to alcohol. In one study, hand cleansing with an alcohol-based handrub was equivalent to no intervention, whereas handwashing with soap and water was most effective for eliminating *C. difficile* contamination (Oughton et al., 2009).

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Conclusions

Clostridium difficile is emerging as an important enteric pathogen in children. With the emergence of epidemic strains and the advent of more sensitive diagnostic methods, CDI prevalence is increasing in the pediatric population, including community-acquired CDI. Historically considered a commensal among infants, CDI has not been well-studied in children. Further studies investigating the significance of *C. difficile* detection among different age groups, the pathogenesis of CDI, and optimal therapeutic and preventative strategies are urgently needed, as recommendations based upon adult studies may not be appropriate for children.

Acknowledgments

This work was supported by the National Institute of Diabetes and Digestive and Kidney Diseases (1K23DK084513-04 to HLK) and the Roderick D. MacDonald Research Fund at St. Luke's Episcopal Hospital (HLK).

References

Al-Jumaili IJ, Shibley M, Lishman AH, Record CO. Incidence and origin of Clostridium difficile in neonates. J Clin Microbiol. 1984; 19:77–78. [PubMed: 6690469]

Alfa MJ, Kabani A, Lyerly D, Moncrief S, Neville LM, Al-Barrak A, Harding GK, Dyck B, Olekson K, Embil JM. Characterization of a toxin A-negative, toxin B-positive strain of Clostridium difficile responsible for a nosocomial outbreak of Clostridium difficile-associated diarrhea. J Clin Microbiol. 2000; 38:2706–2714. [PubMed: 10878068]

American Academy of Pediatrics. Clostridium difficile. In: Pickering, L.; Baker, C.; Bernstein, H.; Kimberlin, D.; Long, S.; Meissner, H., editors. Red Book: 2012 Report of the Committee on Infectious Diseases. 29. American Academy of Pediatrics, Elk Grove Village; IL, USA: 2012. p. 285-287.

Benson L, Song X, Campos J, Singh N. Changing epidemiology of Clostridium difficile-associated in children. Infect Control Hosp Epidemiol. 2007; 28:1233–1235. [PubMed: 17926272]

Best EL, Fawley WN, Parnell P, Wilcox MH. The potential for airborne dispersal of Clostridium difficile from symptomatic patients. Clin Infect Dis. 2010; 50:1450–1457. [PubMed: 20415567]

Bolton R, Culshaw M. Faecal metronidazole concentrations during oral and intravenous therapy for antibiotic associated colitis due to Clostridium difficile. Gut. 1986; 27:1169–1172. [PubMed: 3781329]

Bolton RP, Tait SK, Dear PR, Losowsky MS. Asymptomatic neonatal colonisation by Clostridium difficile. Arch Dis Child. 1984; 59:466–472. [PubMed: 6732277]

Castagnola E, Battaglia T, Bandettini R, Caviglia I, Baldelli I, Nantron M, Moroni C, Garaventa A. Clostridium difficile-associated disease in children with solid tumors. Support Care Cancer. 2009; 17:321–324. [PubMed: 18802726]

Chang JY, Antonopoulos DA, Kalra A, Tonelli A, Khalife WT, Schmidt TM, Young VB. Decreased diversity of the fecal microbiome in recurrent Clostridium difficile-associated diarrhea. J Infect Dis. 2008; 197:435–438. [PubMed: 18199029]

Cooperstock M, Riegle L, Woodruff CW, Onderdonk A. Influence of age, sex, and diet on asymptomatic colonization of infants with Clostridium difficile. J Clin Microbiol. 1983; 17:830–833. [PubMed: 6863502]

Delmee M, Verellen G, Avesani V, Francois G. Clostridium difficile in neonates: serogrouping and epidemiology. Eur J Pediatr. 1988; 147:36–40. [PubMed: 3338476]

Dubberke ER, Gerding DN, Classen D, Arias KM, Podgorny K, Anderson DJ, Burstin H, Calfee DP, Coffin SE, Fraser V, Griffin FA, Gross P, Kaye KS, Klompas M, Lo E, Marschall J, Mermel LA, Nicolle L, Pegues DA, Perl TM, et al. Strategies to prevent Clostridium difficile infections in acute care hospitals. Infect Control Hosp Epidemiol. 2008; 29(Suppl 1):S81–S92. [PubMed: 18840091]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Eglow R, Pothoulakis C, Itzkowitz S, Israel EJ, O'Keane CJ, Gong D, Gao N, Xu YL, Walker WA, Lamont JT. Diminished Clostridium difficile toxin A sensitivity in newborn rabbit ileum is associated with decreased toxin A receptor. J Clin Invest. 1992; 90:822–829. [PubMed: 1325998]

Fekety R, McFarland LV, Surawicz CM, Greenberg RN, Elmer GW, Mulligan ME. Recurrent Clostridium difficile diarrhea: characteristics of and risk factors for patients enrolled in a prospective, randomized, double-blinded trial. Clin Infect Dis. 1997; 24:324–333. [PubMed: 9114180]

Foglia G, Shah S, Luxemburger C, Pietrobon PJ. Clostridium difficile: Development of a novel candidate vaccine. Vaccine. 2012; 30:4307–4309. [PubMed: 22682287]

Fong KS, Fatica C, Hall G, Procop G, Schindler S, Gordon SM, Fraser TG. Impact of PCR testing for Clostridium difficile on incident rates and potential on public reporting: is the playing field level? Infect Control Hosp Epidemiol. 2011; 32:932–933. [PubMed: 21828981]

Garey KW, Jiang ZD, Ghantoji S, Tam VH, Arora V, Dupont HL. A common polymorphism in the interleukin-8 gene promoter is associated with an increased risk for recurrent Clostridium difficile infection. Clin Infect Dis. 2010; 51:1406–1410. [PubMed: 21058913]

Gogate A, De A, Nanivandekar R, Mathur M, Saraswathi K, Jog A, Kulkarni M. Diagnostic role of stool culture & toxin detection in antibiotic associated diarrhoea due to Clostridium difficile in children. Indian J Med Res. 2005; 122:518–524. [PubMed: 16518003]

Janarthanan S, Ditah I, Adler DG, Ehrinpreis MN. Clostridium difficile-associated diarrhea and proton pump inhibitor therapy: a meta-analysis. Am J Gastroenterol. 2012; 7:1001–1010. [PubMed: 22710578]

Kyne L, Hamel MB, Polavaram R, Kelly CP. Health care costs and mortality associated with nosocomial diarrhea due to Clostridium difficile. Clin Infect Dis. 2002; 34:346–353. [PubMed: 11774082]

Hardy SP, Bayston R, Spitz L. Prolonged carriage of Clostridium difficile in Hirschsprung's disease. Arch Dis Child. 1993; 69:221–224. [PubMed: 8215525]

Hall IC, O'Toole E. Intestinal flora in new-born infants: with a description of a new pathogenic anaerobe, Bacillus difficilis. Am J Dis Child. 1935; 49:390–402.

Kato H, Kato N, Watanabe K, Ueno K, Ushijima H, Hashira S, Abe T. Application of typing by pulsed-field gel electrophoresis to the study of Clostridium difficile in a neonatal intensive care unit. J Clin Microbiol. 1994; 32:2067–2070. [PubMed: 7814526]

Khanna S, Pardi DS, Aronson SL, Kammer PP, Orenstein R, St Sauver JL, Harmsen WS, Zinsmeister AR. The epidemiology of community-acquired Clostridium difficile infection: a population-based study. Am J Gastroenterol. 2012; 107:89–95. [PubMed: 22108454]

Kim J, Shaklee JF, Smathers S, Prasad P, Asti L, Zoltanski J, Dul M, Nerandzic M, Coffin SE, Toltzis P, Zaoutis T. Risk factors and outcomes associated with severe clostridium difficile infection in children. Pediatr Infect Dis J. 2012; 31:134–138. [PubMed: 22031485]

Kim J, Smathers SA, Prasad P, Leckerman KH, Coffin S, Zaoutis T. Epidemiological features of Clostridium difficile-associated disease among inpatients at children's hospitals in the United States, 2001-2006. Pediatrics. 2008; 122:1266–1270. [PubMed: 19047244]

Kleesen B, Bunke H, Tovar K, Noack J, Sawatzki G. Influence of two infant formulas and human milk on the development of the faecal flora in newborn infants. Acta Paediatr. 1995; 84:1347–1356. [PubMed: 8645949]

Kyne L, Hamel MB, Polavaram R, Kelly CP. Health care costs and mortality associated with nosocomial diarrhea due to Clostridium difficile. Clin Infect Dis. 2002; 34:346–353. [PubMed: 11774082]

Kyne L, Sougioultzis S, McFarland LV, Kelly CP. Underlying disease severity as a major risk factor for nosocomial Clostridium difficile diarrhea. Infect Control Hosp Epidemiol. 2002; 23:653–659. [PubMed: 12452292]

Kyne L, Warny M, Qamar A, Kelly CP. Association between antibody response to toxin A and protection against recurrent Clostridium difficile diarrhoea. The Lancet. 2001; 357:189–193.

Larson HE, Barclay FE, Honour P, Hill ID. Epidemiology of Clostridium difficile in infants. J Infect Dis. 1982; 146:727–733. [PubMed: 7142747]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Leav BA, Blair B, Leney M, Knauber M, Reilly C, Lowy I, Gerding DN, Kelly CP, Katchar K, Baxter R, Ambrosino D, Molrine D. Serum anti-toxin B antibody correlates with protection from recurrent Clostridium difficile infection (CDI). Vaccine. 2010; 28:965–969. [PubMed: 19941990]

Leung DY, Kelly CP, Boguniewicz M, Pothoulakis C, Lamont JT, Flores A. Treatment with intravenously administered gamma globulin of chronic relapsing colitis induced by Clostridium difficile toxin. J Pediatr. 1991; 118:633–637. [PubMed: 1901084]

Loo VG, Bourgault AM, Poirier L, Lamothe F, Michaud S, Turgeon N, Toye B, Beaudoin A, Frost EH, Gilca R, Brassard P, Dendukuri N, Beliveau C, Oughton M, Brukner I, Dascal A. Host and pathogen factors for Clostridium difficile infection and colonization. N Engl J Med. 2011; 365:1693–1703. [PubMed: 22047560]

Loo VG, Poirier L, Miller MA, Oughton M, Libman MD, Michaud S, Bourgault AM, Nguyen T, Frenette C, Kelly M, Vibien A, Brassard P, Fenn S, Dewar K, Hudson TJ, Horn R, Rene P, Monczak Y, Dascal A. A predominantly clonal multi-institutional outbreak of Clostridium difficile-associated diarrhea with high morbidity and mortality. N Engl J Med. 2005; 353:2442–2449. [PubMed: 16322602]

Louie TJ, Miller MA, Mullane KM, Weiss K, Lentnek A, Golan Y, Gorbach S, Sears P, Shue YK. Fidaxomicin versus vancomycin for Clostridium difficile infection. N Engl J Med. 2011; 364:422–431. [PubMed: 21288078]

Lowy I, Molrine DC, Leav BA, Blair BM, Baxter R, Gerding DN, Nichol G, Thomas WD Jr, Leney M, Sloan S, Hay CA, Ambrosino DM. Treatment with monoclonal antibodies against Clostridium difficile toxins. N Engl J Med. 2010; 362:197–205. [PubMed: 20089970]

Luna RA, Boyanton BL, Mehta S, Courtney EM, Webb CR, Revell PA, Versalovic J. Rapid stool-based diagnosis of Clostridium difficile infection by real-time PCR in a children's hospital. J Clin Microbiol. 2011; 49:851–857. [PubMed: 21209161]

Matsuki S, Ozaki E, Shozu M, Inoue M, Shimizu S, Yamaguchi N, Karasawa T, Yamagishi T, Nakamura S. Colonization by Clostridium difficile of neonates in a hospital, and infants and children in three day-care facilities of Kanazawa, Japan. Int Microbiol. 2005; 8:43–48. [PubMed: 15906260]

McDonald LC, Killgore GE, Thompson A, Owens RC Jr, Kazakova SV, Sambol SP, Johnson S, Gerding DN. An epidemic, toxin gene-variant strain of Clostridium difficile. N Engl J Med. 2005; 353:2433–2441. [PubMed: 16322603]

McFarland LV, Surawicz CM, Greenberg RN, Bowen KE, Melcher SA, Mulligan ME. Possible role of cross-transmission between neonates and mothers with recurrent Clostridium difficile infections. Am J Infect Control. 1999; 27:301–303. [PubMed: 10358237]

McFarland LV, Surawicz CM, Greenberg RN, Fekety R, Elmer GW, Moyer KA, Melcher SA, Bowen KE, Cox JL, Noorani Z, et al. A randomized placebo-controlled trial of Saccharomyces boulardii in combination with standard antibiotics for Clostridium difficile disease. JAMA. 1994; 271:1913–1918. [PubMed: 8201735]

Merida V, Moerman J, Colaert J, Lemmens P, Vandepitte J. Significance of Clostridium difficile and its cytotoxin in children. Eur J Pediatr. 1986; 144:494–496. [PubMed: 3956538]

Mogg GA, Keighley MR, Burdon DW, Alexander-Williams J, Youngs D, Johnson M, Bentley S, George RH. Antibiotic-associated colitis -- a review of 66 cases. Br J Surg. 1979; 66:738–742. [PubMed: 509051]

Morinville V, McDonald J. Clostridium difficile-associated diarrhea in 200 Canadian children. Can J Gastroenterol. 2005; 19:497–501. [PubMed: 16107901]

Mulligan ME, Citron D, Gabay E, Kirby BD, George WL, Finegold SM. Alterations in human fecal flora, including ingrowth of Clostridium difficile, related to cefoxitin therapy. Antimicrob Agents Chemother. 1984; 26:343–346. [PubMed: 6508264]

Naaber P, Klaus K, Sepp E, Bjorksten B, Mikelsaar M. Colonization of infants and hospitalized patients with Clostridium difficile and lactobacilli. Clin Infect Dis. 1997; 25(Suppl 2):S189–S190. [PubMed: 9310674]

O'Brien JA, Lahue BJ, Caro JJ, Davidson DM. The emerging infectious challenge of clostridium difficile-associated disease in Massachusetts hospitals: clinical and economic consequences. Infect Control Hosp Epidemiol. 2007; 28:1219–1227. [PubMed: 17926270]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Ooi CY, Dilley AV, Day AS. Saccharomyces boulardii in a child with recurrent Clostridium difficile. Pediatr Int. 2009; 51:156–158. [PubMed: 19371301]

Oughton MT, Loo VG, Dendukuri N, Fenn S, Libman MD. Hand hygiene with soap and water is superior to alcohol rub and antiseptic wipes for removal of Clostridium difficile. Infect Control Hosp Epidemiol. 2009; 30:939–944. [PubMed: 19715426]

Palmer C, Bik EM, Digiulio DB, Relman DA, Brown PO. Development of the human infant intestinal microbiota. PLoS Biol. 2007; 5:e177. [PubMed: 17594176]

Pascarella F, Martinelli M, MIele E, Del Pezzo M, Roscetto E, Staiano A. Impact of Clostridium difficile infection on pediatric inflammatory bowel disease. J Pediatr. 2009; 154:854–858. [PubMed: 19230908]

Penders J, Vink C, Driessen C, London N, Thijs C, Stobberingh EE. Quantification of Bifidobacterium spp., Escherichia coli and Clostridium difficile in faecal samples of breast-fed and formula-fed infants by real-time PCR. FEMS Microbiol Lett. 2005; 243:141–147. [PubMed: 15668012]

Peterson LR, Manson RU, Paule SM, Hacek DM, Robicsek A, Thomson RB Jr, Kaul KL. Detection of toxigenic Clostridium difficile in stool samples by real-time polymerase chain reaction for the diagnosis of C. difficile-associated diarrhea. Clin Infect Dis. 2007; 45:1152–1160. [PubMed: 17918076]

Planche T, Aghaizu A, Holliman R, Riley P, Poloniecki J, Breathnach A, Krishna S. Diagnosis of Clostridium difficile infection by toxin detection kits: a systematic review. Lancet Infect Dis. 2008; 8:777–784. [PubMed: 18977696]

Pohl JF, Patel R, Zobell JT, Lin E, Korgenski EK, Crowell K, Mackay MW, Richman A, Larsen C, Chatfield BA. Clostridium difficile infection and proton pump inhibitor use in hospitalized pediatric cystic fibrosis patients. Gastroenterol Res Pract. 2011; 2011:1–4.

Rolfe RD, Song W. Immunoglobulin and non-immunoglobulin components of human milk inhibit Clostridium difficile toxin A-receptor binding. J Med Microbiol. 1995; 42:10–19. [PubMed: 7739018]

Rousseau C, Lemee L, Le Monnier A, Poilane I, Pons JL, Collignon A. Prevalence and diversity of Clostridium difficile strains in infants. J Med Microbiol. 2011; 60:1112–1118. [PubMed: 21393454]

Russell G, Kaplan J, Ferraro M, Michelow IC. Fecal bacteriotherapy for relapsing Clostridium difficile infection in a child: a proposed treatment protocol. Pediatrics. 2010; 126:e239–e242. [PubMed: 20547640]

Sandora TJ, Fung M, Flaherty K, Helsing L, Scanlon P, Potter-Bynoe G, Gidengil CA, Lee GM. Epidemiology and risk factors for Clostridium difficile infection in children. Pediatr Infect Dis J. 2011; 30:580–584. [PubMed: 21233782]

Seal D, Borriello SP, Barclay F, Welch A, Piper M, Bonnycastle M. Treatment of relapsing Clostridium difficile diarrhoea by administration of a non-toxigenic strain. Eur J Clin Microbiol. 1987; 6:51–53. [PubMed: 3569251]

Sutphen JL, Grand RJ, Flores A, Chang TW, Bartlett JG. Chronic diarrhea associated with Clostridium difficile in children. Am J Dis Child. 1983; 137:275–278. [PubMed: 6823927]

Stark PL, Lee A, Parsonage BD. Colonization of the large bowel by Clostridium difficile in healthy infants: quantitative study. Infect Immun. 1982; 35:895–899. [PubMed: 7068220]

Stark PL, Lee A. The microbial ecology of the large bowel of breast-fed and formula-fed infants during the first year of life. J Med Microbiol. 1982; 15:189–203. [PubMed: 7143428]

Tenover FC, Baron EJ, Peterson LR, Persing DH. Laboratory diagnosis of Clostridium difficile infection can molecular amplification method move us out of uncertainty? J Mol Diagn. 2011; 13:573–582. [PubMed: 21854871]

Thomas C, Stevenson M, Riley TV. Antibiotics and hospital-acquired Clostridium difficile-associated diarrhoea: a systematic review. J Antimicrob Chemother. 2003; 51:1339–1350. [PubMed: 12746372]

Toltzis P, Kim J, Dul M, Zoltanski J, Smathers S, Zaoutis T. Presence of the epidemic North American Pulsed Field type 1 Clostridium difficile strain in hospitalized children. J Pediatr. 2009; 154:607–608. [PubMed: 19324222]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Turco R, Martinelli M, Miele E, Roscetto E, Del Pezzo M, Greco L, Staiano A. Proton pump inhibitors as a risk factor for paediatric Clostridium difficile infection. Aliment Pharmacol Ther. 2010; 31:754–759. [PubMed: 20047577]

Vernacchio L, Vezina RM, Mitchell AA, Lesko SM, Plaut AG, Acheson DW. Diarrhea in American infants and young children in the community setting. Pediatr Infect Dis J. 2006; 25:2–7. [PubMed: 16395094]

Viscidi R, Willey S, Bartlett JG. Isolation rates and toxigenic potential of Clostridium difficile isolates from various patient populations. Gastroenterology. 1981; 81:5–9. [PubMed: 7239125]

Voth DE, Ballard JD. Clostridium difficile toxins: mechanism of action and role in disease. Clin Microbiol Rev. 2005; 18:247–263. [PubMed: 15831824]

Warny M, Pepin J, Fang A, Killgore G, Thompson A, Brazier J, Frost E, Mcdonald LC. Toxin production by an emerging strain of Clostridium difficile associated with outbreaks of severe disease in North America and Europe. The Lancet. 2005; 366:1079–1084.

Wilcox MH, Fawley WN, Wigglesworth N, Parnell P, Verity P, Freeman J. Comparison of the effect of detergent versus hypochlorite cleaning on environmental contamination and incidence of Clostridium difficile infection. J Hosp Infect. 2003; 54:109–114. [PubMed: 12818583]

Wilcox MH, Mooney L, Bendall R, Settle CD, Fawley WN. A case-control study of community-associated Clostridium difficile infection. J Antimicrob Chemother. 2008; 62:388–396. [PubMed: 18434341]

Wilcox MH, Shetty N, Fawley WN, Shemko M, Coen P, Birtles A, Cairns M, Curran MD, Dodgson KJ, Green SM, Hardy KJ, Hawkey PM, Magee JG, Sails AD, Wren MW. Changing epidemiology of Clostridium difficile infection following the introducion of a national ribotyping based surveillance scheme in England. Clin Infect Dis. Jul 11.2012 epub ahead of print.

Wolfhagen MJ, Meijer K, Fluit AC, Torensma R, Bruinsma RA, Fleer A, Verhoef J. Clinical significance of Clostridium difficile and its toxins in faeces of immunocompromised children. Gut. 1994; 35:1608–1612. [PubMed: 7828982]

Zar FA, Bakkanagari SR, Moorthi KM, Davis MB. A comparison of vancomycin and metronidazole for the treatment of Clostridium difficile-associated diarrhea, stratified by disease severity. Clin Infect Dis. 2007; 45:302–307. [PubMed: 17599306]

Zilberberg MD, Shorr AF, Kollef MH. Increase in Clostridium difficile-related hospitalizations among infants in the United States, 2000–2005. Pediatr Infect Dis J. 2008; 27:1111–1113. [PubMed: 19068517]

Zilberberg MD, Tillotson GS, McDonald C. Clostridium difficile infections among hospitalized children, United States, 1997-2006. Emerg Infect Dis. 2010; 16:604–609. [PubMed: 20350373]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Table 1

Reported Prevalence of Asymptomatic *C. difficile* Colonization in Children by Age Group in the Literature

Year	Study Location	No. of Subjects	Patient Status during *C. difficile* Testing	Frequency of Colonization	Reference
Neonates (< 1 month)					
2005	Netherlands	100	Healthy outpatients	22%	Penders et al., 2005
1994	Japan	67	Hospitalized in the intensive care unit	61%	Kato et al., 1994
1984	United Kingdom	92	Hospitalized in the intensive care unit	71%	Al-Jumaili et al., 1984
1984	United Kingdom	150	Hospitalized in postnatal wards and outpatients	31%	Bolton et al., 1984
1983	United States	36	Healthy Outpatients	33%	Cooperstock et al., 1983
1982	United Kingdom	451	Hospitalized in postnatal wards	14%	Larson et al., 1982
1981	United States	45	Hospitalized in the newborn nursery	29%	Viscidi et al., 1981
Infants (1–12 months)					
1983	United States	71	Healthy outpatients	44%	Cooperstock et al., 1983
Children (> 12 months)					
2001	United States	604	Healthy Outpatients	3.5%*	Vernacchio et al., 2006
1986	Belgium	25	Hospitalized children	4%	Merida et al., 1986

*A minority of children aged 6-12 months were enrolled.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Table 2

Comparison of CDI Characteristics among Adult versus Pediatric Patients

CDI Characteristic	Adult	Children	Reference
Epidemiology			
C. difficile colonization	Uncommon	Frequent among infants	Al-Jumaili et al., 1984; Loo et al., 2005
Community-acquired CDI	Increasing prevalence	Increasing prevalence	Benson et al., 2007; Khanna et al., 2012
BI/NAP1/027 strain prevalence	~20% of isolates	~20% of isolates	Toltzis et al., 2009; Wilcox et al., 2012
Pathogenesis	Toxin-mediated	Poorly understood; frequent asymptomatic carriage hypothesized to be related to intestinal microbiome composition or lack of toxin receptors	Kleesen et al., 1995; Eglow et al., 1992; Voth and Ballard, 2005
Host genetic susceptibility	Possible role for IL-8 gene SNP	Unknown	Garey et al., 2010
Host immunity	Possible protection with antibodies against toxins A and B	Not well studied	Kyne et al., 2000; Leung et al., 1991; Lowy et al., 2010
Risk factors	Older age, antibiotic and healthcare exposure, significant co-morbidities	Antibiotic and healthcare exposure, significant co-morbidities; protection with breast feeding	Sandora et al., 2011; Kyne et al., 2002
Transmission	Fecal-oral	Possible reservoir of colonized infants	Rousseau et al., 2011; Wilcox et al., 2008
Clinical manifestations	Bloody diarrhea rare; recurrence in ~25% patients	Bloody diarrhea relatively common; recurrence in ~25% patients	Morinville and McDonald, 2005; Mogg et al., 1979
Treatment	Mild-moderate: Metronidazole Severe: Vancomycin	No well-designed clinical trials to guide treatment recommendations	Zar et al., 2007
Prevention	Monoclonal antibodies, vaccines, probiotics currently in development	No well-designed clinical trials conducted	Lowy et al., 2010; Foglia et al., 2012; McFarland et al., 1994