**Name of journal: *World J Gastroenterology***

**ESPS Manuscript NO: 23770**

**Manuscript type: review**

**Comparison of pediatric and adult antibiotic-associated diarrhea and *Clostridium difficile* infections**

**Lynne Vernice McFarland, Metehan Ozen, Ener Cagri Dinleyici, Shan Goh**

McFarland LV *et al*. Pediatric versus adult AAD and CDI

**Lynne Vernice McFarland**, Department of Medicinal Chemistry, School of Pharmacy, University of Washington, Seattle, Wa 98108, United States

**Metehan Ozen**, Faculty of Medicine, Department of Pediatrics, Division of Pediatric Infectious Disease, Atakent Acibadem University Hospital, 34303 Istanbul, Turkey

**Ener Cagri Dinleyici**, Faculty of Medicine, Department of Pediatrics, Pediatric Intensive Care Unit, Eskisehir Osmangazi University, TR-26480 Eskisehir, Turkey

**Shan Goh**, Department of Pathology and Pathogen Biology, Royal Veterinary college, Hertfordshire AL9 7TA, United Kingdom

**Author contributions**: McFarland LV designed the research question; all authors contributed to the literature search, analysis and writing the paper.

**Conflict-of-interest statement:** McFarland LV is a paid speaker for Biocodex and Lallemand and is a member of the Scientific Advisory Board for BioK+; Ozen M is a paid speaker for Menarini; Dinleyici EC is a member of Biocodex International Advisory Board; Goh S has no conflicts of interest; none of the authors owns stock or equity in companies discussed in paper.

**Open-Access:** This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

**Correspondence to**: **Lynne Vernice McFarland, PhD, Affiliate Associate Professor**, Department of Medicinal Chemistry, School of Pharmacy, University of Washington 1660 South Columbian Way, Puget Sound Health Care System, S-152 Seattle, WA 98108-1597, United States. [lvmcfarl@u.washington.edu](mailto:lvmcfarl@u.washington.edu)

**Telephone:** +1-206-2771780

**Fax:** +1-206-7631049

**Received:** December 16, 2015

**Peer-review started:** December 17, 2015

**First decision:** December 30, 2015

**Revised:** January 12, 2016

**Accepted:** February 20, 2016

**Article in press:**

**Published online:**

**Abstract**

Antibiotic-associated diarrhea (AAD) and *Clostridum difficile* infections (CDI) have been well studied for adult cases, but not as well in the pediatric population. Whether the disease process or response to treatments differs between pediatric and adult patients is an important clinical concern when following global guidelines based largely on adult patients. A systematic review of the literature using databases PubMed (June 3, 1978-2015) was conducted to compare AAD and CDI in pediatric and adult populations and determine significant differences and similarities that might impact clinical decisions. In general, pediatric AAD and CDI have a more rapid onset of symptoms, a shorter duration of disease and fewer CDI complications (required surgeries and extended hospitalizations) than in adults. Children experience more community-associated CDI and are associated with smaller outbreaks than adult cases of CDI. The ribotype NAP1/027/BI is more common in adults than children. Children and adults share some similar risk factors, but adults have more complex risk factor profiles associated with more co-morbidities, types of disruptive factors and a wider range of exposures to *C. difficile* in the healthcare environment. The treatment of pediatric and adult AAD is similar (discontinuing or switching the inciting antibiotic), but other treatment strategies for AAD have not been established. Pediatric CDI responds better to metronidazole, while adult CDI responds better to vancomycin. Recurrent CDI is not commonly reported for children. Prevention for both pediatric and adult AAD and CDI relies upon integrated infection control programs, antibiotic stewardship and may include the use of adjunctive probiotics. Clinical presentation of pediatric AAD and CDI are different than adult AAD and CDI symptoms. These differences should be taken into account when rating severity of disease and prescribing antibiotics.

**Key words**: Antibiotics; Antibiotic-associated diarrhea; *Clostridium difficile* infections; Adults; Pediatrics; Diarrhea; Risk factors; Treatments; Prevention

**© The Author(s)** 2016. Published by Baishideng Publishing Group Inc. All rights reserved.

**Core tip:** Differences and similarities in clinical presentation and response to treatments were noted in pediatric and adult patients with regards to antibiotic-associated diarrhea and *Clostridium* *difficile* infections. Pediatric patients typically become symptomatic more rapidly, but also recover quicker than adults. While antibiotics are the major risk factor for both children and adult patients, adults have a more complex risk factor profile. Children respond best to metronidazole, while adults respond better to vancomycin. More studies are needed to characterize the disease process in antibiotic-associated diarrhea and treatment guidelines for pediatric patients.

McFarland LV, Ozen M, Dinleyici EC, Goh S. Comparison of pediatric and adult antibiotic-associated diarrhea and *Clostridium difficile* infections. *World J Gastroenterol* 2016; in press

**INTRODUCTION**

Clinical presentation and response to treatments often differ radically in pediatric compared to adult patient populations. Although antibiotic-associated diarrhea (AAD) and *Clostridium difficile* (*C. difficile*) infections (CDI) are widely studied in adult populations, a comparison of the disease processes in the pediatric population is not as well described, especially for *C. difficile* infections[1]. If pediatric and adult patients respond differently to therapies for these conditions, this may be an important clinical concern, as global guidelines are typically based on adult patients, not children[2,3]. Results from clinical trials performed in adults might be extrapolated to pediatric populations if the response is similar in these two populations. Currently, there are limited comprehensive comparisons of these two populations for AAD and CDI. The national prevalence of both pediatric[4-6] and adult cases of CDI[7,8] are increasing over time, but the secular trends for pediatric and adult rates of AAD have not been documented. The impact of AAD and CDI on healthcare systems is high. In the United States, 453000 cases of incident CDI occurred in 2013, associated with 29300 deaths and increased costs of healthcare from $3,427-$9960/patient[9,10]. Many incident cases of adult CDI will recur (up to 136000/year) and these cases are associated with higher costs ($11631/case)[10]. The burden and costs of pediatric AAD have not been documented by national surveillance studies. AAD is also associated with longer hospitalizations, higher healthcare costs, increased risks of mortality and acquiring other nosocomial infections[11]. The aim of this review is to update the literature and compare AAD and CDI in pediatric and adult populations and determine significant differences and similarities that might impact clinical decisions.

**DEFINITIONS**

***Pediatric vs adult***

Generally for AAD, the pediatric population is defined as aged one month to 18 years of age, but for pediatric CDI, the reported age range shifts to 1-21 years old[1,12-14]. For pediatric CDI, infants younger than one year old are typically excluded from being defined as CDI cases due to their high asymptomatic carrier rate associated with the lack of toxin A/B receptors in the immature colon and high prevalence of other etiologies of diarrhea (most commonly viral causes)[15]. Adults are usually defined as ≥ 21 years old, but published studies have included ages as young as 16 years old. The lower limit for pediatric AAD is difficult to define without knowing more about asymptomatic carriage of other etiologies of AAD. Although it is appreciated that the intestinal microbiome is in an active stage of change during early life, few studies report clinical data by finer age strata other than either pediatric or adult. For this review, we include all ages under 21 years as pediatric AAD and ages 1-21 years old as pediatric CDI.

***Diarrhea***

The World Health Organization defined diarrhea in adults and children as 'the passage of three or more loose or liquid stools per day, or more frequently than is normal for the individual'[16]. In clinical studies, diarrhea in adults is usually defined as ≥ 3 liquid stools/d for at least two days[2,17]. Pediatric diarrhea is typically defined using the WHO definition[16],but one study defined pediatric diarrhea as ≥ 5 stools/d[18].

***Antibiotic-associated diarrhea***

AAD is defined as diarrhea associated with antibiotic exposure, either while on antibiotic or for up to eight weeks after antibiotics have been discontinued[19,20] Although the etiologies for AAD are varied and not all the pathogens are identifiable, nearly one-third of AAD cases are due to *C. difficile.* In pediatric AAD, etiologies may include viruses (25% in one study)[21] or *C. difficile* (22%-30%), but also may be due directly to osmotic imbalances in the intestines brought about by antibiotic exposure and microbiota disruption. In adults with AAD, identifiable pathogens include *C. difficile* (13%-28%), *C. perfringens* (3%-21%), *Staphylococcus aureus* (1%-28%) and less commonly *Klebsiella oxytoca*[22-27].

***C. difficile infections***

CDI diagnosis is based on standard definitions in practice guidelines, which are based on a positive result in two factors: (1) presence of *C. difficile* in the stool [*e.g.*, microbial culture, cytotoxin assay, enzyme immunoassay, nucleic acid amplication test, or polymerase chain ribotyping (PCR)]; and (2) the presence of gastrointestinal symptoms (*e.g.*, diarrhea, colitis, *etc*.) without another etiology being present[2,28,29]. While there is no standard definition of severe CDI, most experts agree that severe CDI should include at least one of the following: elevated leukocyte counts, elevated creatinine, albumin counts, intensive care unit admission, surgery or pseudomembranous colitis[2].

***Onset of symptoms***

Laboratory testing and surveillance data allows both the setting (location of disease onset) and the time of onset (incubation time) to be determined. If an etiology can be determined (*e.g.*, *C. difficile*), the source of the infection may be determined. AAD or CDI cases may begin exhibiting symptoms at healthcare settings (including hospitals and long-term care facilities) or in community settings (home, daycares, *etc*.), but the setting is typically only defined for CDI cases. The incubation time for AAD (defined as the time between antibiotic initiation and the onset of diarrhea) falls into two groups: early onset, occurring during antibiotics and delayed onset, which may occur from 2-8 wks after the antibiotics have been discontinued[30,31]. The incubation time for CDI should best be measured from the first day of the inciting antibiotic to the first day of diarrhea associated with a positive *C. difficile* assay, but most studies of CDI have not collected data related to the first day of antibiotic for all their patients. As a consequence, the incubation time for CDI is typically measured starting from either the first day of healthcare facility admission or first positive laboratory test for *C. difficile* and ending at the first day of defineddiarrhea. Healthcare facility-associated (HCFA) cases are assumed to have acquired *C. difficile* either during their current stay or during a previous recent stay at a healthcare facility within the previous 12 wk. The onset of HCFA cases may be either during their current stay (healthcare-onset) or after discharge (community-onset). Community-acquired CDI (CA-CDI) cases are defined as a symptom onset in the community with no associated healthcare facility exposure in the prior 12 wk, or onset ≤ 48 h of a current hospital admission and the last discharge from a healthcare facility beyond 12 wk of the admission[2].

**EPIDEMIOLOGY**

***Incidence and setting***

**Pediatric AAD incidence:**National surveillance studies have not been done documenting the incidence of pediatric AAD in the general population, but estimated frequencies of pediatric AAD ranging from 6-80/100 can be obtained from the control groups in randomized, placebo-controlled clinical trials or from prospective cohort studies, as shown in Table 1. From a meta-analysis of 22 clinical trials of children exposed to antibiotics, AAD in the controls ranged from 4.3% to 80%, with a median incidence of 22%[19].The incidence of pediatric AAD varies largely due to two main factors: the age of the child and the type of antibiotic to which the child is exposed. From birth to 6 mo, infants seem to be protected by maternal antibodies supplied in the breast-milk and by the establishment of normal microbiome during the passage through the birth canal[32,33]. Neonates who are not breast-fed or are delivered by Caesarian section do not benefit from these two protective mechanisms[33]. As infants are transitioned to solid food, the incidence of AAD seems to increase, perhaps reflecting a shift in the normal intestinal microbiome. Few studies have documented the incidence of pediatric AAD in the healthcare setting, but the frequency in outpatients has been reported ranging from 6%-75%, as shown in Table 1. The reported mean age of pediatric AAD ranges from 18-48 mo. old (Table 1). Few studies of pediatric AAD have provided age, gender or racial distribution of their cases, but one study reported no significant differences by gender[34].

**Adult AAD incidence:** The incidence of adult AAD cases ranges from 7-33/100 in adult inpatients to as few as 2.5/100000 person-years for adult outpatients or mixed inpatient and outpatient cases receiving antibiotics, as shown in Table 1. One review of six randomized trials found the frequency of AAD in elderly patients (≥ 65 years old) ranged from 10%-37% in control groups[35]. While few studies of adult AAD have provided age or gender data, two studies reported the mean age was 49-72 years old and 47% were female[36,37]. Few studies of AAD report distribution by race or ethnicity.

**Pediatric CDI incidence:** Incidence of pediatric CDI is dependent upon two main factors: age and hospitalization status. The high prevalence of asymptomatic carriers of *C. difficile* in neonates requires that the diagnosis of pediatric CDI be based on laboratory findings, the presence of intestinal symptoms, and the age of the child. Up to 67% of neonates delivered in hospitals may be colonized with *C. difficile*, but rarely show diarrheal symptoms. This is thought to be due to the lack of *C. difficile* toxin receptors in the neonatal colon, or from the presence of maternal anti-*C. difficile* toxin A/B antibodies in breast milk[1]. The high incidence of *C. difficile* acquisition by neonates may be due to exposures to *C. difficile* spores in the hospital environment[15]. However, in one study at two hospitals in New Zealand, only 3% of the neonates were asymptomatic carriers[38]. The incidence of pediatric asymptomatic colonization with *C. difficile* decreases with the increase in age from 6 mo-1 year. In contrast, to the very low incidence of symptomatic CDI in neonates, symptomatic disease peaks 4-5 years of age, with the median age typically reported ranging from 1.5-10 years old (Table 1). This peak may reflect increased exposure to *C. difficile* spores found in soil or from other children with CDI in daycares or kindergardens[39]. After peaking at age 4-5 years, the incidence of pediatric CDI declines from ages 6-18 years old to rates typically seen in adult CDI cases. Rates of CDI may also range widely depending upon type of healthcare facility exposure: rates range from 2-420/10000 d for pediatric inpatients, while ranging from 14-800/10000 for outpatient children. The wide range of CDI rates shown in Table 1 may reflect differences in data collection methods rather than a true difference in incidence. Inpatient data may be more accurate, as it is usually collected from prospective cohort studies or surveillance programs. The higher rates reported in outpatient studies are often collected from control groups from randomized trials and may not accurately reflect true population rates. Data from the United States Healthcare Cost and Utilization Project Kids' Inpatient Database found rate of pediatric CDI of 12.8/10000 in inpatients, with peak ages of 1-4 years old[5]. A CDC Emerging Infections surveillance program across ten United States states from 2010-2011 found 71% of pediatric CDI was from outpatients, the peak age was < 1 year old (71/100000), and children 2-3 years old had the next highest incidence (34/100000)[4]. Secular trends of increasing incidence for pediatric CDI over time have been noted. A doubling of pediatric CDI cases was noted in two national surveys from 1997-2006[5,14] and another study found a 12-fold increase in pediatric CDI from 1991-2009[40]. From a meta-analysis of six clinical trials of children exposed to antibiotics, CDI in the controls ranged from 0% to 8%, with a median of 4%[19]. Most pediatric CDI is acquired in healthcare facilities, but more CA-CDI cases are being reported. Pediatric CA-CDI ranges from 19%-96%, with a median of 41% (Table 1). Healthcare facility acquisition of pediatric CDI ranges from 25%-74%, with a median of 65% (Table 1). Community sources for pediatric CDI cases may include daycare centers, where CDI outbreaks have been reported[41] or transmission from recently hospitalized family members[39,42]. From a cohort of Danish children attending a general practice for intestinal complaints, 96% of the CDI cases were CA, with 69% also having another pathologic agent (viruses or *E. coli*) and the most common ribotype of *C. difficile* was type 014 (35%), while only < 1% had NAP1 ribotype[43]. Gender seems not to play an important role in pediatric CDI, as the distribution between female and male cases is nearly equivalent (Table 1)**.** From 16 studies of pediatric CDI, the range of frequencies for females was 39%-49%. Few studies report race or ethnicity, but two studies found most (59%-65%) of pediatric CDI cases were Caucasian[38,44].

**Adult CDI incidence*:*** From national surveillance studies of CDI, the incidence of adult CDI has ranged from 1-11/10000 for outpatients to 4.3-131/10000 for adult inpatients (Table 1). Estimates of incidence extrapolated from a clinical trial and a cohort of adults on one hospital ward resulted in higher rates (1000-2080/10000)[23,45]. Even excluding the two highest estimates, rates of adult CDI are typically higher for adult inpatients compared to outpatient populations. In adult CDI cases, most (21%-92%) cases are reported as HCFA-CDI (Table 1), while only 8%-43% have been CA-CDI. Secular trends in adult CDI cases increased by four-fold from 1998-2006[11] and United States national surveillance data show continued increases in the rates of adult CDI from 2000-2013[7,8]. Elderly patients in long-term care facilities are also experiencing increasing CDI rates[46]. The reported median age of adult CDI ranges from 59-77 years old (Table 1). Most cases (47%-67%) of adult CDI are female, while ethnicity or race data is rarely reported in studies of adult CDI.

***Outbreaks***

**Pediatric AAD outbreaks:**Few outbreaks of pediatric AAD have been reported in children < 2 years old. Of 65 children in daycares who were followed for 3.5 mo., five outbreaks of diarrhea occurred (*n* = 21 developed diarrhea), and while most (62%) were due to *C. difficile*, eight (38%) had no known etiology[41]. There are few other reports of pediatric AAD outbreaks excluding those with CDI .

**Adult AAD outbreaks:**The difficulty of determining outbreaks of AAD is that early reports in the literature of outbreaks may have been due to *C. difficile*, but were missed as testing was not standard before 1980's. In addition, the lack of assays for other etiologies of AAD has limited documentation of AAD outbreaks. One study of adult inpatients with diarrhea, 591/4659 (13%) of AAD cases were due to *C. difficile*, 155 (3%) due to *Clostridum perfringens* and 10 (0.2%) due to *Staphylococcus aureus*. No clustering of *C. perfingens* or *S. aureus* DNA fingerprints was found to indicate an outbreak situation[22].

**Pediatric CDI outbreaks:**A few, small CDI outbreaks involving 6-13 children have been reported[41,47,48]. Despite a high rate of *C. difficile* carriage in several pediatric patient studies[39,49], large CDI outbreaks were found to be uncommon. An epidemiological study at a Belgian pediatric hospital found asymptomatic carriage of *C. difficile* was common (76/114, 67% were positive for *C. difficile*)but only 13 children developed CDI and 2 developed necrotizing entercolitis, and no evidence of CDI outbreaks were observed. Clustering of serogroups B and C were observed, but most were asymptomatic carriers[49].

A hypervirulent strain of *C. difficile* (NAP1/027/BI) is responsible for outbreaks in adults, but is detected only rarely in pediatric CDI populations[50], and not found by others[38,51-53], making its contribution to disease in children less certain than in adults. In a study, of 28 isolates of *C. difficile* isolated from children, eight different genotypes were seen, but none were 027 ribotype[52]. While in most studies of pediatric CDI, < 20% of isolates are the hypervirulent strain (Table 1), a few studies found higher frequencies of this ribotype. NAP1/027/BI isolates were found in 19% of 195 samples from children hospital isolates (median age of 2.5 years old)[50] and in 20% of pediatric cases in Poland[18]. Most studies find ribotype 014 is the most common strain isolated from pediatric CDI cases. Two studies in New Zealand and Australia reported ribotype 014 was the most commonly isolated (37% and 48%, respectively)[38,54] and also from a study in Germany (26%)[55].

**Adult CDI outbreaks:**The notoriety of CDI is due to its ability to cause large outbreaks of disease in adults at healthcare facilities that are difficult to control without a multidisciplinary infection control programs. Nosocomial outbreaks have been reported in adult inpatients since the 1980s, with as few as 15 cases to as many as 1703 (Table 1)[55-58]. Large outbreaks of CDI occurred in 12 Canadian hospitals in Quebec providence during 2004 (*n* = 1703 CDI cases) which were associated with high mortality and the increased incidence was associated with the emergence of a hypervirulent strain of *C. difficile* typed as NAP1/027/BI[57]. A large outbreak of CDI with 253 adult nosocomial cases was reported at a teaching hospital following increased fluoroquinolone use[59]. Jump et al. reported outbreaks of CDI in five hospitals during 2006 in Ohio, totally 1269 cases and 66% of the isolates were typed as NAP1/027/BI[60]. However, other strain types of *C. difficile*are also responsible for outbreaks. During one outbreak at a Hong Kong rehabilitation ward, 80% of 15 cases of adult CDI at were due to ribotype 02[61]. NAP1/027/BI *C. difficile* strains continue to be responsible for outbreaks of CDI in adult patients, particularly elderly patients in Canada and this serotype is now frequently isolated in adults globally (Table 1)[57,62].

***Risk factors***

**Pediatric AAD risk factors:**Risk factors for AAD may broadly be divided into two modalities: host factors (*e.g.* age) and disruptive factors (*e.g.* antibiotics) thatmay disturb the normally protective intestinal microbiome[1,20]. The two main risk factors for pediatric AAD are age (1-2 years old) and type of antibiotic exposure, as shown in Table 2. In one study of 650 outpatient children on oral antibiotics, symptomatic pediatric AAD occurred in 18% of outpatient children aged 1-2 years old and in 3% for older children (3-16 years)[63]. The incidence of AAD may be even higher (60% to 70%) if broad-spectrum antibiotics (cephalosporins, penicillins, *etc.*) were used. The number of controlled studies determining risk factors for pediatric AAD is limited. Few other risk factors for pediatric AAD have been established.

**Adult AAD risk factors:**Most studies determining risk factors for AAD have focused on the most common etiology of AAD, namely *C. difficile*. Literature is limited for risk factors of non-*C. difficile* AAD cases. One study prospectively followed 4659 adult inpatients for AAD and found 13% were due to *C. difficile*, 3% were due to *Clost. perfringens* and 0.2% were due to *S. aureus*[22]. Risk factors for adult *C. perfringens*-associated AAD included: age > 80 years (OR = 13.7), female gender (OR = 2.0) and antacid use (OR = 2.8)[22]. Another study of adult patients with AAD found age > 80 years, previous antibiotic use (OR = 2.3) and proton-pump inhibitor (PPI) use (OR = 2.0) increased the risk of AAD, but co-morbidities or surgery had no effect on the risk of AAD[37].

**Pediatric CDI risk factors:**In contrast to AAD, there are numerous studies for CDI risk factors (Table 2). Risk factors for CDI involve a triad of factors: (1) host factors (*e.g.,* age, gender, co-morbidities); (2) factors disruptive of the protective intestinal microbiome (*e.g.*, antibiotics, surgery, other medications, nasogastric tube feeding, gastrostomy); and (3) increased exposure to *C. difficile* spores (*e.g.*, longer healthcare facility stays, prior admissions, infected room-mates)[64,65]. However, not all factors act equally in the pediatric versus adult populations. The risk factors that are common for pediatric CDI include: age 1-4 years old, co-morbidities (especially cancer and inflammatory bowel disease), exposure to antibiotics within the prior 12 wk (particularly multiple antibiotics, cephalosporins, and penicillins), and prior or current hospitalization (Table 2)[38,66-69]. Conversely, risk factors for pediatric CA-CDI are not as strongly associated with antibiotic exposure[70]. From the CDC Emerging Infections Program, data from 10 United States states from 2010-2011 found 71% of the 944 of pediatric CDI cases were CA-CDI and of these, 67% had no antibiotic exposure in the two weeks prior to CA-CDI diagnosis[4]. The five studies that show the highest rate of no prior antibiotic exposures (19%-67%) were largely CA-CDI pediatric cases (Table 2)[4,12,40,70,71]. In a study of 202 children with CDI, CA cases were found to have less co-morbidities (74% *vs* 98%) and less antibiotic exposure (42% *vs* 77%) than HCFA cases, which had a higher rate of CDI recurrences (21% *vs* 9%, respectively)[72]. Conflicting findings on co-morbidity was reported in another study, which found more gastrointestinal co-morbidities (23%) in CA-CDI compared to HCFA-CDI cases (6%)[71]. In two studies, CA-CDI pediatric patients were younger than HCFA cases[40,71], but had similar rates of no antibiotic exposure and recurrence rates. The literature presents different results for proton-pump inhibitors, some showing significant risk, while others do not (Table 2). Further research may help to define the role of proton-pump inhibitors and pediatric CDI.

**Adult CDI risk factors:**The risk factors that are common for adult CDI also include the same triad of factors (Table 2): host factors (age, co-morbidities), disruptive factors (exposure to antibiotics or other medications) and increased exposure to *C. difficile* spores (prolonged lengths of stay at healthcare facilities). A broader range of antibiotics have been identified as high-risk in adults, but there are not as many studies done in children (Table 2). However, many additional types of risk factors were identified in several studies using multivariate models to adjust for other simultaneous risk factors. These included enemas (aRR = 3.3), gastrointestinal stimulants (aRR = 3.1), stool softeners (aRR = 1.7)[64], cytoxic drugs (aRR = 8.1), feeding tubes (aRR = 2.8)[22], albumin level < 2.7 mg/dL (aOR = 3.8), leukocytosis [WBC count > 13000 cells/ml (aOR = 2.7), impaired functional capacity (independent was baseline versus required assistance or bedridden, aOR = 9.14), watery diarrhea (aOR = 17.4)[25], and mechanical ventilation (aOR = 1.9)[73]. A meta-analysis pooled data from five studies of adult CDI and found the same risk factors associated with BI/NAP1/027 strain as with other strain ribotypes: age > 65 years (aOR = 1.77, 95%CI: 1.31-2.4) and fluoroquinolone use (aOR = 1.96, 95%CI: 1.37-2.80)[74]. The one study with the highest report of no antibiotic exposure (96%) was also mostly community cases[75]. Exposure to infected room-mates or proximity pressure has been reported by several studies in adult CDI (Table 2), but not in children, which may be due to the lack of HCFA outbreaks reported in pediatric hospitals. The literature presents different results for proton-pump inhibitors, some showing significant risk, while others do not (Table 2).

**Comparison of epidemiology of pediatric and adult AAD:** The overall median incidence of pediatric AAD averages 27/100 compared to 15/100 for adult AAD, but the range in both populations is wide (< 1%-80%), as shown in Table 1. The incidence from these studies may be confounded by method the data was collected and from differences in the age distributions, the types of antibiotic exposures and whether the antibiotic exposure occurred while the patient is hospitalized or as an outpatient. Data for secular trends of pediatric AAD and adult AAD have not been documented, so it is uncertain if non-*C. difficile* related AAD is increasing or decreasing over time. Limited data is available on non-*C. difficile* etiologies of AAD and, without having a pathologic etiology to link time of occurrence and place, it is impossible to establish the existence of non-*C. difficile* outbreaks of AAD for both pediatric and adult cases of AAD. It is difficult to compare risk factors for pediatric versus adult AAD due to the lack of studies for AAD risk factors.

**Comparison of epidemiology of pediatric and adult CDI:**While the overall median incidence from Table 1 of pediatric CDI (31/10000) may be higher than adult CDI (10/10000), these rates are highly influenced by method in which the data was collected, differences in age distribution, setting (inpatient or outpatient) and underlying risk factor distribution. National, prospective surveillance studies of CDI rates have only recently become established. The prevalence of CDI is not constant over all age ranges; pediatric CDI peaks at age 5, while adult CDI peaks at age 67. The increase in pediatric CDI in early childhood may be due to an increase in antibiotic use, especially associated with respiratory infections and perhaps to exposure to other children in schools and daycare settings. Adult cases of CDI may increase with age due to the development of more chronic co-morbidities, higher rates of hospitalizations and increased exposure to antibiotics with age. Generally, more CA cases are reported for pediatric CDI (41%) compared to adult cases of CA-CDI (30%). The rate of CA-CDI is increasing, especially in children. Significantly more adult CDI cases are female (median of 56%) compared to female pediatric cases (median of 47%, *P* < 0.01). There have been few studies that have reported outbreaks of pediatric cases of CDI, while large outbreaks of CDI in adult inpatients are commonly reported. One difference between adult and pediatric CDI populations is the higher prevalence of the hypervirulent epidemic *C. difficile* strain NAP1/027/BI in adult patients. This may be due to the restriction of fluoroquinolone use in children, as this antibiotic is a risk factor for NAP1/027/BI CDI in adults. Some risk factors are similar for pediatric and adult CDI: age and exposure to antibiotics.In contrast, while prior hospitalization is an established risk factor for adult CDI, its role in pediatric CDI is unclear, especially as pediatric CA-CDI rates continue to increase. Adults with CDI have a more complex risk factor profile than pediatric CDI.

**CLINICAL PRESENTATION**

***Incubation time***

**Pediatric AAD incubation time**: The mean incubation times for pediatric AAD is from 2-6 d, with AAD typically occurring while the children are on antibiotics (85%-92% of cases); only 8%-15% report delayed-onset AAD post-antibiotics (Table 3). For example, in 225 outpatient children given antibiotics, the mean onset was 2.3 ± 1.1 d and all cases of AAD occurred while the children were taking the antibiotics[76]. The time of onset is similar for outpatients (2-5 d)[63,76] and for inpatients (4-6 d)[77,78].

**Adult AAD incubation time**: The mean incubation time for adult AAD cases is 3-18 d, but the time of onset (while on antibiotics versus delayed-onset) was not as consistently reported as in studies of pediatric AAD. Studies with lower rates of delayed-onset AAD tend to suffer from an insufficient follow-up after antibiotics were discontinued[79,80]. In one controlled trial of adults on antibiotics randomized to a probiotic drink or control group, only 5 (26%) of the 62 control patients developed AAD while on antibiotics, while most (74%) had delayed-onset AAD [81].

The incubation period of AAD is related to time of normal flora recovery after antibiotic exposure. In one study of six healthy adult volunteers exposed to oral amoxicillin (1.5 g/d for 5 d), a major shift in the normal flora was detected within 24 h after antibiotic exposure; 88% of the normal flora recovered within 30 d and only 89% recovered after 60 d[82].One case of an adult patient with amoxillcin-clavulanic acid treatment was followed for changes in normal flora[83]. After day four of antibiotic exposure, there was a complete absence of Clostridium cluster XIVa (down from 20% from day 0) and the presence of Faecalibacterium decreased from 33% to 15%. These two taxa are the main ones associated with the production of butyrate (the preferred energy source of colonocytes). The intestinal microflora of three healthy adult human volunteers was characterized using 16S rRNA sequencing before and after exposure to ciprofloxacin (500 mg bid for 5 d). Ciprofloxacin impacted 33% of the bacterial taxa in gut, reducing both diversity and taxonomic richness. Taxonomic composition mostly recovered within 4 wk post-antibiotic exposure, but several taxa failed to recover within 6 mo. Ciprofloxacin was found to reduce 30% of the taxa in these individuals[84].

**Pediatric CDI incubation time:**The mean incubation period for pediatric CDI is 3-10 d, as shown in Table 3[71,85].

**Adult CDI incubation time:**The mean onset of the initial episode of adult CDI cases is 6-12 d (Table 3), although delayed-onset (> 21 or 31 d post-discharge) has been reported in several studies ranging from 10%-53% of CDI cases[45, 86,87].

**Time between recurrent episodes of CDI**: The time between adult CDI recurrences has been reported in several studies, but there are no reports of this time interval in pediatric CDI. In 24 adults with *C. difficile* colitis, the mean time between episodes was 69.6 ± 42.2 d, ranging from 3-32 d post-vancomycin treatment[88]. In another study of 209 adults with recurrent CDI, the mean time between episodes was 69.6 ± 42 d[89]. Figueroa et al. reported the mean time to recurrence was 12.2 ± 6.4 d[90]. Mean time to CDI recurrences in a mixed pediatric and adult population (aged 1-96 years old) was 42 d, and ranged from 10-211 d[91].

***Severity***

**Pediatric AAD severity:**The definition of severity of disease for diarrhea has been well documented for adults, but is less standardized for pediatric cases. Most clinical trials define pediatric diarrhea as one to three abnormally loose stools per 24 to 48 h[19,20,21,92]. Additionally, stool frequency is more difficult to quantify in diaper-aged children. The reported mean duration for pediatric AAD is 3-9 d (Table 3)[63,76,93]. The severity of pediatric AAD ranges from mild, self-limited diarrhea to moderate diarrhea (Table 3). In one study of 250 pediatric inpatients (5-12 years old) who developed diarrhea, most (82%) were not due to *C. difficile*, but 16% had severe diarrhea, 36% had abdominal pain and 11% reported vomiting[94]. If the symptoms of diarrhea are severe (> 10 movements/d), pediatric AAD may lead to electrolyte disturbances and dehydration[94]. Few cases of pediatric antibiotic-associated colitis or pseudomembranous colitis (PMC) have been reported. There is one case report of a 16 year old girl who developed PMC not associated with *C. difficile*[95].

**Adult AAD severity:**Frequency of diarrhea, colitis and PMC associated with adult cases of AAD (not due to*C. difficile*) are infrequently reported. The mean duration of adult AAD is 1-22 d (Table 3). From one study, the mean duration adult AAD was fourdays while on antibiotics, but the mean duration was longer (18 d) if the cases were delayed-onset AAD[96].

**Pediatric CDI severity:**The range of symptoms for pediatric CDI is wide: children can develop mild-moderate diarrhea or severe disease or recurrent episodes of CDI (Table 3). Most symptoms of pediatric CDI are mild-moderate diarrhea (23%-87%)[13,40]. The mean duration of pediatric CDI is not as well documented in the literature, but ranges 2-9 d based on limited reports (Table 3)[1,12,97].A population-based surveillance study of pediatric CDI cases found 87% reported only diarrhea, 9% had severe CDI and 4% had severe CDI with complications[40]. Severe cases of pediatric CDI (defined variously as having > 2 severe indicators including fever, leukocytosis, requirement for ICU stay or surgery) have been reported in 8%-76% of cases (Table 3). Disease severity in pediatric CDI may be overestimated if adult criteria are used. In two studies reporting a high frequency of severe CDI in children, a re-assessment found the majority had low rates of morbidity and mortality and were successfully treated with standard antibiotic therapy[71,98]. Kim *et al*[98] defined severe pediatric CDI as having at least one complication (PMC, CDI-related surgery, intestinal perforation, toxic megacolon, or ICU stay) or ≥ 2 laboratory/clinical indicators (elevated white blood cell count, or high albumin, or high creatinine, fecal blood or fever). Pai et al. defined severe pediatric CDI if any of the following were present: elevated white blood cell counts, rising serum creatinine, fever or signs of severe colitis[71]. Hence new criteria for determining diarrhea severity in pediatric CDI are being studied. Infrequently, very severe forms of pediatric CDI have been reported. A case of CDI in a four year-old boy who had been treated with amoxicillin-clavulanic acid developed toxic megacolon[99]. Recurrences of pediatric CDI are common (10%-31% recurrence rates, as shown in Table 3), which may result in longer hospitalizations if the child is an inpatient[40,91,100]. Rates of recurrent CDI were found to be higher in children with severe CDI (31%) compared to a lower frequency (15%) if the child had mild-moderate CDI[98].

**Adult CDI severity:**Mild to moderate diarrhea is seen in 35-61% of adult CDI cases, while severe disease occurs less frequently (3%-41%), as shown in Table 3. In one study of 73 adult CDI cases, 18 (25%) had mild, self-limiting disease, 26 (36%) developed moderate diarrhea, 23 (31%) developed prolonged diarrhea and 6 (8%) developed complicated CDI[101]. The reported mean duration of adult CDI ranges from 5-26 d (Table 3)[89,102,103]. Adults with severe CDI report abdominal pain and fever in addition to diarrheal symptoms[104]. Attributable mortality is significantly higher in adult patients with severe CDI compared to mild-moderate CDI (60% *vs* 28%, *p* = 0.046, respectively)[105]. A hypervirulent strain of *C. difficile* (NAP1/027/BI) was the predominant strain associated with outbreaks of CDI cases in 88 hospitals in Quebec Canada in 2003-2004 which were associated with twice the rate of severe CDI cases with higher mortality rates[106]. More recent surveillance studies for endemic cases across 10 United States states also found a significantly elevated risk of severe CDI with the NAP1/027/BI strain[107]. Fortunately, the most severe forms of CDI (pseudomembraneous colitis, toxic megacolon or fulminant disease) are infrequently reported (1%-6%). Fulminant CDI is a systemic inflammatory syndrome that occurs infrequently, but typically requires colectomy and often results in death[108]. Although diarrhea is the hallmark of CDI, it may be absent in fulminant CDI, secondary to severe colonic dysmotility making fulminant colitis difficult to diagnose[109,110].

Recurrent CDI may occur in 19%-42% of adults after their initial episode of CDI has resolved, as shown in Table 3. As many as 10%-30% recur once after an initial CDI episode, 40% have two recurrences and 50% of those continue to have multiple recurrences, which may occur over a period of several years[111]. The CDC estimates in the United States during 2011, 483120 had initial CDI episodes and an estimated 77000-232000 would have recurred, providing a conservative national estimate of 715,000 cases of total CDI/year[9].

**Comparison of clinical presentations of pediatric and adult AAD:**The onset of pediatric AAD appears to be slightly quicker than adult cases of AAD and most pediatric AAD cases become symptomatic while the child is on antibiotics. In contrast, more cases of delayed-onset adult AAD cases are reported. However, whether this is a valid observation or due to the infrequent follow-up of children with antibiotic exposure is unknown. Most AAD cases are mild-moderate both in pediatric and adults. Pediatric cases of AAD and CDI typically have a shorter duration than adult cases of AAD and CDI.

**Comparison of the clinical presentation for pediatric versus adult CDI**: The onset of CDI is fairly rapid for pediatric cases (3-10 d), while symptoms appear slightly later in adult CDI (2-15 d) and recurrences of adult CDI may appear within two months of the previous episode. Pediatric and adult cases of CDI are both typically mild-moderate disease and the frequency of severe disease is similar for pediatric and adult cases, despite the finding that the hypervirulent strain of BI/NAP1/027, which is associated with severe CDI, is rarely found in children. However, severe complications of CDI, especially fulminent CDI and PMC, are more common in adults and are rarely seen in pediatric CDI. Recurrent CDI is slightly more common in adults (averaging 25%) than for pediatric CDI (averaging 20%).

**CONSEQUENCES OF INFECTION**

***Pediatric AAD consequences***

The consequences of pediatric AAD for inpatients may include increased length of hospitalization and, for outpatients, parents may discontinue the inciting antibiotics due to the diarrhea, without fully treating the child for the inciting infection[76]. Other consequences of pediatric AAD have rarely been reported (Table 4).

***Adult AAD consequences***

Prolonged length of stay and higher mortality rates have been reported for adult AAD cases[37,112]. Several studies have estimated that the cost of healthcare associated with adult AAD ranges from ***$***1400-$1968/person[113,114]. As with pediatric cases, development of AAD may also lead to premature discontinuation of antibiotic therapy, resulting in low cure rates[37].

***Pediatric CDI consequences***

Consequences of pediatric CDI may include increased length-of-stays for inpatients, increased mortality, rates of surgery (colectomies), higher healthcare costs, and re-admissions to healthcare systems, as shown in Table 4. Crude mortality rates (1%-5%) and CDI attributable mortality rates (2-3%) are also low. Caution should be used when comparing mortality rates, as the observation periods vary from just during hospitalization stays[44,69], to 2-3 mo[71,115] to 6 mo[12], or were not reported[14,100]. Even though the proportion of severe CDI can be higher in children, the requirement for colectomy is low (approximately 1%) in mild-moderate CDI. However, the rate can be higher in cases of severe CDI. In one study of 151 children with severe CDI, 8.6% required colectomies with a 50% associated mortality rate[116].The median cost for healthcare for pediatric CDI is not trivial ($19000-$32000/child). As an increase in incidence rates of pediatric CDI was observed from 1997-2006, there were also increases seen for costs for healthcare (averaging $20000/case) and an increased risk of colectomies[14]. In a survey of CDI in 22 Children’s hospitals in United States from 2004-2006, 26% of the 4895 inpatient CDI cases were children < 1 year old and 1.2% required colectomies. The all-cause 60-d mortality rate among pediatric patients was reported to be 4% in a study of 22 pediatric hospitals surveyed[115]. Costs for healthcare associated with pediatric CDI are generally > $20000 United States dollars. Additional increases in length of hospitalizations are also observed for pediatric CDI cases (Table 4) ranging from 4-23 additional days, which may explain the higher healthcare costs associated with this disease.

***Adult CDI consequences***

As with pediatric CDI, the consequences of adult CDI may also include increased mortality, higher rates of surgery (colectomies), higher healthcare costs, longer length-of-stays for inpatients and re-admissions to healthcare systems (Table 4). Reported crude mortality rates can be high (10%-38%), and CDI attributable mortality ranged from 6%-17%. As with pediatric studies, the follow-up for mortality ranges from only during hospitalization[117,118], to 30 d[57,58,102,119,120], to 60 d[121], to 90 d[73], or to 6 mo.[122]. Adult CDI was sufficiently severe to require colectomy in only 1%-9% of patients, but the mortality associated with this type of surgery is of clinical concern. A meta-analysis of 31 studies of adults with CDI found overall, 1.1% needed a colectomy, but the rate increased to 30% if it was a severe case of CDI and post-colectomy mortality was exceedingly high (41%)[123]. Colectomy rates range from 0.3%-1.3% of CDI cases during outbreaks and 1.9%-6.2% during endemic periods[10]. The healthcare costs of adult CDI ranges from $3427-$9960 for initial episodes of CDI and costs may reach as high as $33000 for recurrent cases[9,124]. The cost of adult CDI care was determined from 2012 HCUP data and ranged from $3427 to $33055/patient, depending if it is an initial or recurrent CDI case and the total CDI costs for United States during 2012 ranged from $1-$6 billion dollars[10]. For cases of adult HCFA-CDI cases, hospitalization was typically prolonged from 3-24 d (Table 4). For adults with CDI, the likelihood of being re-admitted to a healthcare facility is high (21%-52%), especially for patients with recurrent CDI.

***Comparison of pediatric and adult consequences for AAD or CDI***

A consequence of pediatric CDI may include dehydration, especially for younger children, unlike adults. Pediatric cases of CDI have lower mortality rates and less frequent rates of colectomies. However, for both pediatric and adult CDI, if symptoms are sufficiently severe to require colectomy, there are high mortality rates associated with this type of surgery. For inpatients, development of CDI is associated with longer lengths-of-stay and its associated increased cost of care.

**PREVENTION**

***Prevention of Pediatric AAD***

Prevention of AAD has traditionally relied on appropriate use of antibiotics, for instance, limiting the use of broad-spectrum antibiotics whenever possible. However, studies documenting the impact of these practices on pediatric AAD are lacking (Table 5). AAD results from the disruption of the normal, protective microbes in the intestine caused by unintended killing of non-pathogenic organisms by the antibiotics. Probiotics (living microbes, which when given at a sufficient dose, having a proven health benefit on the host) may be given at the same time as the antibiotics to prevent the development of AAD by helping to stabilize the normal microbiome[125]. Caution should be exercised to not give a bacterial strain of probiotic that is susceptible to the prescribed antibiotic. This is not of concern if the probiotic is a yeast strain. Of 17 different types of probiotics tested for AAD, only a few strains have evidence-based efficacy for preventing pediatric AAD[126,127]. A meta-analysis of 22 randomized controlled trials testing various probiotics for the prevention of pediatric AAD found only two types of probiotics were significantly effective for pediatric AAD: a yeast, *Saccharomyces boulardii* CNCM I-745(*S. boulardii*) (pooled RR = 0.43, 95%CI: 0.32-0.60) and a bacterial probiotic, *Lactobacillus rhamnosus* GG (LGG) (pooled RR = 0.36, 95%CI: 0.19-0.69)[19]. Other meta-analyses (Table 5) have confirmed this finding.

***Prevention of Adult AAD***

Of 20 different probiotic types tested for the prevention of adult AAD, only a few have solid evidence for efficacy (Table 5). Videlock *et al*[128]pooled the results from 24 randomized controlled trials in adults and found in general, probiotics were effective in preventing AAD (pooled RR = 0.53, 95%CI: 0.43-0.66), but they did not report which strain(s) were independently protective. Many meta-analyses have reported combined data from a mixed population of adults and children or mixed types of probiotic strains[129,130]. One method to determine which probiotic strain is more effective is to only use data from one type of probiotic, or use sensitivity analysis to assess the effectiveness, grouping trials by the same strain of probiotic. A meta-analysis of 10 randomized controlled trials using only *S. boulardii* for the prevention of adult AAD found significant efficacy for this probiotic (pooled RR = 0.47, 95%CI: 0.35-0.63)[131]. Another meta-analysis pooled 15 trials and confirmed *S. boulardii* is effective for preventing adult AAD[132]. Hempel *et al*[129]conducted a meta-analysis of probiotics for AAD, but pooled 62 trials (32 different types of probiotics) that were a mixture of adult and pediatric populations and also mixed strains within some probiotic sub-groups. Their 'Lactobacillus' subgroup contained many different strains of Lactobacilli, but extracting three trials in adult patients and limiting the pooled results to one type of probiotic mixture (*L. casei* and *L. acidophilus* and *L. rhamnosus,* "BioK+"), the pooled RR (pRR = 0.51, 95%CI: 0.30-0.87) shows this mixture is significantly effective in preventing adult AAD, while other Lactobacilli probiotics were not effective. Xie *et al*[35]reviewed six trials for the prevention of AAD in elderly adults. Only one type of probiotic (*B. licheniformis*) in one trial was found to be effective, although the amount of evidence in the elderly population is extremely limited. Another meta-analysis pooled the data from six trials in adults randomized to either *L. rhamnosus* GG or placebo and did not find that this probiotic was effective to prevent adult AAD[133].Although the data for the prevention of adult AAD by probiotics is extensive, the challenge is having sufficient numbers of clinical trials for each type of probiotic strain to allow a valid conclusion to be formulated.

***Prevention of Pediatric CDI***

The prevention of CDI is typically targeted at a common source of infection (healthcare facilities) and relies upon a multi-pronged approach of infection control programs, antibiotic stewardship and measures to support the host's defenses. However, since HCFA pediatric CDI is not common, prevention of community-based CDI needs to rely on rational use of antibiotics and the use of probiotics. There are no studies of HCFA infection control programs in pediatric hospitals. The use of probiotics has been investigated in the pediatric population at risk. In one study of 283 children receiving antibiotics for respiratory infections, only 0.7% randomized to *S. boulardii* CNCM I-745 developed CDI compared to 5.6% of those given placebo, *p* = 0.04[93]. A meta-analysis of probiotics for the prevention of CDI was done, pooling the results of three pediatric trials and found probiotics reduced the incidence of pediatric CDI by 60% (pooled RR = 0.40, 95%CI: 0.17-0.96)[134]. However, this analysis was limited by the small numbers of trials done per probiotic strain in pediatric patients. Another meta-analysis and systematic review of probiotics for pediatric CDI was also limited by the scarcity of controlled trials in this population. Although the pooled data from five randomized controlled trials showed probiotics, in general, were protective of pediatric CDI (pooled RR = 0.35, 95%CI: 0.13-0.92), four types of probiotics had no second, confirmatory trial, and only *S. boulardii* showed efficacy using data pooled from two trials (Table 5)[19].

***Prevention of Adult CDI***

Current guidelines recommend a bundled program of surveillance, contact precautions, CDI patient isolation, hand hygiene, use of disposable equipment when possible and environmental disinfection[2,135]. Rampant inappropriate antibiotic use was documented in the 1990-2000's in hospitalized patients and outpatients, and while antibiotic stewardship programs reduced this rate, one recent study still found 74% of antibiotics given to 126 inpatients with CDI were inappropriately prescribed[136]. There have been many studies showing the use of a multi-disciplinary infection program resulted in a decrease of adult CDI cases. One important foundation of these programs is the use of antibiotic stewardship oversight, which has been shown to reduce CDI rates in adult inpatients from 46%-66% (Table 5). Probiotics have also been tested to assess if they can be effective for preventing adult cases of CDI. A meta-analysis of 11 randomized controlled trials for the prevention of CDI tested five different types of probiotics and found only one mixture of probiotics (*L. casei*, *L. acidophilus* and *L. rhamnosus,* "BioK+") had a significant preventive effect (pooled from three trials, RR=0.21, 95%CI: 0.11-0.42), while the pooled data from four trials using *S. boulardii* was not effective (RR = 0.70, 95%CI: 0.29-1.69)[137]. The other four trials did not have confirmatory trials and were excluded. A more recent meta-analysis of 21 randomized trials testing probiotics for CDI found four types of probiotics were significantly effective for preventing CDI, but when pediatric trials were excluded, only two probiotic types were effective in adults: *L. casei* DN114001 "Actimel" [pooled from two trials (RR = 0.08, 95%CI: 0.01-0.63) and a mixture of *L. acidophilus* and *L. casei* and *L. rhamnosus* "BioK+" (pooled from three trials with four treatment arms, RR = 0.21, 95%CI: 0.08-0.58)[138].

***Comparison between prevention strategies for pediatric vs adult AAD and CDI***

Prevention of pediatric and adult AAD may rely on rational use of antibiotics, but there have been no studies testing this intervention in pediatric or adult patients. There are studies of preventive strategies for adult CDI that include improved infection control programs focused on limiting *C. difficile* transmission at healthcare facilities, in addition to antibiotic stewardship programs to limit unnecessary or inappropriate antibiotic use. The data is supportive for the use of these programs to prevent adult CDI, but studies are lacking for pediatric populations. The use of preventive probiotics is supported by studies and children and adults seem to respond differently to the type of probiotic strain depending upon the outcome to be prevented. To prevent AAD, children responded better to *S. boulardii* or *L. rhamnosus* GG, while adults responded better to *S. boulardii* or the multi-strain mix of three Lactobacilli called 'BioK+'. To prevent CDI, *S. boulardii* was effective in pediatric patients, while BioK+ or *L. casei* DN114001 worked well in preventing adult CDI cases.

**TREATMENT**

***Treatment for pediatric AAD***

Current treatment for pediatric AAD usually involves discontinuation or changing the type of the inciting antibiotic and giving oral rehydration therapy. As the etiology is typically only known for a proportion of the cases (approximately 1/3 is due to *C. difficile*), effective antibiotic treatment for AAD is limited. If the diarrhea is moderate-severe, oral rehydration therapy may be sufficient to assist spontaneous recovery[93].

***Treatment for adult AAD***

Current treatment for adult cases of AAD usually involves discontinuation or changing the type of the inciting antibiotic (Table 5). In one study of 743 hospitalized adult patients in four Belgian hospitals who were given antibiotics, AAD developed in 71 (9.6%), with only four patients positive for *C. difficile*. Of the 71, only 46 (65%) were treated for AAD: IV hydration (24%), patient isolation (22%), probiotics (20%), antidiarrheal medications (20%), metronidazole (6%), discontinuation of the inciting antibiotic (6%), or other antibiotics (2%)[37]. Very few randomized controlled trials have been done to treat adult cases of AAD, including those assessing the use of probiotics. One trial compared a mixture of *L. casei* and *Bifidobacterium breve* with placebo in 70 adults with AAD and found no significant difference in the duration of AAD (4.9 d *vs* 4.5 d, respectively)[139]. Another study randomized 20 adults with mild AAD to either *S. boulardii* or placebo and found significantly more were cured with *S. boulardii* (70% *vs* 10%, *p* < 0.01, respectively)[140]. No other trials for the treatment of adult AAD have been reported.

***Treatment for pediatric CDI***

Discontinuation or changing the type of the inciting antibiotic is still recommended as the first step for treating mild pediatric CDI, along with oral rehydration therapy if the diarrhea is severe[71]. For children with moderate CDI, empirical antibiotic treatment directed against *C. difficile* is recommended. The first choice of treatment is oral metronidazole (20-40 mg/kg/d), followed by oral vancomycin (40 mg/kg/d) given orally or by enema if they do not respond to metronidazole[1]. In one study of 4895 inpatient pediatric CDI cases, 74% responded to metronidazole or vancomycin treatment[115]. Most studies have enrolled children with their first episode of CDI (Table 5) and show effective cure rates with either metronidazole (ranging from 31%-97%) or vancomycin (ranging from 83%-100%). No studies on treatments have included children with recurrent CDI disease.

***Treatment for adult CDI***

Treatment for the initial episode of adult CDI typically relies upon one of three antibiotics, while treatment of recurrent CDI may require adjunctive use of probiotics or immune stimulators. Once CDI has been diagnosed in adults, treatment with antibiotics directed against *C. difficile* is recommended (metronidazole or vancomycin or fidaxomicin)[2,28,141]. For mild to moderate CDI or for initial episodes of CDI, the recommended dose of metronidazole is 500 mg, three times daily and for vancomycin the dose is 125 mg four times daily, but if there is no response or if the CDI is severe, higher doses of vancomycin can be used (up to 2 g/d)[2,142,143]. Failure to respond to the antibiotic used within 5-7 d should prompt the switch to the other type of antibiotic. A meta-analysis of 15 treatment trials for adult CDI found vancomycin has a higher cure rate (mean 88% ± 9.1%) compared to metronidazole (76% ± 11.3%) and a lower rate of CDI recurrences (13% ± 9.9% and 31% ± 44%, respectively)[144]. For severe cases of adult CDI, treatment with vancomycin has been found to be more effective than metronidazole (97% cured *vs* 76% cured, respectively)[145]. Treatment recommendations vary according to whether the CDI episode is an initial episode, or if the patient has recurrent CDI disease and Table 5 presents the effectiveness of various treatments for studies that provide data separately for initial versus recurrent CDI disease. Vancomycin has slightly higher cure rates (91%-100%) for adults with initial CDI compared to metronidazole (75%-94%). Fidaxomicin was found to be equivalent to vancomycin for the initial episode of CDI in adult patients[141]. One study using monoclonal antibodies against *C. difficile* showed a trend (*p* = 0.07) for better cure rates (93%) compared to placebo (82%) for the initial episode of CDI[146].

From 20%-60% of adults treated with antibiotics have at least one recurrence of CDI, and many suffer from repeated recurrences that may occur over a period of years[143]. Effective treatments for adult recurrent disease have included vancomycin (55%-100% cured), while metronidazole seems to be less effective (50%-80% cured). Fidaxomicin was shown to successfully treat recurrent CDI, when it reduced the recurrence rate to 14% compared to 26% in vancomycin[147]. The first recurrence should be treated with a repeated 10-d course of vancomycin, while the subsequent recurrences are recommended to be treated with pulsed or tapered vancomycin regimes or use an adjunctive probiotic[2]. In one study of 163 adults with recurrent CDI, higher cure rates were noted for treatment with vancomycin pulse (86%) or vancomycin taper (69%) compared to a single 10-d vancomycin (46%) or metronidazole (58%) regime[143]. By the end of therapy, vancomycin was more effective at clearing *C. difficile* culture and/or toxins (89%) than metronidazole (59%, *p* < 0.001). The evidence for probiotics to treat adult CDI is limited by the small number of randomized controlled trials for each probiotic strain. One type of probiotic, *S. boulardii*, has two trials which provide evidence that this probiotic may be effective for preventing recurrences of CDI in adults, especially if combined with high dose (2 g/d) vancomycin[131,148]. Fecal microbial transplants (FMT) have been tested to treat adults with recurrent CDI and this method uses stool infusions from healthy donors containing a mixture of microbes[149].Two controlled trials found significantly higher cure rates for those patients receiving FMT (81% and 90%) compared to the control patients (Table 5). Many other investigational treatments are being tested for adult CDI, including passive immunization using monoclonal antibodies and vaccines to *C. difficile* toxins, but the evidence is not yet conclusive[150].

***Comparison between treatments for pediatric vs adult AAD and CDI***

The paucity of studies evaluating treatments for pediatric and adult AAD limits any conclusions, except to discontinue or switch the inciting antibiotic and use of oral rehydration therapy to prevent dehydration in children. To treat the initial episode of CDI, discontinuing the inciting antibiotic is more commonly seen in the pediatric patient compared to adults. Pediatric patients with initial CDI appear to respond slightly better to metronidazole, while adults respond slightly better to vancomycin. The choice should be balanced against the side-effects and toxicities of each antibiotic. For recurrent disease, the only studies that provided separate cure rates for metronidazole, vancomycin or fidaxomicin were in adult patients with recurrent CDI. Treatment with high doses of vancomycin, use of pulsed or tapered regimes of vancomycin, fidaxomicin or adjunctive use of some probiotic strains or FMT may be beneficial for adults with recurrent disease, but whether these treatments are effective in children with recurrent CDI has not been established.

**CONCLUSION**

This is the first comprehensive exploration comparing the similarities and differences of pediatric versus adult AAD and CDI. In summary, some of the major differences between pediatric and adult AAD and CDI relate to incubation periods, severity of the disease and treatment strategies. Most pediatric AAD/CDI cases become symptomatic while on antibiotics; in contrast, most adult cases have delayed-onset of symptoms that appear after the antibiotics have been discontinued and before the normal colonic microbiome has recovered. Pediatric CDI cases have lower mortality rates and fewer complications than adult CDI cases. Community acquired cases of CDI are more common in children, while most cases of adult CDI are associated with healthcare facilities. Adult CDI has a more diverse risk factor profile (more co-morbidities, types of hospital exposures, disruptive medications, *etc.*) than pediatric CDI, but both populations share increased risk for antibiotic exposure as a major risk factor. Pediatric CDI responds better to metronidazole, while adult CDI cases favor vancomycin. Recurrent CDI is reported more frequently in adults and treatment relies on a combination of antibiotic therapy and measures to restore the normal colonic microbiota including the use of probiotics or FMT.

***Gaps in the knowledge base***

By reviewing the literature, it became apparent there are several gaps in our knowledge about AAD and CDI. While national and global surveillance programs have been started for CDI to document incidence and trends over time, these programs have not been established for AAD. Basic demographic information (age, gender and race) and the spectrum of disease severity are infrequently reported for pediatric and adult cases of AAD. In addition, as the character of the intestinal microbiome shifts widely during the early childhood periods (neonatal, infant, pre-school, school-age, *etc.*) as children change nutritional status (bottle-fed, solid food, *etc*.) and are exposed to different environments (day-care, schools, *etc.*), a finer delination of AAD and CDI disease data by age categories might illuminate how children respond to these diseases as these other types of life-factors change. Broadly pooling data by a 'pediatric' classification may be masking some age-related responses. Sources of non-CDI associated AAD are difficult to determine due to the lack of documentation for specific etiologies. The lack of reported complications of pediatric and adult AAD may be due to either a true lack of disease progression, or due to the lack of adequate follow-up times for studies involving AAD. The lack of reported treatment studies for AAD and pediatric CDI requires further studies. It also would be interesting to determine if pediatric CDI is a risk factor when these children grow into adults.

**REFERENCES**

1 **McFarland LV**, Brandmarker SA, Guandalini S. Pediatric Clostridium difficile: a phantom menace or clinical reality? *J Pediatr Gastroenterol Nutr* 2000; **31**: 220-231 [PMID: 10997362]

2 **Surawicz CM**, Brandt LJ, Binion DG, Ananthakrishnan AN, Curry SR, Gilligan PH, McFarland LV, Mellow M, Zuckerbraun BS. Guidelines for diagnosis, treatment, and prevention of Clostridium difficile infections. *Am J Gastroenterol* 2013; **108**: 478-98; quiz 499 [PMID: 23439232]

3 **Cheng AC**, Ferguson JK, Richards MJ, Robson JM, Gilbert GL, McGregor A, Roberts S, Korman TM, Riley TV. Australasian Society for Infectious Diseases guidelines for the diagnosis and treatment of Clostridium difficile infection. *Med J Aust* 2011; **194**: 353-358 [PMID: 21470086]

4 **Wendt JM**, Cohen JA, Mu Y, Dumyati GK, Dunn JR, Holzbauer SM, Winston LG, Johnston HL, Meek JI, Farley MM, Wilson LE, Phipps EC, Beldavs ZG, Gerding DN, McDonald LC, Gould CV, Lessa FC. Clostridium difficile infection among children across diverse US geographic locations. *Pediatrics* 2014; **133**: 651-658 [PMID: 24590748 DOI: 10.1542/peds.2013-3049]

5 **Zilberberg MD**, Tillotson GS, McDonald C. Clostridium difficile infections among hospitalized children, United States, 1997-2006. *Emerg Infect Dis* 2010; **16**: 604-609 [PMID: 20350373 DOI: 10.3201/eid1604.090680]

6 **Sammons JS**, Toltzis P. Recent trends in the epidemiology and treatment of C. difficile infection in children. *Curr Opin Pediatr* 2013; **25**: 116-121 [PMID: 23241874 DOI: 10.1097/MOP.obo13e32835bf6c0]

7 **Zilberberg MD**, Tabak YP, Sievert DM, Derby KG, Johannes RS, Sun X, McDonald LC. Using electronic health information to risk-stratify rates of Clostridium difficile infection in US hospitals. *Infect Control Hosp Epidemiol* 2011; **32**: 649-655 [PMID: 21666394 DOI: 10.1086/660360]

8 **Evans CT**, Safdar N. Current Trends in the Epidemiology and Outcomes of Clostridium difficile Infection. *Clin Infect Dis* 2015; **60 Suppl 2**: S66-S71 [PMID: 25922403 DOI: 10.1093/cid/civ140]

9 **Lessa FC**, Winston LG, McDonald LC. Burden of Clostridium difficile infection in the United States. *N Engl J Med* 2015; **372**: 2369-2370 [PMID: 26061850 DOI: 10.1056/NEJMc1505190]

10 **Kwon JH**, Olsen MA, Dubberke ER. The morbidity, mortality, and costs associated with Clostridium difficile infection. *Infect Dis Clin North Am* 2015; **29**: 123-134 [PMID: 25677706 DOI: 10.1016/j.idc.2014.11.003]

11 **McFarland LV**. Antibiotic-associated diarrhea: epidemiology, trends and treatment. *Future Microbiol* 2008; **3**: 563-578 [PMID: 18811240 DOI: 10.2217/17460913.3.5.563]

12 **Crews JD**, Koo HL, Jiang ZD, Starke JR, DuPont HL. A hospital-based study of the clinical characteristics of Clostridium difficile infection in children. *Pediatr Infect Dis J* 2014; **33**: 924-928 [PMID: 25361022 DOI: 10.1097/INF.0000000000000338]

13 **Na JY**, Park JM, Lee KS, Kang JO, Oh SH, Kim YJ. Clinical Characteristics of Symptomatic Clostridium difficile Infection in Children: Conditions as Infection Risks and Whether Probiotics Is Effective. *Pediatr Gastroenterol Hepatol Nutr* 2014; **17**: 232-238 [PMID: 25587523 DOI: 10.5223/pghn.2014.17.4.232]

14 **Nylund CM**, Goudie A, Garza JM, Fairbrother G, Cohen MB. Clostridium difficile infection in hospitalized children in the United States. *Arch Pediatr Adolesc Med* 2011; **165**: 451-457 [PMID: 21199971 DOI: 10.1001/archpediatrics.2010.282]

15 **Jangi S**, Lamont JT. Asymptomatic colonization by Clostridium difficile in infants: implications for disease in later life. *J Pediatr Gastroenterol Nutr* 2010; **51**: 2-7 [PMID: 20512057 DOI: 10.1097/MPG.0b013e3181d29767]

16 **World Health Organization.** WHO definition of diarrhea. Accessed on November 13, 2015. Available from: URL: http://www.who.int/topics/diarrhoea/en/

17 **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 [PMID: 22108454 DOI: 10.1038/ajg.2011.398]

18 **Dulęba K**, Pawłowska M, Wietlicka-Piszcz M. Clostridium difficile infection in children hospitalized due to diarrhea. *Eur J Clin Microbiol Infect Dis* 2014; **33**: 201-209 [PMID: 24213847 DOI: 10.1007/s10096-013-1946-1]

19 **McFarland LV**, Goh S. Preventing Pediatric Antibiotic-Associated Diarrhea and Clostridium difficile Infections with Probiotics: a meta-analysis. *World J Meta-analysis* 2013; **1**: 102-120 [doi: 10.13105/wjma.v1.i3. 02]

20 **Alam S**, Mushtaq M. Antibiotic associated diarrhea in children. *Indian Pediatr* 2009; **46**: 491-496 [PMID: 19556659]

21 **Arvola T**, Laiho K, Torkkeli S, Mykkänen H, Salminen S, Maunula L, Isolauri E. Prophylactic Lactobacillus GG reduces antibiotic-associated diarrhea in children with respiratory infections: a randomized study. *Pediatrics* 1999; **104**: e64 [PMID: 10545590]

22 **Asha NJ**, Tompkins D, Wilcox MH. Comparative analysis of prevalence, risk factors, and molecular epidemiology of antibiotic-associated diarrhea due to Clostridium difficile, Clostridium perfringens, and Staphylococcus aureus. *J Clin Microbiol* 2006; **44**: 2785-2791 [PMID: 16891493]

23 **Dietrich CG**, Kottmann T, Alavi M. Commercially available probiotic drinks containing Lactobacillus casei DN-114001 reduce antibiotic-associated diarrhea. *World J Gastroenterol* 2014; **20**: 15837-15844 [PMID: 25400470 DOI: 10.3748/wjg.v20.i42.15837]

24 **Pituch H**, Obuch-Woszczatyński P, Wultańska D, van Belkum A, Meisel-Mikołajczyk F, Łuczak M. Laboratory diagnosis of antibiotic-associated diarrhea: a Polish pilot study into the clinical relevance of Clostridium difficile and Clostridium perfringens toxins. *Diagn Microbiol Infect Dis* 2007; **58**: 71-75 [PMID: 17300901]

25 **Peled N**, Pitlik S, Samra Z, Kazakov A, Bloch Y, Bishara J. Predicting Clostridium difficile toxin in hospitalized patients with antibiotic-associated diarrhea. *Infect Control Hosp Epidemiol* 2007; **28**: 377-381 [PMID: 17385141]

26 **Högenauer C**, Langner C, Beubler E, Lippe IT, Schicho R, Gorkiewicz G, Krause R, Gerstgrasser N, Krejs GJ, Hinterleitner TA. Klebsiella oxytoca as a causative organism of antibiotic-associated hemorrhagic colitis. *N Engl J Med* 2006; **355**: 2418-2426 [PMID: 17151365]

27 **Ackermann G**, Thomalla S, Ackermann F, Schaumann R, Rodloff AC, Ruf BR. Prevalence and characteristics of bacteria and host factors in an outbreak situation of antibiotic-associated diarrhoea. *J Med Microbiol* 2005; **54**: 149-153 [PMID: 15673508]

28 **Cohen SH**, Gerding DN, Johnson S, Kelly CP, Loo VG, McDonald LC, Pepin J, Wilcox MH. Clinical practice guidelines for Clostridium difficile infection in adults: 2010 update by the society for healthcare epidemiology of America (SHEA) and the infectious diseases society of America (IDSA). *Infect Control Hosp Epidemiol* 2010; **31**: 431-455 [PMID: 20307191 DOI: 10.1086/651706]

29 **Lübbert C**, John E, von Müller L. Clostridium difficile infection: guideline-based diagnosis and treatment. *Dtsch Arztebl Int* 2014; **111**: 723-731 [PMID: 25404529 DOI: 10.3238/arztebl.2014.0723]

30 **McFarland LV**. [Risk factor for antibiotic-associated diarrhea. A review of the literature]. *Ann Med Interne (Paris)* 1998; **149**: 261-266 [PMID: 9791558]

31 **Wiström J**, Norrby SR, Myhre EB, Eriksson S, Granström G, Lagergren L, Englund G, Nord CE, Svenungsson B. Frequency of antibiotic-associated diarrhoea in 2462 antibiotic-treated hospitalized patients: a prospective study. *J Antimicrob Chemother* 2001; **47**: 43-50 [PMID: 11152430]

32 **Benno Y**, Sawada K, Mitsuoka T. The intestinal microflora of infants: composition of fecal flora in breast-fed and bottle-fed infants. *Microbiol Immunol* 1984; **28**: 975-986 [PMID: 6513816]

33 **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 [PMID: 15668012]

34 **Vanderhoof JA**, Whitney DB, Antonson DL, Hanner TL, Lupo JV, Young RJ. Lactobacillus GG in the prevention of antibiotic-associated diarrhea in children. *J Pediatr* 1999; **135**: 564-568 [PMID: 10547243]

35 **Xie C**, Li J, Wang K, Li Q, Chen D. Probiotics for the prevention of antibiotic-associated diarrhoea in older patients: a systematic review. *Travel Med Infect Dis* 1977; **13**: 128-134 [PMID: 25805164 DOI: 10.1016/j.tmaid.2015.03.001]

36 **Lusk RH**, Fekety FR, Silva J, Bodendorfer T, Devine BJ, Kawanishi H, Korff L, Nakauchi D, Rogers S, Siskin SB. Gastrointestinal side effects of clindamycin and ampicillin therapy. *J Infect Dis* 1977; **135 Suppl**: S111-S119 [PMID: 850084]

37 **Elseviers MM**, Van Camp Y, Nayaert S, Duré K, Annemans L, Tanghe A, Vermeersch S. Prevalence and management of antibiotic associated diarrhea in general hospitals. *BMC Infect Dis* 2015; **15**: 129 [PMID: 25888351 DOI: 10.1186/s12879-015-08690]

38 **Sathyendran V**, McAuliffe GN, Swager T, Freeman JT, Taylor SL, Roberts SA. Clostridium difficile as a cause of healthcare-associated diarrhoea among children in Auckland, New Zealand: clinical and molecular epidemiology. *Eur J Clin Microbiol Infect Dis* 2014; **33**: 1741-1747 [PMID: 24810967 DOI: 10.1007/s10096-014-2139-2]

39 **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 [PMID: 15906260]

40 **Khanna S**, Baddour LM, Huskins WC, Kammer PP, Faubion WA, Zinsmeister AR, Harmsen WS, Pardi DS. The epidemiology of Clostridium difficile infection in children: a population-based study. *Clin Infect Dis* 2013; **56**: 1401-1406 [PMID: 23408679 DOI: 10.1093/cid/cit075]

41 **Kim K**, DuPont HL, Pickering LK. Outbreaks of diarrhea associated with Clostridium difficile and its toxin in day-care centers: evidence of person-to-person spread. *J Pediatr* 1983; **102**: 376-382 [PMID: 6827409 DOI: 10.1016/S0022-3476(83)80652-0]

42 **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 [PMID: 10358237]

43 **Søes LM**, Holt HM, Böttiger B, Nielsen HV, Torpdahl M, Nielsen EM, Ethelberg S, Mølbak K, Andreasen V, Kemp M, Olsen KE. The incidence and clinical symptomatology of Clostridium difficile infections in a community setting in a cohort of Danish patients attending general practice. *Eur J Clin Microbiol Infect Dis* 2014; **33**: 957-967 [PMID: 24352841 DOI: 10.1007/s10096-013-2033-3]

44 **Sammons JS**, Localio R, Xiao R, Coffin SE, Zaoutis T. Clostridium difficile infection is associated with increased risk of death and prolonged hospitalization in children. *Clin Infect Dis* 2013; **57**: 1-8 [PMID: 23532470]

45 **McFarland LV**, Mulligan ME, Kwok RY, Stamm WE. Nosocomial acquisition of Clostridium difficile infection. *N Engl J Med* 1989; **320**: 204-210 [PMID: 2911306]

46 **Chopra T**, Goldstein EJ. Clostridium difficile Infection in Long-term Care Facilities: A Call to Action for Antimicrobial Stewardship. *Clin Infect Dis* 2015; **60 Suppl 2**: S72-S76 [PMID: 25922404]

47 **Ferroni A**, Merckx J, Ancelle T, Pron B, Abachin E, Barbut F, Larzul J, Rigault P, Berche P, Gaillard JL. Nosocomial outbreak of Clostridium difficile diarrhea in a pediatric service. *Eur J Clin Microbiol Infect Dis* 1997; **16**: 928-933 [PMID: 9495676]

48 **Cartwright CP**, Stock F, Beekmann SE, Williams EC, Gill VJ. PCR amplification of rRNA intergenic spacer regions as a method for epidemiologic typing of Clostridium difficile. *J Clin Microbiol* 1995; **33**: 184-187 [PMID: 7699038]

49 **Delmée M**, Verellen G, Avesani V, Francois G. Clostridium difficile in neonates: serogrouping and epidemiology. *Eur J Pediatr* 1988; **147**: 36-40 [PMID: 3338476]

50 **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 [PMID: 19324222 DOI: 10.1016/j.jpeds.2008.10.016]

51 **von Müller L**, Mock M, Halfmann A, Stahlmann J, Simon A, Herrmann M. Epidemiology of Clostridium difficile in Germany based on a single center long-term surveillance and German-wide genotyping of recent isolates provided to the advisory laboratory for diagnostic reasons. *Int J Med Microbiol* 2015; **305**: 807-813 [PMID: 26341328 DOI: 10.1016/j.ijmm.2015.08.035]

52 **Stoesser N**, Crook DW, Fung R, Griffiths D, Harding RM, Kachrimanidou M, Keshav S, Peto TE, Vaughan A, Walker AS, Dingle KE. Molecular epidemiology of Clostridium difficile strains in children compared with that of strains circulating in adults with Clostridium difficile-associated infection. *J Clin Microbiol* 2011; **49**: 3994-3996 [PMID: 21940476 DOI: 10.1128/JCM.05349-11]

53 **Rousseau C**, Poilane I, De Pontual L, Maherault AC, Le Monnier A, Collignon A. Clostridium difficile carriage in healthy infants in the community: a potential reservoir for pathogenic strains. *Clin Infect Dis* 2012; **55**: 1209-1215 [PMID: 22843784 DOI: 10.1093/cid/cis637]

54 **Hart J**, Putsathit P, Knight DR, Sammels L, Riley TV, Keil A. Clostridium difficile infection diagnosis in a paediatric population: comparison of methodologies. *Eur J Clin Microbiol Infect Dis* 2014; **33**: 1555-1564 [PMID: 24781004 DOI: 10.1007/s10096-014-2108-9]

55 **Gaynes R**, Rimland D, Killum E, Lowery HK, Johnson TM, Killgore G, Tenover FC. Outbreak of Clostridium difficile infection in a long-term care facility: association with gatifloxacin use. *Clin Infect Dis* 2004; **38**: 640-645 [PMID: 14986246]

56 **Johnson S**, Samore MH, Farrow KA, Killgore GE, Tenover FC, Lyras D, Rood JI, DeGirolami P, Baltch AL, Rafferty ME, Pear SM, Gerding DN. Epidemics of diarrhea caused by a clindamycin-resistant strain of Clostridium difficile in four hospitals. *N Engl J Med* 1999; **341**: 1645-1651 [PMID: 10572152]

57 **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, René 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 [PMID: 16322602]

58 **Pépin J**, Valiquette L, Cossette B. Mortality attributable to nosocomial Clostridium difficile-associated disease during an epidemic caused by a hypervirulent strain in Quebec. *CMAJ* 2005; **173**: 1037-1042 [PMID: 16179431]

59 **Muto CA**, Pokrywka M, Shutt K, Mendelsohn AB, Nouri K, Posey K, Roberts T, Croyle K, Krystofiak S, Patel-Brown S, Pasculle AW, Paterson DL, Saul M, Harrison LH. A large outbreak of Clostridium difficile-associated disease with an unexpected proportion of deaths and colectomies at a teaching hospital following increased fluoroquinolone use. *Infect Control Hosp Epidemiol* 2005; **26**: 273-280 [PMID: 15796280]

60 **Jump RL**, Riggs MM, Sethi AK, Pultz MJ, Ellis-Reid T, Riebel W, Gerding DN, Salata RA, Donskey CJ. Multihospital outbreak of Clostridium difficile infection, Cleveland, Ohio, USA. *Emerg Infect Dis* 2010; **16**: 827-829 [PMID: 20409374 DOI: 10.3201/eid1605.071606]

61 **Lam TS**, Yuk MT, Tsang NC, Wong MH, Chuang SK. Clostridium difficile infection outbreak in a male rehabilitation ward, Hong Kong Special Administrative Region (China), 2011. *Western Pac Surveill Response J* 2012; **3**: 59-60 [PMID: 23908942 DOI: 10.5365/wpsar.2012.3.4.001]

62 **Miller M**, Gravel D, Mulvey M, Taylor G, Boyd D, Simor A, Gardam M, McGeer A, Hutchinson J, Moore D, Kelly S. Health care-associated Clostridium difficile infection in Canada: patient age and infecting strain type are highly predictive of severe outcome and mortality. *Clin Infect Dis* 2010; **50**: 194-201 [PMID: 20025526 DOI: 10.1086/649213]

63 **Turck D**, Bernet JP, Marx J, Kempf H, Giard P, Walbaum O, Lacombe A, Rembert F, Toursel F, Bernasconi P, Gottrand F, McFarland LV, Bloch K. Incidence and risk factors of oral antibiotic-associated diarrhea in an outpatient pediatric population. *J Pediatr Gastroenterol Nutr* 2003; **37**: 22-26 [PMID: 12827001]

64 **McFarland LV**, Surawicz CM, Stamm WE. Risk factors for Clostridium difficile carriage and C. difficile-associated diarrhea in a cohort of hospitalized patients. *J Infect Dis* 1990; **162**: 678-684 [PMID: 2387993]

65 **Huang H**, Wu S, Chen R, Xu S, Fang H, Weintraub A, Nord CE. Risk factors of Clostridium difficile infections among patients in a university hospital in Shanghai, China. *Anaerobe* 2014; **30**: 65-69 [PMID: 25219941 DOI: 10.1016/j.anaerobe.2014.08.015]

66 **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 [PMID: 21233782 DOI: 10.1097/INF.0b013e31820bfb29]

67 **Tai E**, Richardson LC, Townsend J, Howard E, Mcdonald LC. Clostridium difficile infection among children with cancer. *Pediatr Infect Dis J* 2011; **30**: 610-612 [PMID: 21206395 DOI: 10.1097/INF.0b013e31820970d1]

68 **Samady W**, Bush R, Pong A, Andrews A, Fisher ES. Predictors of Clostridium difficile infections in hospitalized children. *J Hosp Med* 2014; **9**: 94-98 [PMID: 24343932 DOI: 10.1002/jhm.2135]

69 **de Blank P**, Zaoutis T, Fisher B, Troxel A, Kim J, Aplenc R. Trends in Clostridium difficile infection and risk factors for hospital acquisition of Clostridium difficile among children with cancer. *J Pediatr* 2013; **163**: 699-705.e1 [PMID: 23477996 DOI: 10.1016/j.jpeds.2013.01.062]

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

71 **Pai S**, Aliyu SH, Enoch DA, Karas JA. Five years experience of Clostridium difficile infection in children at a UK tertiary hospital: proposed criteria for diagnosis and management. *PLoS One* 2012; **7**: e51728 [PMID: 23300561 DOI: 10.1371/journal.pone.0051728]

72 **Tschudin-Sutter S**, Tamma PD, Naegeli AN, Speck KA, Milstone AM, Perl TM. Distinguishing community-associated from hospital-associated Clostridium difficile infections in children: implications for public health surveillance. *Clin Infect Dis* 2013; **57**: 1665-1672 [PMID: 24046303 DOI: 10.1093/cid/cit581]

73 **Vesteinsdottir I**, Gudlaugsdottir S, Einarsdottir R, Kalaitzakis E, Sigurdardottir O, Bjornsson ES. Risk factors for Clostridium difficile toxin-positive diarrhea: a population-based prospective case-control study. *Eur J Clin Microbiol Infect Dis* 2012; **31**: 2601-2610 [PMID: 22441775]

74 **Vardakas KZ**, Konstantelias AA, Loizidis G, Rafailidis PI, Falagas ME. Risk factors for development of Clostridium difficile infection due to BI/NAP1/027 strain: a meta-analysis. *Int J Infect Dis* 2012; **16**: e768-e773 [PMID: 22921930 DOI: 10.1016/j.ijid.2012.07.010]

75 **Fellmeth G**, Yarlagadda S, Iyer S. Epidemiology of community-onset Clostridium difficile infection in a community in the South of England. *J Infect Public Health* 2010; **3**: 118-123 [PMID: 20869672 DOI: 10.1016/j.jiph.2010.07.002]

76 **Damrongmanee A**, Ukarapol N. Incidence of antibiotic-associated diarrhea in a pediatric ambulatory care setting. *J Med Assoc Thai* 2007; **90**: 513-517 [PMID: 17427529]

77 **Corrêa NB**, Péret Filho LA, Penna FJ, Lima FM, Nicoli JR. A randomized formula controlled trial of Bifidobacterium lactis and Streptococcus thermophilus for prevention of antibiotic-associated diarrhea in infants. *J Clin Gastroenterol* 2010; **39**: 385-389 [PMID: 15815206]

78 **Ruszczyński M**, Radzikowski A, Szajewska H. Clinical trial: effectiveness of Lactobacillus rhamnosus (strains E/N, Oxy and Pen) in the prevention of antibiotic-associated diarrhoea in children. *Aliment Pharmacol Ther* 2008; **28**: 154-161 [PMID: 18410562 DOI: 10.111/j.1365-2036.2008.03714.x]

79 **Can M**, Beşirbellioglu BA, Avci IY, Beker CM, Pahsa A. Prophylactic Saccharomyces boulardii in the prevention of antibiotic-associated diarrhea: a prospective study. *Med Sci Monit* 2006; **12**: PI19-PI22 [PMID: 16572062]

80 **Yapar N**, Sener A, Karaca B, Yucesoy M, Tarakci H, Cakir N, Yuce A. Antibiotic-associated diarrhea in a Turkish outpatient population: investigation of 288 cases. *J Chemother* 2005; **17**: 77-81 [PMID: 15828448]

81 **Hickson M**, D'Souza AL, Muthu N, Rogers TR, Want S, Rajkumar C, Bulpitt CJ. Use of probiotic Lactobacillus preparation to prevent diarrhoea associated with antibiotics: randomised double blind placebo controlled trial. *BMJ* 2007; **335**: 80 [PMID: 17604300]

82 **De La Cochetière MF**, Durand T, Lalande V, Petit JC, Potel G, Beaugerie L. Effect of antibiotic therapy on human fecal microbiota and the relation to the development of Clostridium difficile. *Microb Ecol* 2008; **56**: 395-402 [PMID: 18209965]

83 **Young VB**, Schmidt TM. Antibiotic-associated diarrhea accompanied by large-scale alterations in the composition of the fecal microbiota. *J Clin Microbiol* 2004; **42**: 1203-1206 [PMID: 15004076]

84 **Dethlefsen L**, Huse S, Sogin ML, Relman DA. The pervasive effects of an antibiotic on the human gut microbiota, as revealed by deep 16S rRNA sequencing. *PLoS Biol* 2008; **6**: e280 [PMID: 19018661 DOI: 10.1371/journal.pbio.0060280]

85 **Mitchell DK**, Van R, Mason EH, Norris DM, Pickering LK. Prospective study of toxigenic Clostridium difficile in children given amoxicillin/clavulanate for otitis media. *Pediatr Infect Dis J* 1996; **15**: 514-519 [PMID: 8783348]

86 **Chang HT**, Krezolek D, Johnson S, Parada JP, Evans CT, Gerding DN. Onset of symptoms and time to diagnosis of Clostridium difficile-associated disease following discharge from an acute care hospital. *Infect Control Hosp Epidemiol* 2007; **28**: 926-931 [PMID: 17620239]

87 **Kutty PK**, Benoit SR, Woods CW, Sena AC, Naggie S, Frederick J, Engemann J, Evans S, Pien BC, Banerjee SN, Engel J, McDonald LC. Assessment of Clostridium difficile-associated disease surveillance definitions, North Carolina, 2005. *Infect Control Hosp Epidemiol* 2008; **29**: 197-202 [PMID: 18241032 DOI: 10.1086/528813]

88 **Walters BA**, Roberts R, Stafford R, Seneviratne E. Relapse of antibiotic associated colitis: endogenous persistence of Clostridium difficile during vancomycin therapy. *Gut* 1983; **24**: 206-212 [PMID: 6826104]

89 **McFarland LV**, Surawicz CM, Rubin M, Fekety R, Elmer GW, Greenberg RN. Recurrent Clostridium difficile disease: epidemiology and clinical characteristics. *Infect Control Hosp Epidemiol* 1999; **20**: 43-50 [PMID: 9927265]

90 **Figueroa I**, Johnson S, Sambol SP, Goldstein EJ, Citron DM, Gerding DN. Relapse versus reinfection: recurrent Clostridium difficile infection following treatment with fidaxomicin or vancomycin. *Clin Infect Dis* 2012; **55 Suppl 2**: S104-S109 [PMID: 22752857 DOI: 10.1093/cid/cis357]

91 **Barbut F**, Richard A, Hamadi K, Chomette V, Burghoffer B, Petit JC. Epidemiology of recurrences or reinfections of Clostridium difficile-associated diarrhea. *J Clin Microbiol* 2000; **38**: 2386-2388 [PMID: 10835010]

92 **Johnston BC**, Shamseer L, da Costa BR, Tsuyuki RT, Vohra S. Measurement issues in trials of pediatric acute diarrheal diseases: a systematic review. *Pediatrics* 2010; **126**: e222-e231 [PMID: 20566617 DOI: 10.1542/peds.2009-3667]

93 **Shan LS**, Hou P, Wang ZJ, Liu FR, Chen N, Shu LH, Zhang H, Han XH, Han XX, Cai XX, Shang YX, Vandenplas Y. Prevention and treatment of diarrhoea with Saccharomyces boulardii in children with acute lower respiratory tract infections. *Benef Microbes* 2013; **4**: 329-334 [PMID: 24311316]

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

95 **Vidrine SR**, Cortina C, Black M, Vidrine SB. Simultaneous acute appendicitis and pseudomembranous colitis in a pediatric patient. *J La State Med Soc* 2012; **164**: 265-267 [PMID: 23362591]

96 **McFarland LV**, Bauwens JE, Melcher SA, Surawicz CM, Greenberg RN, Elmer GW. Ciprofloxacin-associated Clostridium difficile disease. *Lancet* 1995; **346**: 977-978 [PMID: 7564771]

97 **Denno DM**, Shaikh N, Stapp JR, Qin X, Hutter CM, Hoffman V, Mooney JC, Wood KM, Stevens HJ, Jones R, Tarr PI, Klein EJ. Diarrhea etiology in a pediatric emergency department: a case control study. *Clin Infect Dis* 2012; **55**: 897-904 [PMID: 22700832 DOI: 10.1093/cid/cis553]

98 **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 [PMID: 22031485 DOI: 10.1097/INF.0b013e3182352e2c]

99 **Castillo A**, López J, Panadero E, Cerdá J, Padilla B, Bustinza A. Conservative surgical treatment for toxic megacolon due to Clostridium difficile infection in a transplanted pediatric patient. *Transpl Infect Dis* 2012; **14**: E34-E37 [PMID: 22726419 DOI: 10.1111/j.1399-3062.2012.00756.x]

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

101 **Kyne L**, Merry C, O'Connell B, Kelly A, Keane C, O'Neill D. Factors associated with prolonged symptoms and severe disease due to Clostridium difficile. *Age Ageing* 1999; **28**: 107-113 [PMID: 10350405]

102 **Wenisch JM**, Schmid D, Kuo HW, Simons E, Allerberger F, Michl V, Tesik P, Tucek G, Wenisch C. Hospital-acquired Clostridium difficile infection: determinants for severe disease. *Eur J Clin Microbiol Infect Dis* 2012; **31**: 1923-1930 [PMID: 22210266 DOI: 10.1007/s10096-011-1522-5]

103 **Hsu MS**, Wang JT, Huang WK, Liu YC, Chang SC. Prevalence and clinical features of Clostridium difficile-associated diarrhea in a tertiary hospital in northern Taiwan. *J Microbiol Immunol Infect* 2006; **39**: 242-248 [PMID: 16783456]

104 **Fujitani S**, George WI, Murthy AR. Comparison of clinical severity score indices for Clostridium difficile infection. *Infect Control Hosp Epidemiol* 2011; **32**: 220-228 [PMID: 21460506 DOI: 10.1086/658336]

105 **Khanafer N**, Touré A, Chambrier C, Cour M, Reverdy ME, Argaud L, Vanhems P. Predictors of Clostridium difficile infection severity in patients hospitalised in medical intensive care. *World J Gastroenterol* 2013; **19**: 8034-8041 [PMID: 24307797 DOI: 10.3748/wjg.v19.i44.8034]

106 **Pépin J**, Valiquette L, Alary ME, Villemure P, Pelletier A, Forget K, Pépin K, Chouinard D. Clostridium difficile-associated diarrhea in a region of Quebec from 1991 to 2003: a changing pattern of disease severity. *CMAJ* 2004; **171**: 466-472 [PMID: 15337727]

107 **See I**, Mu Y, Cohen J, Beldavs ZG, Winston LG, Dumyati G, Holzbauer S, Dunn J, Farley MM, Lyons C, Johnston H, Phipps E, Perlmutter R, Anderson L, Gerding DN, Lessa FC. NAP1 strain type predicts outcomes from Clostridium difficile infection. *Clin Infect Dis* 2014; **58**: 1394-1400 [PMID: 24604900 DOI: 10.1093/cid/ciu125]

108 **Dallal RM**, Harbrecht BG, Boujoukas AJ, Sirio CA, Farkas LM, Lee KK, Simmons RL. Fulminant Clostridium difficile: an underappreciated and increasing cause of death and complications. *Ann Surg* 2002; **235**: 363-372 [PMID: 11882758]

109 **Koss K**, Clark MA, Sanders DS, Morton D, Keighley MR, Goh J. The outcome of surgery in fulminant Clostridium difficile colitis. *Colorectal Dis* 2006; **8**: 149-154 [PMID: 16412077]

110 **Longo WE**, Mazuski JE, Virgo KS, Lee P, Bahadursingh AN, Johnson FE. Outcome after colectomy for Clostridium difficile colitis. *Dis Colon Rectum* 2004; **47**: 1620-1626 [PMID: 15540290]

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

112 **Selinger CP**, Bell A, Cairns A, Lockett M, Sebastian S, Haslam N. Probiotic VSL#3 prevents antibiotic-associated diarrhoea in a double-blind, randomized, placebo-controlled clinical trial. *J Hosp Infect* 2013; **84**: 159-165 [PMID: 23618760 DOI: 10.1016/j.jhin.2013.02.019]

113 **Song X**, Bartlett JG, Speck K, Naegeli A, Carroll K, Perl TM. Rising economic impact of clostridium difficile-associated disease in adult hospitalized patient population. *Infect Control Hosp Epidemiol* 2008; **29**: 823-828 [PMID: 18643746 DOI: 10.1016/j.jhin.2013.02.019]

114 **Kale-Pradhan PB**, Jassal HK, Wilhelm SM. Role of Lactobacillus in the prevention of antibiotic-associated diarrhea: a meta-analysis. *Pharmacotherapy* 2010; **30**: 119-126 [PMID: 20099986 DOI: 10.1592/phco.30.2.119]

115 **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 [PMID: 19047244 DOI: 10.1532/peds.2008-0469]

116 **Mc Laughlin D**, Friedmacher F, Puri P. The impact of Clostridium difficile on paediatric surgical practice: a systematic review. *Pediatr Surg Int* 2014; **30**: 853-859 [PMID: 25008231 DOI: 10.1007/s00383-014-3543-5]

117 **Tabak YP**, Zilberberg MD, Johannes RS, Sun X, McDonald LC. Attributable burden of hospital-onset Clostridium difficile infection: a propensity score matching study. *Infect Control Hosp Epidemiol* 2013; **34**: 588-596 [PMID: 23651889 DOI: 10.1086/670621]

118 **Eyre DW**, Walker AS, Wyllie D, Dingle KE, Griffiths D, Finney J, O'Connor L, Vaughan A, Crook DW, Wilcox MH, Peto TE. Predictors of first recurrence of Clostridium difficile infection: implications for initial management. *Clin Infect Dis* 2012; **55 Suppl 2**: S77-S87 [PMID: 22752869 DOI: 10.1093/cid/cis356]

119 **Gravel D**, Miller M, Simor A, Taylor G, Gardam M, McGeer A, Hutchinson J, Moore D, Kelly S, Boyd D, Mulvey M. Health care-associated Clostridium difficile infection in adults admitted to acute care hospitals in Canada: a Canadian Nosocomial Infection Surveillance Program Study. *Clin Infect Dis* 2009; **48**: 568-576 [PMID: 19191641 DOI: 10.1086/596703]

120 **Bacci S**, Mølbak K, Kjeldsen MK, Olsen KE. Binary toxin and death after Clostridium difficile infection. *Emerg Infect Dis* 2011; **17**: 976-982 [PMID: 21749757 DOI: 10.3201/eid/1706.101483]

121 **McFarland LV**, Clarridge JE, Beneda HW, Raugi GJ. Fluoroquinolone use and risk factors for Clostridium difficile-associated disease within a Veterans Administration health care system. *Clin Infect Dis* 2007; **45**: 1141-1151 [PMID: 17918075]

122 **Wullt M**, Odenholt I. A double-blind randomized controlled trial of fusidic acid and metronidazole for treatment of an initial episode of Clostridium difficile-associated diarrhoea. *J Antimicrob Chemother* 2004; **54**: 211-216 [PMID: 15163651]

123 **Bhangu S**, Bhangu A, Nightingale P, Michael A. Mortality and risk stratification in patients with Clostridium difficile-associated diarrhoea. *Colorectal Dis* 2010; **12**: 241-246 [PMID: 19508548 DOI: 10.1111/j.1463-1318.2009.01832.x]

124 **Lawrence SJ**, Puzniak LA, Shadel BN, Gillespie KN, Kollef MH, Mundy LM. Clostridium difficile in the intensive care unit: epidemiology, costs, and colonization pressure. *Infect Control Hosp Epidemiol* 2007; **28**: 123-130 [PMID: 17265392]

125 **McFarland LV**. From yaks to yogurt: the history, development, and current use of probiotics. *Clin Infect Dis* 2015; **60 Suppl 2**: S85-S90 [PMID: 25922406 DOI: 10.1093/cid/civ054]

126 **Johnston BC**, Goldenberg JZ, Vandvik PO, Sun X, Guyatt GH. Probiotics for the prevention of pediatric antibiotic-associated diarrhea. *Cochrane Database Syst Rev* 2011; **(11)**: CD004827 [PMID: 22071814 DOI: 10.1002/14651858.CD004827.pub3]

127 **Dinleyici EC**, Kara A, Ozen M, Vandenplas Y. Saccharomyces boulardii CNCM I-745 in different clinical conditions. *Expert Opin Biol Ther* 2014; **14**: 1593-1609 [PMID: 24995675 DOI: 10.1517/14712598.2014.937419]

128 **Videlock EJ**, Cremonini F. Meta-analysis: probiotics in antibiotic-associated diarrhoea. *Aliment Pharmacol Ther* 2012; **35**: 1355-1369 [PMID: 22531096 DOI: 10.1111/j.1365-]

129 **Hempel S**, Newberry SJ, Maher AR, Wang Z, Miles JN, Shanman R, Johnsen B, Shekelle PG. Probiotics for the prevention and treatment of antibiotic-associated diarrhea: a systematic review and meta-analysis. *JAMA* 2012; **307**: 1959-1969 [PMID: 22570464 DOI: 10.1001/jama.2012.3507]

130 **Pattani R**, Palda VA, Hwang SW, Shah PS. Probiotics for the prevention of antibiotic-associated diarrhea and Clostridium difficile infection among hospitalized patients: systematic review and meta-analysis. *Open Med* 2013; **7**: e56-e67 [PMID: 24348885]

131 **McFarland LV**. Systematic review and meta-analysis of Saccharomyces boulardii in adult patients. *World J Gastroenterol* 2010; **16**: 2202-2222 [PMID: 20458757 DOI: 10.3748/wjg.v16.i18.2202]

132 **Szajewska H**, Horvath A, Kołodziej M. Systematic review with meta-analysis: Saccharomyces boulardii supplementation and eradication of Helicobacter pylori infection. *Aliment Pharmacol Ther* 2015; **41**: 1237-1245 [PMID: 25898944 DOI: 10.1111/apt.13214]

133 **Szajewska H**, Kołodziej M. Systematic review with meta-analysis: Lactobacillus rhamnosus GG in the prevention of antibiotic-associated diarrhoea in children and adults. *Aliment Pharmacol Ther* 2015; **42**: 1149-1157 [PMID: 26365389 DOI: 10.1111/apt.13404]

134 **Johnston BC**, Ma SS, Goldenberg JZ, Thorlund K, Vandvik PO, Loeb M, Guyatt GH. Probiotics for the prevention of Clostridium difficile-associated diarrhea: a systematic review and meta-analysis. *Ann Intern Med* 2012; **157**: 878-888 [PMID: 23362517]

135 **Goldstein EJ**, Johnson S, Maziade PJ, McFarland LV, Trick W, Dresser L, Millette M, Mazloum H, Low DE. Pathway to Prevention of Nosocomial Clostridium difficile Infection. *Clin Infect Dis* 2015; **60 Suppl 2**: S148-S158 [PMID: 25922401 DOI: 10.1093/cid/civ142,]

136 **Srigley JA**, Brooks A, Sung M, Yamamura D, Haider S, Mertz D. Inappropriate use of antibiotics and Clostridium difficile infection. *Am J Infect Control* 2013; **41**: 1116-1118 [PMID: 23932828 DOI: 10.1016/j.ajic.2013.04.017]

137 **Johnson S**, Maziade PJ, McFarland LV, Trick W, Donskey C, Currie B, Low DE, Goldstein EJ. Is primary prevention of Clostridium difficile infection possible with specific probiotics? *Int J Infect Dis* 2012; **16**: e786-e792 [PMID: 22863358 DOI: 10.1016/j.ijid.2012.06.005]

138 **McFarland LV**. Probiotics for the primary and secondary prevention of C. difficile infections: a meta-analysis and systemic review. *Antibiotics* 2015; **4**: 160-178 [doi: 10.3390/antibiotics4020160]

139 **Souza DN**, Jorge MT. The effect of Lactobacillus casei and Bifidobacterium breve on antibiotic-associated diarrhea treatment: randomized double-blind clinical trial. *Rev Soc Bras Med Trop* 2012; **45**: 112-116 [PMID: 22370839 DOI: 10.1590/S0037-86822012000100021]

140 **Ligny** **G.** Le traitement par l'ultra-levure des troubles intestinaux secondaires a l'antibiotherapie etude en double aveugle et etude clinique simple. [Ultra-Levure treatment of intestinal disorders secondary to antibiotics, a double-blind study and an open clinical study] In French. *Revue Française de Gastroentérologie* 1975; **114**: 45-50

141 **Cornely OA**, Crook DW, Esposito R, Poirier A, Somero MS, Weiss K, Sears P, Gorbach S. Fidaxomicin versus vancomycin for infection with Clostridium difficile in Europe, Canada, and the USA: a double-blind, non-inferiority, randomised controlled trial. *Lancet Infect Dis* 2012; **12**: 281-289 [PMID: 22321770 DOI: 10.1016/S1473-3099(11)70374-7]

142 **Surawicz CM**, McFarland LV, Greenberg RN, Rubin M, Fekety R, Mulligan ME, Garcia RJ, Brandmarker S, Bowen K, Borjal D, Elmer GW. The search for a better treatment for recurrent Clostridium difficile disease: use of high-dose vancomycin combined with Saccharomyces boulardii. *Clin Infect Dis* 2000; **31**: 1012-1017 [PMID: 11049785]

143 **McFarland LV**, Elmer GW, Surawicz CM. Breaking the cycle: treatment strategies for 163 cases of recurrent Clostridium difficile disease. *Am J Gastroenterol* 2002; **97**: 1769-1775 [PMID: 12135033]

144 **Vardakas KZ**, Polyzos KA, Patouni K, Rafailidis PI, Samonis G, Falagas ME. Treatment failure and recurrence of Clostridium difficile infection following treatment with vancomycin or metronidazole: a systematic review of the evidence. *Int J Antimicrob Agents* 2012; **40**: 1-8 [PMID: 22398198 DOI: 10.1016/j.ijantimicag.2012.01.004]

145 **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 [PMID: 17599306]

146 **Lowy I**, Molrine DC, Leav BA, Blair BM, Baxter R, Gerding DN, Nichol G, Thomas WD, Leney M, Sloan S, Hay CA, Ambrosino DM. Treatment with monoclonal antibodies against Clostridium difficile toxins. *N Engl J Med* 2010; **362**: 197-205 [PMID: 20089970 DOI: 10.1056/NEJMoa0907635,]

147 **Cornely OA**, Miller MA, Louie TJ, Crook DW, Gorbach SL. Treatment of first recurrence of Clostridium difficile infection: fidaxomicin versus vancomycin. *Clin Infect Dis* 2012; **55 Suppl 2**: S154-S161 [PMID: 22752865 DOI: 10.1093/cid/cis462]

148 **Surawicz CM**, Elmer GW, Speelman P, McFarland LV, Chinn J, van Belle G. Prevention of antibiotic-associated diarrhea by Saccharomyces boulardii: a prospective study. *Gastroenterology* 1989; **96**: 981-988 [PMID: 2494098]

149 **Borody T**, Fischer M, Mitchell S, Campbell J. Fecal microbiota transplantation in gastrointestinal disease: 2015 update and the road ahead. *Expert Rev Gastroenterol Hepatol* 2015; **9**: 1379-1391 [PMID: 26414076]

150 **Jarrad AM**, Karoli T, Blaskovich MA, Lyras D, Cooper MA. Clostridium difficile drug pipeline: challenges in discovery and development of new agents. *J Med Chem* 2015; **58**: 5164-5185 [PMID: 25760275 DOI: 10.1021/jm5016846]

151 **Jirapinyo** **P**, DensupsoontornN, Thamonsiri N, Wongarn R. Prevention of antibiotic-associated diarrhea in infants by probiotics. *J Med Assoc Thai* 2002; **85 Suppl 2**: S739-S742 [PMID: 12403254]

152 **Ahmad K**, Fatemeh F, Mehri N, Maryam S. Probiotics for the treatment of pediatric helicobacter pylori infection: a randomized double blind clinical trial. *Iran J Pediatr* 2013; **23**: 79-84 [PMID: 23446685]

153 **Saneeyan H**, Samira L, Hamid R. [Effectiveness of probiotic on treatment of Helicobacter pylori infection in children]. Iranian. *J Isfahan Med School* 2011; **29**: 882-889

154 **Seki H**, Shiohara M, Matsumura T, Miyagawa N, Tanaka M, Komiyama A, Kurata S. Prevention of antibiotic-associated diarrhea in children by Clostridium butyricum MIYAIRI. *Pediatr Int* 2003; **45**: 86-90 [PMID: 12654076]

155 **La Rosa M**, Bottaro G, Gulino N, Gambuzza F, Di Forti F, Inì G, Tornambè E. [Prevention of antibiotic-associated diarrhea with Lactobacillus sporogens and fructo-oligosaccharides in children. A multicentric double-blind vs placebo study]. *Minerva Pediatr* 2003; **55**: 447-452 [PMID: 14608267]

156 **Fox MJ**, Ahuja KD, Robertson IK, Ball MJ, Eri RD. Can probiotic yogurt prevent diarrhoea in children on antibiotics? A double-blind, randomised, placebo-controlled study. *BMJ Open* 2015; **5**: e006474 [PMID: 25588782 DOI: 10.1136/bmjopen-2014-006474]

157 **Kotowska M**, Albrecht P, Szajewska H. Saccharomyces boulardii in the prevention of antibiotic-associated diarrhoea in children: a randomized double-blind placebo-controlled trial. *Aliment Pharmacol Ther* 2005; **21**: 583-590 [PMID: 15740542]

158 **Duman DG**, Bor S, Ozütemiz O, Sahin T, Oğuz D, Iştan F, Vural T, Sandkci M, Işksal F, Simşek I, Soytürk M, Arslan S, Sivri B, Soykan I, Temizkan A, Beşşk F, Kaymakoğlu S, Kalayc C. Efficacy and safety of Saccharomyces boulardii in prevention of antibiotic-associated diarrhoea due to Helicobacterpylori eradication. *Eur J Gastroenterol Hepatol* 2005; **17**: 1357-1361 [PMID: 16292090]

159 **Allen SJ**, Wareham K, Wang D, Bradley C, Sewell B, Hutchings H, Harris W, Dhar A, Brown H, Foden A, Gravenor MB, Mack D, Phillips CJ. A high-dose preparation of lactobacilli and bifidobacteria in the prevention of antibiotic-associated and Clostridium difficile diarrhoea in older people admitted to hospital: a multicentre, randomised, double-blind, placebo-controlled, parallel arm trial (PLACIDE). *Health Technol Assess* 2013; **17**: 1-140 [PMID: 24309198 DOI: 10.3310/hta17570]

160 **Pozzoni P**, Riva A, Bellatorre AG, Amigoni M, Redaelli E, Ronchetti A, Stefani M, Tironi R, Molteni EE, Conte D, Casazza G, Colli A. Saccharomyces boulardii for the prevention of antibiotic-associated diarrhea in adult hospitalized patients: a single-center, randomized, double-blind, placebo-controlled trial. *Am J Gastroenterol* 2012; **107**: 922-931 [PMID: 22472744 DOI: 10.1038/ajg.2012.56]

161 **Li D**, Wang H, Tan M, Shao Y. Use of probiotics for prevention of antibiotic-associated diarrhea in elderly patients. *Wei chang bing xue* 2010; **15**: 154-156

162 **Surawicz CM**, McFarland LV, Elmer G, Chinn J. Treatment of recurrent Clostridium difficile colitis with vancomycin and Saccharomyces boulardii. *Am J Gastroenterol* 1989; **84**: 1285-1287 [PMID: 2679049]

163 **Ouwehand AC**, DongLian C, Weijian X, Stewart M, Ni J, Stewart T, Miller LE. Probiotics reduce symptoms of antibiotic use in a hospital setting: a randomized dose response study. *Vaccine* 2014; **32**: 458-463 [PMID: 24291194 DOI: 10.1016/j.vaccine.2013.11.053]

164 **Hirschhorn LR**, Trnka Y, Onderdonk A, Lee ML, Platt R. Epidemiology of community-acquired Clostridium difficile-associated diarrhea. *J Infect Dis* 1994; **169**: 127-133 [PMID: 8277174]

165 **Levy DG**, Stergachis A, McFarland LV, Van Vorst K, Graham DJ, Johnson ES, Park BJ, Shatin D, Clouse JC, Elmer GW. Antibiotics and Clostridium difficile diarrhea in the ambulatory care setting. *Clin Ther* 2000; **22**: 91-102 [PMID: 10688393]

166 **Meropol SB**, Localio AR, Metlay JP. Risks and benefits associated with antibiotic use for acute respiratory infections: a cohort study. *Ann Fam Med* 2013; **11**: 165-172 [PMID: 23508604]

167 **Chen KT**, Stephens DJ, Anderson E, Acton R, Saltzman D, Hess DJ. Clostridium difficile infection in the pediatric surgery population. *J Pediatr Surg* 2012; **47**: 1385-1389 [PMID: 22813801]

168 **Kim MN**, Kim N, Lee SH, Park YS, Hwang JH, Kim JW, Jeong SH, Lee DH, Kim JS, Jung HC, Song IS. The effects of probiotics on PPI-triple therapy for Helicobacter pylori eradication. *Helicobacter* 2008; **13**: 261-268 [PMID: 18665934 DOI: 10.1111/j.1523-5378.2008.00601.x]

169 **Deshpande A**, Pant C, Anderson MP, Donskey CJ, Sferra TJ. Clostridium difficile infection in the hospitalized pediatric population: increasing trend in disease incidence. *Pediatr Infect Dis J* 2013; **32**: 1138-1140 [PMID: 23546535]

170 **Boenning DA**, Fleisher GR, Campos JM, Hulkower CW, Quinlan RW. Clostridium difficile in a pediatric outpatient population. *Pediatr Infect Dis* 1982; **1**: 336-338 [PMID: 7155966]

171 **Hyams JS**, Feder H, Krause PJ, Frick J, McLaughlin JC, Furth T, Hine P. Occurrence of Clostridium difficile toxin-associated gastroenteritis following antibiotic therapy for otitis media in young children. *Pediatr Infect Dis* 1984; **3**: 433-436 [PMID: 6333674]

172 **Destura RV**. Bacillus clausii in preventing antibiotic-associated diarrhea among Filipino infants and children: A multi-center, randomized, open-label clinical trial of efficacy and safety. 2008. Accessed June 3, 2013. Available from: URL: http://en.sanofi.com/img/content/study/ENTER\_L\_01125\_summary.pdf.

173 **Stevens V**, Dumyati G, Fine LS, Fisher SG, van Wijngaarden E. Cumulative antibiotic exposures over time and the risk of Clostridium difficile infection. *Clin Infect Dis* 2011; **53**: 42-48 [PMID: 21653301 DOI: 10.1093/cid/cir301]

174 **Kuntz JL**, Chrischilles EA, Pendergast JF, Herwaldt LA, Polgreen PM. Incidence of and risk factors for community-associated Clostridium difficile infection: a nested case-control study. *BMC Infect Dis* 2011; **11**: 194 [PMID: 21762504 DOI: 10.1186/1471-2334-11-194]

175 **Jarvis WR**, Schlosser J, Jarvis AA, Chinn RY. National point prevalence of Clostridium difficile in US health care facility inpatients, 2008. *Am J Infect Control* 2009; **37**: 263-270 [PMID: 19278754]

176 **Schwartz KL**, Darwish I, Richardson SE, Mulvey MR, Thampi N. Severe clinical outcome is uncommon in Clostridium difficile infection in children: a retrospective cohort study. *BMC Pediatr* 2014; **14**: 28 [PMID: 24485120 DOI: 10.1186/1471-2431-14-28]

177 **Kociolek LK**, Patel SJ, Shulman ST, Gerding DN. Molecular epidemiology of Clostridium difficile infections in children: a retrospective cohort study. *Infect Control Hosp Epidemiol* 2015; **36**: 445-451 [PMID: 25782900 DOI: 10.1017/ice.2014.89]

178 **Garg S**, Mirza YR, Girotra M, Kumar V, Yoselevitz S, Segon A, Dutta SK. Epidemiology of Clostridium difficile-associated disease (CDAD): a shift from hospital-acquired infection to long-term care facility-based infection. *Dig Dis Sci* 2013; **58**: 3407-3412 [PMID: 24154638 DOI: 10.1007/s10620-013-2848-x]

179 **Leung J**, Burke B, Ford D, Garvin G, Korn C, Sulis C, Bhadelia N. Possible association between obesity and Clostridium difficile infection. *Emerg Infect Dis* 2013; **19**: 1791-1798 [PMID: 24188730 DOI: 10.3201/eid1911.130618]

180 **Kazakova SV**, Ware K, Baughman B, Bilukha O, Paradis A, Sears S, Thompson A, Jensen B, Wiggs L, Bessette J, Martin J, Clukey J, Gensheimer K, Killgore G, McDonald LC. A hospital outbreak of diarrhea due to an emerging epidemic strain of Clostridium difficile. *Arch Intern Med* 2006; **166**: 2518-2524 [PMID: 17159019]

181 **Nylund CM**, Eide M, Gorman GH. Association of Clostridium difficile infections with acid suppression medications in children. *J Pediatr* 2014; **165**: 979-84.e1 [PMID: 25112692 DOI: 10.1016/j.jpeds.2014.06.062]

182 **El Feghaly RE**, Stauber JL, Deych E, Gonzalez C, Tarr PI, Haslam DB. Markers of intestinal inflammation, not bacterial burden, correlate with clinical outcomes in Clostridium difficile infection. *Clin Infect Dis* 2013; **56**: 1713-1721 [PMID: 23487367 DOI: 10.1093/cid/cit147]

183 **Carignan A**, Allard C, Pépin J, Cossette B, Nault V, Valiquette L. Risk of Clostridium difficile infection after perioperative antibacterial prophylaxis before and during an outbreak of infection due to a hypervirulent strain. *Clin Infect Dis* 2008; **46**: 1838-1843 [PMID: 18462108 DOI: 10.1086/588291]

184 **Crabtree TD**, Pelletier SJ, Gleason TG, Pruett TL, Sawyer RG. Clinical characteristics and antibiotic utilization in surgical patients with Clostridium difficile-associated diarrhea. *Am Surg* 1999; **65**: 507-11; discussion 511-2 [PMID: 10366203]

185 **See I**, Bagchi S, Booth S, Scholz D, Geller AI, Anderson L, Moulton-Meissner H, Finks JL, Kelley K, Gould CV, Patel PR. Outbreak of Clostridium difficile Infections at an Outpatient Hemodialysis Facility-Michigan, 2012-2013. *Infect Control Hosp Epidemiol* 2015; **36**: 972-974 [PMID: 25913501 DOI: 10.1017/ice.2015.90]

186 **Scardina T**, Labuszewski L, Pacheco SM, Adams W, Schreckenberger P, Johnson S. Clostridium difficile infection (CDI) severity and outcome among patients infected with the NAP1/BI/027 strain in a non-epidemic setting. *Infect Control Hosp Epidemiol* 2015; **36**: 280-286 [PMID: 25695169 DOI: 10.1017/ice.2014.45]

187 **Hourigan SK**, Oliva-Hemker M, Hutfless S. The prevalence of Clostridium difficile infection in pediatric and adult patients with inflammatory bowel disease. *Dig Dis Sci* 2014; **59**: 2222-2227 [PMID: 24788321 DOI: 10.1007/s10620-014-3169-4]

188 **Kelsen JR**, Kim J, Latta D, Smathers S, McGowan KL, Zaoutis T, Mamula P, Baldassano RN. Recurrence rate of Clostridium difficile infection in hospitalized pediatric patients with inflammatory bowel disease. *Inflamm Bowel Dis* 2011; **17**: 50-55 [PMID: 20722068 DOI: 10.1002/ibd.21421]

189 **Hu MY**, Katchar K, Kyne L, Maroo S, Tummala S, Dreisbach V, Xu H, Leffler DA, Kelly CP. Prospective derivation and validation of a clinical prediction rule for recurrent Clostridium difficile infection. *Gastroenterology* 2009; **136**: 1206-1214 [PMID: 19162027 DOI: 10.1053/j.gastro.2008.12.038]

190 **Beaulieu M**, Williamson D, Pichette G, Lachaine J. Risk of Clostridium difficile-associated disease among patients receiving proton-pump inhibitors in a Quebec medical intensive care unit. *Infect Control Hosp Epidemiol* 2007; **28**: 1305-1307 [PMID: 17926283 DOI: 10.1086/521664]

191 **Marwick CA**, Yu N, Lockhart MC, McGuigan CC, Wiuff C, Davey PG, Donnan PT. Community-associated Clostridium difficile infection among older people in Tayside, Scotland, is associated with antibiotic exposure and care home residence: cohort study with nested case-control. *J Antimicrob Chemother* 2013; **68**: 2927-2933 [PMID: 23825381 DOI: 10.1093/jac/dkt257]

192 **Dubberke ER**, Reske KA, Yan Y, Olsen MA, McDonald LC, Fraser VJ. Clostridium difficile--associated disease in a setting of endemicity: identification of novel risk factors. *Clin Infect Dis* 2007; **45**: 1543-1549 [PMID: 18190314 DOI: 10.1086/523582]

193 **Zerey M**, Paton BL, Lincourt AE, Gersin KS, Kercher KW, Heniford BT. The burden of Clostridium difficile in surgical patients in the United States. *Surg Infect (Larchmt)* 2007; **8**: 557-566 [PMID: 18171114 DOI: 10.1089/sur.2006.062]

194 **Brown KE**, Knoderer CA, Nichols KR, Crumby AS. Acid-Suppressing Agents and Risk for Clostridium difficile Infection in Pediatric Patients. *Clin Pediatr (Phila)* 2015; **54**: 1102-1106 [PMID: 25644650 DOI: 10.1177/0009922815569201]

195 **Lee KS**, Shin WG, Jang MK, Kim HS, Kim HS, Park CJ, Lee JY, Kim KH, Park JY, Lee JH, Kim HY, Cho SJ, Yoo JY. Who are susceptible to pseudomembranous colitis among patients with presumed antibiotic-associated diarrhea? *Dis Colon Rectum* 2006; **49**: 1552-1558 [PMID: 17028914]

196 **Enoch DA**, Butler MJ, Pai S, Aliyu SH, Karas JA. Clostridium difficile in children: colonisation and disease. *J Infect* 2011; **63**: 105-113 [PMID: 21664931 DOI: 10.1016/j.jinf.2011.05.016]

197 **James AH**, Katz VL, Dotters DJ, Rogers RG. Clostridium difficile infection in obstetric and gynecologic patients. *South Med J* 1997; **90**: 889-892 [PMID: 9305296]

198 **Morrow LE**, Kollef MH, Casale TB. Probiotic prophylaxis of ventilator-associated pneumonia: a blinded, randomized, controlled trial. *Am J Respir Crit Care Med* 2010; **182**: 1058-1064 [PMID: 20522788 DOI: 10.1164/rccm.200912-1853OC]

199 **Bruns AH**, Oosterheert JJ, Kuijper EJ, Lammers JW, Thijsen S, Troelstra A, Hoepelman AI. Impact of different empirical antibiotic treatment regimens for community-acquired pneumonia on the emergence of Clostridium difficile. *J Antimicrob Chemother* 2010; **65**: 2464-2471 [PMID: 20823105 DOI: 10.1093/jac/dkq329]

200 **Leekha S**, Aronhalt KC, Sloan LM, Patel R, Orenstein R. Asymptomatic Clostridium difficile colonization in a tertiary care hospital: admission prevalence and risk factors. *Am J Infect Control* 2013; **41**: 390-393 [PMID: 23622704 DOI: 10.1016/j.ajic.2012.09.023]

201 **McFarland LV**, Elmer GW, Stamm WE, Mulligan ME. Correlation of immunoblot type, enterotoxin production, and cytotoxin production with clinical manifestations of Clostridium difficile infection in a cohort of hospitalized patients. *Infect Immun* 1991; **59**: 2456-2462 [PMID: 2050409]

202 **Ramanathan S**, Johnson S, Burns SP, Kralovic SM, Goldstein B, Smith B, Gerding DN, Evans CT. Recurrence of Clostridium difficile infection among veterans with spinal cord injury and disorder. *Am J Infect Control* 2014; **42**: 168-173 [PMID: 24485372 DOI: 10.1016/j.ajic.2013.08.009]

203 **Qualman SJ**, Petric M, Karmali MA, Smith CR, Hamilton SR. Clostridium difficile invasion and toxin circulation in fatal pediatric pseudomembranous colitis. *Am J Clin Pathol* 1990; **94**: 410-416 [PMID: 1699407]

204 **Rivlin J**, Lerner A, Augarten A, Wilschanski M, Kerem E, Ephros MA. Severe Clostridium difficile-associated colitis in young patients with cystic fibrosis. *J Pediatr* 1998; **132**: 177-179 [PMID: 9470027]

205 **Nicholson MR**, Thomsen IP, Slaughter JC, Creech CB, Edwards KM. Novel risk factors for recurrent Clostridium difficile infection in children. *J Pediatr Gastroenterol Nutr* 2015; **60**: 18-22 [PMID: 25199038 DOI: 10.1097/MPG.0000000000000553]

206 **Jardin CG**, Palmer HR, Shah DN, Le F, Beyda ND, Jiang Z, Garey KW. Assessment of treatment patterns and patient outcomes before vs after implementation of a severity-based Clostridium difficile infection treatment policy. *J Hosp Infect* 2013; **85**: 28-32 [PMID: 23834988 DOI: 10.1016/j.jhin.2013.04.017]

207 **Bartlett JG**. Clinical practice. Antibiotic-associated diarrhea. *N Engl J Med* 2002; **346**: 334-339 [PMID: 11821511]

208 **Rubin MS**, Bodenstein LE, Kent KC. Severe Clostridium difficile colitis. *Dis Colon Rectum* 1995; **38**: 350-354 [PMID: 7720439]

209 **Khanna S**, Pardi DS, Aronson SL, Kammer PP, Baddour LM. Outcomes in community-acquired Clostridium difficile infection. *Aliment Pharmacol Ther* 2012; **35**: 613-618 [PMID: 22229532 DOI: 10.1111/j.1365-2036.2011.04984.x]

210 **Sailhamer EA**, Carson K, Chang Y, Zacharias N, Spaniolas K, Tabbara M, Alam HB, DeMoya MA, Velmahos GC. Fulminant Clostridium difficile colitis: patterns of care and predictors of mortality. *Arch Surg* 2009; **144**: 433-49; discussion 433-49; [PMID: 19451485 DOI: 10.1001/archsurg.2009.51]

211 **van der Wilden GM**, Chang Y, Cropano C, Subramanian M, Schipper IB, Yeh DD, King DR, de Moya MA, Fagenholz PJ, Velmahos GC. Fulminant Clostridium difficile colitis: prospective development of a risk scoring system. *J Trauma Acute Care Surg* 2014; **76**: 424-430 [PMID: 24458048 DOI: 10.1097/TA.0000000000000105]

212 **Drudy D**, Harnedy N, Fanning S, Hannan M, Kyne L. Emergence and control of fluoroquinolone-resistant, toxin A-negative, toxin B-positive Clostridium difficile. *Infect Control Hosp Epidemiol* 2007; **28**: 932-940 [PMID: 17620240]

213 **Dubberke ER**, Butler AM, Reske KA, Agniel D, Olsen MA, D'Angelo G, McDonald LC, Fraser VJ. Attributable outcomes of endemic Clostridium difficile-associated disease in nonsurgical patients. *Emerg Infect Dis* 2008; **14**: 1031-1038 [PMID: 18598621 DOI: 10.3201/eid1407.070867]

214 **Halabi WJ**, Nguyen VQ, Carmichael JC, Pigazzi A, Stamos MJ, Mills S. Clostridium difficile colitis in the United States: a decade of trends, outcomes, risk factors for colectomy, and mortality after colectomy. *J Am Coll Surg* 2013; **217**: 802-812 [PMID: 24011436 DOI: 10.1016/j.jamcollsurg.2013.05.028]

215 **Kamdeu Fansi AA**, Guertin JR, LeLorier J. Savings from the use of a probiotic formula in the prophylaxis of antibiotic-associated diarrhea. *J Med Econ* 2012; **15**: 53-60 [PMID: 22023067 DOI: 10.3111/13696998.2011.629015]

216 **Dubberke ER**, Schaefer E, Reske KA, Zilberberg M, Hollenbeak CS, Olsen MA. Attributable inpatient costs of recurrent Clostridium difficile infections. *Infect Control Hosp Epidemiol* 2014; **35**: 1400-1407 [PMID: 25333435 DOI: 10.1086/678428]

217 **Dubberke ER**, Reske KA, Olsen MA, McDonald LC, Fraser VJ. Short- and long-term attributable costs of Clostridium difficile-associated disease in nonsurgical inpatients. *Clin Infect Dis* 2008; **46**: 497-504 [PMID: 18197759]

218 **Abdelsattar ZM**, Krapohl G, Alrahmani L, Banerjee M, Krell RW, Wong SL, Campbell DA, Aronoff DM, Hendren S. Postoperative burden of hospital-acquired Clostridium difficile infection. *Infect Control Hosp Epidemiol* 2015; **36**: 40-46 [PMID: 25627760 DOI: 10.1017/ice.2014.8]

219 **You E**, Song H, Cho J, Lee J. Reduction in the incidence of hospital-acquired Clostridium difficile infection through infection control interventions other than the restriction of antimicrobial use. *Int J Infect Dis* 2014; **22**: 9-10 [PMID: 24583565 DOI: 10.1016/j.ijid.2014.01.011]

220 **Kallen AJ**, Thompson A, Ristaino P, Chapman L, Nicholson A, Sim BT, Lessa F, Sharapov U, Fadden E, Boehler R, Gould C, Limbago B, Blythe D, McDonald LC. Complete restriction of fluoroquinolone use to control an outbreak of Clostridium difficile infection at a community hospital. *Infect Control Hosp Epidemiol* 2009; **30**: 264-272 [PMID: 19215193 DOI: 10.1086/595694]

221 **Kim YS**, Jeon H, Nam S, Cho BM, Park SH, Oh SM. Analysis of clinical characteristics and risk factors to neurosurgical patients with C. difficile-associated diarrhea. *J Kor Neurotraumatol Soc* 2011; **7**: 92-98

222 **Wenisch C**, Parschalk B, Hasenhündl M, Hirschl AM, Graninger W. Comparison of vancomycin, teicoplanin, metronidazole, and fusidic acid for the treatment of Clostridium difficile-associated diarrhea. *Clin Infect Dis* 1996; **22**: 813-818 [PMID: 8722937]

223 **Wullt M**, Hagslätt ML, Odenholt I. Lactobacillus plantarum 299v for the treatment of recurrent Clostridium difficile-associated diarrhoea: a double-blind, placebo-controlled trial. *Scand J Infect Dis* 2003; **35**: 365-367 [PMID: 12953945]

224 **van Nood E**, Dijkgraaf MG, Keller JJ. Duodenal infusion of feces for recurrent Clostridium difficile. *N Engl J Med* 2013; **368**: 2145 [PMID: 23718168]

225 **Cammarota G**, Masucci L, Ianiro G, Bibbò S, Dinoi G, Costamagna G, Sanguinetti M, Gasbarrini A. Randomised clinical trial: faecal microbiota transplantation by colonoscopy vs. vancomycin for the treatment of recurrent Clostridium difficile infection. *Aliment Pharmacol Ther* 2015; **41**: 835-843 [PMID: 25728808 DOI: 10.1111/apt.13144]

**P-Reviewer:** Feuerstadt P, Freedberg DE, Luo HS,

Teramoto-Matsubara OT, Trifan A **S-Editor:** Gong ZM

**L-Editor:** **E-Editor:**

**Table 1 Comparison of epidemiologic factors for pediatric antibiotic-associated diarrhea *vs* adult antibiotic-associated diarrhea and pediatric *Clostridium difficile* infections *vs* adult *Clostridium difficile* infections**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Characteristics** | **Pediatric AAD rate/100 (n/total)** | **Ref.** | **Adult AAD rate/100 unless noted (n/total)** | **Ref.** | **Pediatric CDI rate/10000 (n/total)** | **Ref.** | **Adult CDI rate/10000 (n/total)** | **Ref.** |
| Incidence:  inpatient | 29 (42/144)1 80 (8/10)1 | Shan[93]  Jirapinyo[151] | 7 (14/204)1  9 (10/112)1  9.6 (67/743)2  10.4 (153/1471)1  13 (13/98)1  15 (14/96)1  19 (48/257)1  22 (14/64)1  23 (55/242)2  25 (41/167)1  29 (42/144)1  33 (10/30)1 | Duman[158]  Selinger[112]  Elseviers[37]  Allen[159]  Pozzoni[160]  McFarland[96]  Li[161] Surawicz[162] Lusk[36] Ouwehand[163] Shan[93]  Dietrich[23] | 22  5.8 ad3  6.5 pd4  6.8 v3 12.8 ad4  13.4 pd5   31.5 d4 135.0 ad3 416.71 | Sathyendan[38] Chen[167] Kim[168] Benson[70] Zilberberg[5] de Blank[69] Deshpande[169] Duleba[18]  Shan [93] | 4.3 pd3 5.4 py4  5.7 hd2  10 pd2  12 py5  29.2 pd2  72 ad5  1282  131 ad6 1000 (93/30)1 2080 (83/399)2 | Stevens[173] Vesteinsdottir[73] Wenisch[102] Hsu[103] Kuntz[174] McFarland[121] Zilberberg[7]  Huang[65]  Jarvis[175] Dietrich[23]   McFarland[45] |
| outpatient | 6.2 (14/225)2 11 (71/650)2 16 (9/58) 1 24 (8/33) 1 26 (25/95)1 29 (22/76)2 52 (13/25)1 59 (16/27)1 62 (31/50)1 75 (27/36)1 | Damrongmanne [76] Turck[63] Arvola[21] Ahmad[152] Vanderhoof[34] Mitchell[85] Saneeyan[153] Seki [154] LaRosa[155] Fox[156] | 7.7/100000 py5 12/100000 py2 15/1005 | Hirschhorn[164]  Levy[165]  Yapar[80] | 143 200 (1/58)1 390 (12/306)1 780 (9/115)1 790 (6/76)2 | Benson[70] Arvola[21]   Boenning[170]  Hyams [171]  Mitchell [85] | 1.15 1.22 11.1 py5 | Fellmeth[75] Levy[165] Kuntz[174] |
| mixed in- and out-patients | 17 (20/120)1 23 (29/127)1 | Ruszczynski[78] Kotowska [157] | 2.5/100000 v 2 | Meropol[166] | 1.45 2.14 60 (1/161)1  600 (7/120)1  800 (10/127)1 | Khanna[40] Wendt[4] Destura[172]  Ruszczynski[78]   Kotowska[157] | 2.5 py5 5.42 | Khanna[17] Vesteinsdottir[73] |
| *Setting*  Health-care facility associated (HCFA) (% cases) | NR |  | NR |  | 25% 46% 48% 65% 69% 71% 74% | Khanna[40] Crews[12] Sammons[44] Pai[71] Sandora[66] Tschudin[72] Schwartz[176] | 21% 53% 59% 68% 89% 92% | Garg[178] Leung[179] Khanna[17]  Zilberberg[7] McFarland[45] Kazadova[180] |
| Community-acquired (CA) (% cases) | NR |  | NR |  | 19% 25% 26% 29% 30% 39% 41% 52% 54% 67% 71% 75% 96% | Tschudin[72] Sandora[66] Schwartz[176] Pai[71] Samady[68] Kociolek[177] Crews[12]  Duleba[18]  Sammons[44] Benson[70] Wendt[4]  Khanna[40] Soes[43] | 8% 11% 23% 27% 33% 34% 41% 43% | Kazadova[180] McFarland[121] Zilberberg[7] Vesteinsdottir[73] Garg[178]  Kutty[87] Khanna[17] Leung[179] |
| Long term care facility acquired | NR |  | NR |  | NR | -- | 46% | Garg[178] |

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| *Age* mean (range) | 18 (4-31) mo  25 ± 9 mo 48 mo | Shan[93]  Mitchell[85] Vanderhoof[34] | 49 yr 72 yr | Lusk[36] Elseviers[37] | 1.5 yr 2 yr 2 yr 2 yr 3 yr 3 yr 3-6 yr 4 yr 5.4 yr 6 yr 6.5 yr 6.5 yr 6.7 yr 7 yr 8 yr 9 yr 10 yr | Shan[93] Khanna[40] Chen [167] Duleba[18] Pai[71] Hart[54] Kociolek[177]  Kim[115] Morinville[100] Sammons[44] Schwartz[176] Wendt[4] Na[13] Crews[12] Nylund[181] Nylund[14] Deshpande[169] | 59 yr 61 yr 62 yr 64 yr 64 yr 65 yr 66 yr 68 yr 70 yr 71 yr 74 yr 74 yr 75 yr 77 yr | Stevens[173] El Feghaly[182] Huang[65] Muto[59] Kim[98] Vesteinsdottir[73] McFarland[121] Khanna[17] McFarland[64] Garg[178] Wenisch[102] Tabak[117] Loo[57] Eyre[118] |
| *Gender* (% female) | 56% | Vanderhoof [34] | 46% 48% | Elseviers[37] Lusk[36] | 39% 41% 42% 46% 46% 46% 46% 47% 47% 47% 48% 48% 49% 49% 49% 49% | Crews[12] Kociolek[177]  Schwartz[176]  Hart [54] Khanna[40] Kim[115]  Morinville[100]  Chen[167] Wendt[4] de Blank[69] Nylund[14] Soes [43] Sammons[44] Duleba[18] Pai [71] Na[13] | 47% 47% 47% 49% 49% 49% 53% 58% 63% 64% 64% 64% 66% 66% 67% | Kim[98] Loo[57] El Feghaly[182] Carignan[183] Muto[59] Stevens[173] Tabak[117] Eyre[118] Garg[178] Huang[65] Wenisch[102] Vesteinsdottir[73] Fellmeth[75] Crabtree[184] Khanna[17] |
| *Race:* Caucasian | NR |  | NR |  | 59% 65% | Sathyendan[38] Sammons [44] | NR |  |
| *Outbreaks* (number of cases) | *n* = 18 | Kim[41] | NR |  | *n* = 6 *n* = 6 *n* = 13 | Cartwright[48] Ferroni[47] Kim[41] | *n* = 6 *n* = 15 *n* = 21 *n* = 98-174 *n* = 253 *n* = 293 *n* = 1269 *n* = 1703 | See[185] Lam[61] Gaynes[55] Johnson[56]  Muto[59] Pepin[58] Jump[60] Loo[57] |
| *Ribotype* NAP1/027/BI prevalence | NR |  | NR |  | 0% 0% 0% < 1% < 1% 11% 11% 19% 20% | von Muller[51] Stoesser[52] Sathyendan [38] Kociolek[177] Soes[43] Schwartz[176]  Kim[98] Toltzis[50] Duleba[18] | 6.6% 18% 28% 31% 31% 50% | Wenisch[102] Scardina[186] See[107] Miller[62] von Muller[51] Toltzis[50] |

1Data from control group of randomized control trial; 2Data from prospective cohort study of hospital or community population; 3Data from retrospective review of limited number of hospitals; 4Data from population-based surveillance; 5Data from retrospective review of national database or several hospitals or population-based ; 6Data from national point-prevalence survey. References are given by last name of first author and citation number in brackets. ad: admissions; AAD: antibiotic-associated diarrhea; CDI: *Clostridium difficile* infection; d: discharges; hd: hospital-days; NR: Not reported; pd: patient-days; pop: population; py: person-years; v: Visits.

**Table 2 Comparison of risk factors for pediatric antibiotic-associated diarrhea *vs* adult antibiotic-associated diarrhea and pediatric *Clostridium difficile* infections *vs* adult *Clostridium difficile* infections from multivariate analyses**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Host Factors** | **Pediatric AAD** | **Reference** | **Adult AAD** | **Reference** | **Pediatric CDI** | **Reference** | **Adult CDI** | **Ref.** |
| Age | < 2 yr (RR = 1.8) | Turck[63] | > 70 yr > 70 yr | Elseviers[37] Asha[22] | 1-4 yr 6 mo-2 yr | Tai[67] McFarland[1] | > 65 yr > 65 yr > 65 yr > 65 yr > 65 yr > 85 yr Yes (RR = 1.2) Yes (HR = 1.4) | Hu[189] Beaulieu[190] Vardakas[74] Pepin[106] McFarland[89] Vesteinsdottir[73] Eyre[118]  Marwick[191] |
| Comorbidity | NR |  | no | Elseviers[37] | Yes (OR = 1.1) Yes (OR = 1.1) Yes (OR = 2.0) | Sammons[44]  Tai[67]  Samady [68] | Yes (OR = 1.3) Yes (OR = 4) No No | McFarland[121] Wenisch[102] Tabak[117] Vesteinsdottir[73] |
| Chemotherapy  or cancer | NR |  | no | Elseviers[37] | Yes (HR = 1.9) Yes (OR = 3.8) Yes (RR = 2.7) | de Blank[69]  Tai[67]  Sathyendan[38] | Yes (OR =2.3) Yes (OR = 3.6) | Dubberke[192]   Huang[65] |
| IBD | NR |  | no | Elseviers[37] | Yes (OR = 11.4) Yes (OR = 11.4) Yes (OR = 4.5) | Hourigan[187]  Nyland [14]  Kelsen[188] | Yes (OR = 3.3)  no | Hourigan[187]  Leung[179] |
| Prior GI condition | NR |  | NR |  | nr |  | Yes (OR = 2.8) | McFarland[121] |
| Immuno-deficiency | NR |  | NR |  | Yes (OR = 6.0) Yes (OR = 8.1) | Samady[68] Sandora[66] | nr |  |

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Disruptive factors** |  |  |  |  |  |  |  |  |
| Previous antibiotics | NR |  | OR = 2.3 | Elseviers[37] | Yes (OR = 1.2) Yes (OR = 2.2) Yes (RR = 2.8) | Sathyendan [38] Sandora[66] Samady[68] | Yes (OR = 1.3) Yes (HR = 1.4)  Yes (RR = 2.1) Yes (HR = 3.4) Yes (OR = 3.6) | Loo[57] Stevens[173] McFarland[121] Marwick [191] Huang[65] |
| Type of antibiotic | amoxicillin/  clavulanate (RR = 2.4) | Turck[63] |  |  | Amino (HR = 1.3) and Ceph (HR = 2.4)  Quino (OR = 17.0) | de Blank[69]     Sandora[66] | Clind (OR = 4.3) Ceph (RR = 3.8) Diclox, Clind,   Ceftriaxone   (OR = 2.2-7.5) Ceph and Pen  (OR = 2.1) Clind, Quino,   Ceph (OR = 3.8) Clind/Levo/Ceftrizone (OR = 3.0)  Cefoxitin (OR = 2.7) Ceph (OR = 5.6) Quino  (HR = 3.4) | Johnson[56]  Asha[22] Vesteinsdottir [73]  McFarland[64]  Loo[57]   Muto[59]   Carignan[183]  Dubberke[192] Pepin[58] |
| No prior antibiotics < 2-8 wk prior | NR |  | NR |  | 2% 5% 8% 13% 19% 22% 27% 43% (CO) 67% (CO) | Sammons[44] Duleba[18] Samady[68] Chen[167] Crews[12] Khanna[40] Pai[71] Benson[70] Wendt[4] | 6% 13% 20% 40% 96% (CO) | McFarland[64] Khanna[17] McFarland[121] Loo[57] Fellmeth[75] |

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Abdominal surgery | NR |  | NR |  | Yes (OR = 3.3) | Sandora[66] | Yes (OR = 2.6) Yes (OR = 2.8) | Huang[65] Zerey[193] |
| PPI | NR |  | OR = 2.0 OR = 2.8 | Elseviers[37] Asha[22] | Yes (HR = 1.4) Yes (RR= 1.7) Yes (RR = 2.4) Yes (OR = 4.2) No No No | de Blank[69]  Sathyendan[38] Nylund[181] Samady[68]  Brown[194] Sandora[66] Sammons [44] | Yes (OR = 1.6) Yes (OR = 1.8) Yes (OR = 2.8) Yes (OR = 6.1) No No No  No No No | Dubberke[192] Muto[59] Stevens[173] Peled[25] Khanna[17] Leung[179] Vesteinsdottir[73] Pepin[58] Marwick[191] Huang[65] |
| Histamine-2 receptor antagonist | NR |  | NR |  | Yes (RR = 2.2) | Brown[194] | Yes (OR = 3.1) | Peled[25] |
| **Exposure to *C. difficile* spores** |  |  |  |  |  |  |  |  |
| Prior hospitalization | NR |  | NR |  | Yes (OR = 1.7) Yes  (OR = 2.3) No | Tai[67] Samady[68]  Sandora[66] | Yes (OR = 1.3) Yes (OR = 2.0) Yes (RR = 2.3)  Yes (HR = 4.7) Yes (RR = 5.1) No | McFarland[121] Eyre[118] Vesteinsdottir [73] Marwick[191] McFarland[64] Huang[65] |
| Prior long term care residence | NR |  | NR |  | no |  | Yes (OR = 3.9)   Yes (HR = 4.1) | Vesteinsdottir[73]  Marwick[191] |
| Prolonged length of stay (current) | NR |  | NR |  | Yes (OR = 15) | Tai[67] | Yes (RR = 1.01) Yes (OR = 2.8) Yes (OR = 5.1) No | Asha[22]  Huang[65]  Lee[195] Carignan[183] |
| Infected roommates/CD proximity/CD pressure | NR |  | NR |  | NR |  | Yes (RR = 1.7) Yes (OR = 4.0) | McFarland[45] Dubberke[192] |
| Previous CDI | NR |  | NR |  | NR |  | Yes (HR = 4.5) No | Stevens[173]  Khanna[17] |

References are given by last name of first author and citation number in brackets.AAD: Antibiotic-associated diarrhea; amino: Aminoglycoside; CDI: *Clostridium difficile* infections; IBD: Inflammatory bowel disease; ceph: Cephalosporins; clind: Clindamycin; CO: Community-onset; diclox: Dicloxacillin; HR: Hazard ratio; levo: Levofloxacin; NR: Not reported; OR: Odds ratio; pen: Penicillin; PPI: Proton-pump inhibitor; RR: Relative risk; quino: Quinolones.

**Table 3 Comparison of clinical presentation for pediatric antibiotic-associated diarrhea *vs* adult antibiotic-associated diarrhea and pediatric *Clostridium difficile* infections *vs* adult *Clostridium difficile* infections**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Ped AAD** | **Ref.** | **Adult AAD** | **Ref.** | **Ped CDI** | **Ref.** | **Adult CDI** | **Ref.** |
| *Incubation period* (mean days after antibiotic start or  *C. difficile* positive) | 2. 3 ± 1.1 d  2.4 (1-8) d 4.0 ± 4.3 d 4.9 ± 2.5 d  4.9 ± 3 d 5.3 ± 3.5 d 6.2 ± 4.2 d | Damrongmanee [76]  Mitchell[85] Correa[77] Shan[93] Kotowska[157] Turck[63] Ruszczynski[78] | 3.2 ± 2 d 3.7 ± 2.6 d 7 d 8 d (1-30 d) 9 ± 1 d 16 d (6-60 d) 18 d | Dietrich[23] Duman[158] Hickson[81] Lusk[36] Yapar[80] Pozzoni[160]  McFarland[96] | 3 d 10 d | Mitchell[85] Pai [71] | 2 d 6 d 10 d 12 d 13 d | McFarland[45] Chang[86] James[197] Figueroa [90]  Wenisch[102] |
| *Time of Onset* (while on antibiotics *vs* delayed-onset post-antibiotic) | 85% *vs* 15% 92% *vs* 8% | Turck[63]  Correa [77] | 26% *vs* 74% 27% *vs* 73% 38% *vs* 62% 71% *vs* 29% 75% *vs* 25% 85% *vs* 15% | Hickson [81] McFarland[96] Pozzoni [160] Can[79] Duman[158] Yapar[80] | 80% *vs* 20% | Duleba[18] | 23% vs 77% | Chang[86] |
| **Severity of disease** | | | | | | | | |
| *Duration* (mean ± std. dev.) or median (range) days | 2.6 ± 1.1 d  3.9 ± 2.3 d 4 ± 3 d 4.1 ± 2.1 d 5 ± 2.8 d 9 ± 1 d | Damrongmanee[76] Destura[172] Turck[63] Ruszczynski[78] Correa[77] Shan[93] | 1-6 d 2-25 d 3 (2-5) d 4.4 ± 2.5 d 4.9 ± 2 d 5.4 ± 1.8 d 21.5 (1-72) d | Allen[159] McFarland[96] Pozzoni[160] Dietrich[23] de Souza[139] Ouwehand[163] Lusk[36] | 2 d 2-9 d  6 d 7-8 d | Denno[97] McFarland[1] Crews[12] Duleba[18] | 5.4 ± 1.8 d  6.6 d  13 ± 13 d 13 ± 7.4 d 26 ± 56 d | Ouwehand[163] Wenisch[102] McFarland[89] Morrow[198] Hsu[103] |
| Asymptomatic carriers | NR |  | NR |  | 26% 35% 45% 67% | Sandora[66] Enoch[196] Rousseau[53] Delmee[49] | 6% 9.4% 9.7% 61% | Jarvis[175] Bruns[199] Leekha[200] McFarland [45] |
| Mild-moderate diarrhea | most common |  | most common |  | 23% 66% 71% 72% 87% | Pai[71] Schwartz[176] Na[13] Wendt[4] Khanna[40] | 35% 48% 59% 61% 61% | McFarland[201] Ramanathan[202] Jardin[206] Kyne[101] Bartlett [207] |
| Severe disease | rare |  | 16% | Gogate[94] | 8% 12% 21% 27% 76% | Wendt[4] Khanna[40] Crews [12] Schwartz[176] Pai[71] | 3%  3%  8%  9% 16.4% 18% 18% 34% 47% 52% | McFarland[201] Rubin[208] Bartlett[207] El Feghaly[182] Pepin[106] Wenisch[102] See[185] Khanna[209] Jardin[206] Ramanathan[202] |
| PMC | 1 case | Vidrine[95] | 1% | Lusk[36] | 0.1% 1.6% 4.9% | Wendt[4] Duleba[18] Kim[98] | 0.1% 1% | Wenisch[102] McFarland[201] |
| Toxic megacolon | NR |  | NR |  | 1 case | Castillo[99] | 0.1% | Wenisch[102] |
| Fulminant disease | NR |  | NR |  | rare *n* = 4 | Qualman[203] Rivlin[204] | 2% 4% 6% | Dallal[108] Sailhamer [210] Van de Wilden[211] |
| Recurrent disease | NR |  | 28% | de Souza[139] | 10% 11% 16.5% 17% 17% 20% 22% 24% 31% | Sandora[66] Wendt[4] Crews[12] Nylund[181] Schwartz[176] Khanna[40] Nicholson[205] Kim[98] Morinville[100] | 18.8% 21% 22% 22% 27% 29% 29% 36% 42% | Wenisch[102] Vesteinsdottlir [73] Eyre[118] Ramanathan[202] McFarland[121] Wullt[122] Khanna[17] Drudy[212] McFarland [89] |

References are given by last name of first author and citation number in brackets. AAD: Antibiotic-associated diarrhea; CDI: *Clostridium difficile* infections; NR: Not reported; PMC: Pseudomembraneous colitis.

**Table 4 Comparison of consequences of pediatric antibiotic-associated diarrhea *vs* adult antibiotic-associated diarrhea and pediatric *Clostridium difficile* infections *vs* adult *Clostridium difficile* infections**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Pediatric AAD** | **Ref.** | **Adult AAD** | **Ref.** | **Pediatric CDI** | **Ref.** | **Adult CDI** | **Ref.** |
| Premature stop of antibiotic therapy | yes | Damrongmanee[76] | 4% | Elseviers [37] | NR |  | NR |  |
| Dehydration | NR |  | 17% | Elseviers [37] | 75% | Duleba[18] | NR |  |
| Attributable mortality | NR |  | NR |  | 2%  2.2% 3% | Despandi[169] Sammons[44] de Blank[69] | 5.7% 5.7% 4.5% 6.3% 6.9% 15% 17% | Dubberke[213] Gravel[119] Tabak[117] Vesteinsdottir [73] Loo[57] McFarland[121] Pepin[58] |
| Crude mortality | NR |  | 3.6% | Selinger [112] | 1% 2%  3.8% 4.6% 5% 5.4% | Morinville[100] Nylund[14] Kim[115]  Crews[12] de Blank[69] Pai[71] | 10% 16.5% 28% 35%  38% | Tabak[117] Wenisch[102] Bacci[120] Eyre[118] Dubberke[213] |
| Colectomy | NR |  | NR |  | 0.1% 0.9% 0.9% 1% 1.2% | Wendt[4] Despandi[169] Nylund[14] Pai [71] Kim [115] | 0.3% 0.7% 1.2% 2% 6.2% 9.1% | See[107] Halabi[214] Dallal[108] McFarland[121] Muto[59] Jarvis[175] |
| Cost ($/patient) | NR |  | $1400 $1968 | Song[113] Kamdeu[215] | $18900-$93000 $28404 $31957 | Sammons [44]   Despande[169] Nylund[14] | $3103 $3427-$33,055 $3427-99601 $7179 $11,6312 $11,3533  $23,643 | McFarland[89] Kwon[10]  Dubberke[216]  Dubberke[217] Dubberke[216] Lawrence[124] Tabak[117] |
| Length of stay (days additional stay) | NR |  | 8.5 d | Elseviers[37] | 4 d  4 d  6 d  23d | Despande[169] Nylund[14] Sammons[44] De Blank[69] | 3 d 4 d 6 d 10 d 13 d 14 d 16 d 24 d | Lawrence[124] Dubberke[217] Vesteinsdottir[73] Abdelsattar[218] Tabak[117] Crabtree[184] Zerey[193] McFarland[121] |
| Re-admissions | NR |  | 8% | Pozzoni[160] | NR |  | 21%  39%  52% | McFarland[121] Abdelsattar[218] Dubberke[213] |

1 for initial CDI episodes only, 2 for recurrent CDI episodes only, 3 in intensive care unit. References are given by last name of first author and citation number in brackets.AAD: antibiotic-associated diarrhea; CDI: *Clostridium difficile* infections; LOS: length of stay; NR: not reported.

**Table 5 Comparison of prevention and treatment strategies for pediatric antibiotic-associated diarrhea *vs* adult antibiotic-associated diarrhea and pediatric *Clostridium difficile* infections *vs* adult *Clostridium difficile* infections**

|  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Pediatric AAD** | | **Ref.** | **Adult AAD** | **Ref.** | | **Pediatric CDI** | **Ref.** | **Adult CDI** | | | **Ref.** |
| **Prevention** | | | | | | | | | | | | |
| Enhanced infection control programs (% CDI reduced) | NR | |  | NR |  | | NR |  | | 67% | You[219] | |
| Antibiotic stewardship (% CDI reduced) | NR | |  | NR |  | | NR |  | | 46% 66% | Wenisch[102] Kallen[220] | |
| Probiotics | *S. boulardii* (pRR = 0.43) *L. rhamnosus GG* (pRR = 0.36)  *S. boulardii* (pRR = 0.43) *L. rhamnosus GG* (pRR = 0.48) | | McFarland[19]  McFarland[19]    Szajewska[132]  Szajewska[132] | *S. boulardii* (pRR = 0.47) *S. boulardii* (pRR = 0.49) *La+Lc+Lr* (pRR = 0.51) *L. rhamnosus GG* (no) | McFarland[131]  Szajewska[132]  Hempel[129]  Szajewska[132] | | *S. boulardii* (pRR = 0.25)  *S. boulardii* (pRR = 0.25) | McFarland[138]  Szajewska[132] | | *La+Lc+Lr* (pRR = 0.21) *La+Lc+Lr* (pRR = 0.21) *L. casei* DN114001 (pRR = 0.08) *S. boulardii* (no) | Johnson[137]  McFarland[138]  McFarland [138]  Szajewska[132] | |
| **Treatment** | | | | | | | | | | | | |
| **Initial episode1** | |  |  |  | |  |  |  |  | |  | |
| No treatment given or stop inciting antibiotic (% done) | | NR |  | 4% | | Elseviers[37] | 0% 4% 20% 53% 69% | Khanna[40] Kim[98]  Duleba[18] Pai[71] Gogate[94] | 10%  24% 53% | | Vensteinsdottir [73] McFarland[121] Huang[65] | |
| Oral rehydration therapy (% cured) | | 21% | Shan[93] | 17% | | Elseviers [37] | nr |  | nr | |  | |
| Metronidazole (% cured) | | NR |  | NR | |  | 31% 69% 82% 90 93% 97% | Gogat[94] Morinville[100] Khanna[40] Pai[71] Kim[98] Duleba[18] | 75%   84% 86% 94% | | Vesteindottlir [73] Zar[145] Kim[221] Wenisch[222] | |
| Vancomycin (% cured) | | NR |  | NR | |  | 83% 85% 100% | Duleba[18] Jardin[206] Khanna[40] | 91%  94% 94% 97% 100% | | Kim [221] Cornely[141] Wenisch[222] Zar[145] Vesteindottlir[73] | |
| Severe disease (% cured) | | NR |  | NR | |  |  |  | 97% vanco *vs* 76% metro | | Zar[145] | |
| Probiotics (% cured) | | NR |  | *S. boulardii* (70%) | | Ligny[140] | NR |  | *S. boulardii* (19%, ns) | | McFarland[111] | |
| Monoclonal antibodies (% cured) | | NR |  | NR | |  |  |  | 93% (*p* = 0.07) | | Lowy[146] | |

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Recurrent  disease1** |  |  |  |  |  |  |  |  |
| Metronidazole (% no further recurrences) | NR |  | NR |  | NR |  | 33%  50% 58% 80% | Wullt[223] Surawicz[142] McFarland[143] Vesteindottlir[73] |
| Vancomycin (% no further recurrences) | NR |  | NR |  | NR |  | 46% (10 d) 55% 69% (taper)  86% (pulse) 100% | McFarland[143] Surawicz[142] McFarland[143]  McFarland [143]  Vesteindottlir [73] |
| Fidaxomycin (% no further recurrences) | NR |  | NR |  | NR |  | 86% | Cornely[147] |
| Probiotics (% no further recurrences) | NR |  | NR |  | NR |  | *S. boulardii* (65%) *S. boulardii* with high dose vanco (83%) | McFarland[111]  Surawicz[142] |
| Fecal replacement therapy (% no further recurrences) | NR |  | NR |  | NR |  | 81%  90% | Van Nood[224] Cammatora[225] |

1studies not reporting cure rates by initial or recurrent CDI cases were excluded. References are given by last name of first author and citation number in brackets. AAD: antibiotic-associated diarrhea; CDI: *Clostridium difficile* infections; *L.*: *Lactobacillus*; La: *L. acidophilus* CL1285; Lc: *L. casei* LBC80R; Lr: *L. rhamnosus* CLR2; NR: not reported; pRR: pooled relative risk from meta-analysis; *S.*: *Saccharomyces*.