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REVIEW

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

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Abstract

Antibiotic-associated diarrhea (AAD) and *Clostridium 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

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.

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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 $3427-$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 antibiotics 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); 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 wk 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 defined diarrhea. 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.

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:	29 (42/144)[1]	Shan[93]	7 (14/204)[1]	Duman[158]	2[2]	Sathyendan[38]	4.3 pd[3]	Stevens[173]
Inpatient	80 (8/10)[1]	Jirapinyo[151]	9 (10/112)[1]	Selinger[112]	5.8 ad[3]	Chen[167]	5.4 py[4]	Vesteinsdottir[73]
			9.6 (67/743)[2]	Elseviers[37]	6.5 pd[4]	Kim[168]	5.7 hd[2]	Wenisch[102]
			10.4 (153/1471)[1]	Allen[159]	6.8 v[3]	Benson[70]	10 pd[2]	Hsu[103]
			13 (13/98)[1]	Pozzoni[160]	12.8 ad[4]	Zilberberg[5]	12 py[5]	Kuntz[174]
			15 (14/96)[1]	McFarland[96]	13.4 pd[5]	de Blank[69]	29.2 pd[2]	McFarland[121]
			19 (48/257)[1]	Li[161]	31.5 d[4]	Deshpande[169]	72 ad[5]	Zilberberg[7]
			22 (14/64)[1]	Surawicz[162]	135.0 ad[3]	Duleba[18]	128[2]	Huang[65]
			23 (55/242)[2]	Lusk[36]	416.7[1]	Shan[93]	131 ad[6]	Jarvis[175]
			25 (41/167)[1]	Ouwehand[163]			1000 (93/30)[1]	Dietrich[23]
			29 (42/144)[1]	Shan[93]			2080 (83/399)[2]	McFarland[45]
			33 (10/30)[1]	Dietrich[23]				
Outpatient	6.2 (14/225)[2]	Damrongmanne[76]	7.7/100000 py[5]	Hirschhorn[164]	14[3]	Benson[70]	1.1[5]	Fellmeth[75]
	11 (71/650)[2]	Turck[63]	12/100000 py[2]	Levy[165]	200 (1/58)[1]	Arvola[21]	1.2[2]	Levy[165]
	16 (9/58)[1]	Arvola[21]	15/100[5]	Yapar[80]	390 (12/306)[1]	Boenning[170]	11.1 py[5]	Kuntz[174]
	24 (8/33)[1]	Ahmad[152]			780 (9/115)[1]	Hyams[171]		
	26 (25/95)[1]	Vanderhoof[34]			790 (6/76)[2]	Mitchell[85]		
	29 (22/76)[2]	Mitchell[85]						
	52 (13/25)[1]	Saneeyan[153]						
	59 (16/27)[1]	Seki[154]						
	62 (31/50)[1]	La Rosa[155]						
	75 (27/36)[1]	Fox[156]						
Mixed in- and out-patients	17 (20/120)[1]	Ruszczyński[78]	2.5/100000 v[2]	Meropol[166]	1.4[5]	Khanna[40]	2.5 py[5]	Khanna[17]
	23 (29/127)[1]	Kotowska[157]			2.1[4]	Wendt[4]	5.4[2]	Vesteinsdottir[73]
					60 (1/161)[1]	Destura[172]		
					600 (7/120)[1]	Ruszczyński[78]		
					800 (10/127)[1]	Kotowska[157]		
Setting	NR		NR		25%	Khanna[40]	21%	Garg[178]
Health-care facility associated (HCFA) (% cases)					46%	Crews[12]	53%	Leung[179]
					48%	Sammons[44]	59%	Khanna[17]
					65%	Pai[71]	68%	Zilberberg[7]
					69%	Sandora[66]	89%	McFarland[45]
					71%	Tschudin-Sutter[72]	92%	Kazadova[180]
					74%	Schwartz[176]		
Community-acquired (CA) (% cases)	NR		NR		19%	Tschudin-Sutter[72]	8%	Kazadova[180]
					25%	Sandora[66]	11%	McFarland[121]
					26%	Schwartz[176]	23%	Zilberberg[7]
					29%	Pai[71]	27%	Vesteinsdottir[73]
					30%	Samady[68]	33%	Garg[178]
					39%	Kociolek[177]	34%	Kutty[87]
					41%	Crews[12]	41%	Khanna[17]
					52%	Duleba[18]	43%	Leung[179]
					54%	Sammons[44]		
					67%	Benson[70]		
					71%	Wendt[4]		
					75%	Khanna[40]		
					96%	Søes[43]		
Long term care facility acquired	NR		NR		NR	--	46%	Garg[178]
Age	18 (4-31) mo	Shan[93]	49 yr	Lusk[36]	1.5 yr	Shan[93]	59 yr	Stevens[173]
mean (range)	25 ± 9 mo	Mitchell[85]	72 yr	Elseviers[37]	2 yr	Khanna[40]	61 yr	El Feghaly[182]
	48 mo	Vanderhoof[34]			2 yr	Chen[167]	62 yr	Huang[65]
					2 yr	Duleba[18]	64 yr	Muto[59]
					3 yr	Pai[71]	64 yr	Kim[98]
					3 yr	Hart[54]	65 yr	Vesteinsdottir[73]

					3-6 yr	Kociolek[177]	66 yr	McFarland[121]
					4 yr	Kim[115]	68 yr	Khanna[17]
					5.4 yr	Morinville[100]	70 yr	McFarland[64]
					6 yr	Sammons[44]	71 yr	Garg[178]
					6.5 yr	Schwartz[176]	74 yr	Wenisch[102]
					6.5 yr	Wendt[4]	74 yr	Tabak[117]
					6.7 yr	Na[13]	75 yr	Loo[57]
					7 yr	Crews[12]	77 yr	Eyre[118]
					8 yr	Nylund[181]		
					9 yr	Nylund[14]		
					10 yr	Deshpande[169]		
Gender (% female)	56%	Vanderhoof[34]	46%	Elseviers[37]	39%	Crews[12]	47%	Kim[98]
			48%	Lusk[36]	41%	Kociolek[177]	47%	Loo[57]
					42%	Schwartz[176]	47%	El Feghaly[182]
					46%	Hart[54]	49%	Carignan[183]
					46%	Khanna[40]	49%	Muto[59]
					46%	Kim[115]	49%	Stevens[173]
					46%	Morinville[100]	53%	Tabak[117]
					47%	Chen[167]	58%	Eyre[118]
					47%	Wendt[4]	63%	Garg[178]
					47%	de Blank[69]	64%	Huang[65]
					48%	Nylund[14]	64%	Wenisch[102]
					48%	Søes[43]	64%	Vesteinsdottir[73]
					49%	Sammons[44]	66%	Fellmeth[75]
					49%	Duleba[18]	66%	Crabtree[184]
					49%	Pai[71]	67%	Khanna[17]
					49%	Na[13]		
Race: Caucasian	NR		NR		59%	Sathyendan[38]	NR	
					65%	Sammons[44]		
Outbreaks (number of cases)	n = 18	Kim[41]	NR		n = 6	Cartwright[48]	n = 6	See[185]
					n = 6	Ferroni[47]	n = 15	Lam[61]
					n = 13	Kim[41]	n = 21	Gaynes[55]
							n = 98-174	Johnson[56]
							n = 253	Muto[59]
							n = 293	Pépin[58]
							n = 1269	Jump[60]
							n = 1703	Loo[57]
Ribotype NAP1/027/BI prevalence	NR		NR		0%	von Müller[51]	6.60%	Wenisch[102]
					0%	Stoesser[52]	18%	Scardina[186]
					0%	Sathyendan[38]	28%	See[107]
					< 1%	Kociolek[177]	31%	Miller[62]
					< 1%	Søes[43]	31%	von Müller[51]
					11%	Schwartz[176]	50%	Toltzis[50]
					11%	Kim[98]		
					19%	Toltzis[50]		
					20%	Duleba[18]		

[1]Data from control group of randomized control trial; [2]Data from prospective cohort study of hospital or community population; [3]Data from retrospective review of limited number of hospitals; [4]Data from population-based surveillance; [5]Data from retrospective review of national database or several hospitals or population-based; [6]Data 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.

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 kindergartens[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 enterocolitis, 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*[60] 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. 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) that may 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 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 *vs* 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,

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	Ref.	Adult AAD	Ref.	Pediatric CDI	Ref.	Adult CDI	Ref.
Age	< 2 yr (RR = 1.8)	Turck[63]	> 70 yr	Elseviers[37]	1-4 yr	Tai[67]	> 65 yr	Hu[189]
			> 70 yr	Asha[22]	6 mo-2 yr	McFarland[1]	> 65 yr	Beaulieu[190]
							> 65 yr	Vardakas[74]
							> 65 yr	Pepin[106]
							> 65 yr	McFarland[89]
							> 85 yr	Vesteinsdottir[73]
							Yes (RR = 1.2)	Eyre[118]
							Yes (HR = 1.4)	Marwick[191]
Comorbidity	NR		No	Elseviers[37]	Yes (OR = 1.1)	Sammons[44]	Yes (OR = 1.3)	McFarland[121]
					Yes (OR = 1.1)	Tai[67]	Yes (OR = 4)	Wenisch[102]
					Yes (OR = 2.0)	Samady[68]	No	Tabak[117]
							No	Vesteinsdottir[73]
Chemotherapy or cancer	NR		No	Elseviers[37]	Yes (HR = 1.9)	de Blank[69]	Yes (OR =2.3)	Dubberke[192]
					Yes (OR = 3.8)	Tai[67]	Yes (OR = 3.6)	Huang[65]
					Yes (RR = 2.7)	Sathyendan[38]		
IBD	NR		No	Elseviers[37]	Yes (OR = 11.4)	Hourigan[187]	Yes (OR = 3.3)	Hourigan[187]
					Yes (OR = 11.4)	Nyland[14]	No	Leung[179]
					Yes (OR = 4.5)	Kelsen[188]		
Prior GI condition	NR		NR		NR		Yes (OR = 2.8)	McFarland[121]
Immuno-deficiency	NR		NR		Yes (OR = 6.0)	Samady[68]	NR	
					Yes (OR = 8.1)	Sandora[66]		
Disruptive factors								
Previous antibiotics	NR		OR = 2.3	Elseviers[37]	Yes (OR = 1.2)	Sathyendan[38]	Yes (OR = 1.3)	Loo[57]
					Yes (OR = 2.2)	Sandora[66]	Yes (HR = 1.4)	Stevens[173]
							Yes (RR = 2.1)	McFarland[121]
					Yes (RR = 2.8)	Samady[68]	Yes (HR = 3.4)	Marwick[191]
							Yes (OR = 3.6)	Huang[65]
Type of antibiotic	Amoxicillin/ clavulanate (RR = 2.4)	Turck[63]			Amino (HR = 1.3) and Ceph (HR = 2.4)	de Blank[69]	Clind (OR = 4.3)	Johnson[56]
							Ceph (RR = 3.8)	Asha[22]
					Quino (OR = 17.0)	Sandora[66]	Diclox, Clind, Ceftriaxone (OR = 2.2-7.5)	Vesteinsdottir[73]
							Ceph and Pen (OR = 2.1)	McFarland[64]
							Clind, Quino, Ceph (OR = 3.8)	Loo[57]
							Clind/Levo/ Ceftrizone (OR = 3.0)	Muto[59]
							Cefoxitin (OR = 2.7)	Carignan[183]
							Ceph (OR = 5.6)	Dubberke[192]
							Quino (HR = 3.4)	Pépin[58]
No prior antibiotics < 2-8 wk prior	NR		NR		2%	Sammons[44]	6%	McFarland[64]
					5%	Duleba[18]	13%	Khanna[17]
					8%	Samady[68]	20%	McFarland[121]
					13%	Chen[167]	40%	Loo[57]
					19%	Crews[12]	96% (CO)	Fellmeth[75]
					22%	Khanna[40]		
					27%	Pai[71]		
					43% (CO)	Benson[70]		
					67% (CO)	Wendt[4]		
Abdominal surgery	NR		NR		Yes (OR = 3.3)	Sandora[66]	Yes (OR = 2.6)	Huang[65]
							Yes (OR = 2.8)	Zerey[193]
PPI	NR		OR = 2.0	Elseviers[37]	Yes (HR = 1.4)	de Blank[69]	Yes (OR = 1.6)	Dubberke[192]
			OR = 2.8	Asha[22]	Yes (RR= 1.7)	Sathyendan[38]	Yes (OR = 1.8)	Muto[59]
					Yes (RR = 2.4)	Nylund[181]	Yes (OR = 2.8)	Stevens[173]
					Yes (OR = 4.2)	Samady[68]	Yes (OR = 6.1)	Peled[25]
					No	Brown[194]	No	Khanna[17]

			No	Sandora[66]	No	Leung[179]
			No	Sammons[44]	No	Vesteinsdottir[73]
					No	Pépin[58]
					No	Marwick[191]
					No	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)	Tai[67]	Yes (OR = 1.3)	McFarland[121]
			Yes (OR = 2.3)	Samady[68]	Yes (OR = 2.0)	Eyre[118]
					Yes (RR = 2.3)	Vesteinsdottir[73]
			No	Sandora[66]	Yes (HR = 4.7)	Marwick[191]
					Yes (RR = 5.1)	McFarland[64]
					No	Huang[65]
Prior long term care residence	NR	NR	NR		Yes (OR = 3.9)	Vesteinsdottir[73]
					Yes (HR = 4.1)	Marwick[191]
Prolonged length of stay (current)	NR	NR	Yes (OR = 15)	Tai[67]	Yes (RR = 1.01)	Asha[22]
					Yes (OR = 2.8)	Huang[65]
					Yes (OR = 5.1)	Lee[195]
					No	Carignan[183]
Infected roommates/CD proximity/CD pressure	NR	NR	NR		Yes (RR = 1.7)	McFarland[45]
					Yes (OR = 4.0)	Dubberke[192]
Previous CDI	NR	NR	NR		Yes (HR = 4.5)	Stevens[173]
					No	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.

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 *vs* 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 *vs* 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 *vs* 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

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] Corrêa[77] Shan[93] Kotowska[157] Turck[63] Ruszczyński[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] Corrêa[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] Ruszczyński[78] Corrêa[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] Delmée[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] Vesteinsdottir[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.

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*[90] reported the mean time to recurrence was 12.2 ± 6.4 d. 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 four days 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*[71] 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. 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 (pseudomembranous 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 715000 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 *vs* 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 fulminant 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.

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%	Despandi[169]	5.7%	Dubberke[213]
					2.2%	Sammons[44]	5.7%	Gravel[119]
					3%	de Blank[69]	4.5%	Tabak[117]
							6.3%	Vesteinsdottir[73]
							6.9%	Loo[57]
							15%	McFarland[121]
							17%	Pépin[58]
Crude mortality	NR		3.6%	Selinger[112]	1%	Morinville[100]	10%	Tabak[117]
					2%	Nylund[14]	16.5%	Wenisch[102]
					3.8%	Kim[115]	28%	Bacci[120]
					4.6%	Crews[12]	35%	Eyre[118]
					5%	de Blank[69]	38%	Dubberke[213]
					5.4%	Pai[71]		
Colectomy	NR		NR		0.1%	Wendt[4]	0.3%	See[107]
					0.9%	Despandi[169]	0.7%	Halabi[214]
					0.9%	Nylund[14]	1.2%	Dallal[108]
					1%	Pai[71]	2%	McFarland[121]
					1.2%	Kim[115]	6.2%	Muto[59]
							9.1%	Jarvis[175]
Cost ($/patient)	NR		$1400	Song[113]	$18900-$93000	Sammons[44]	$3103	McFarland[89]
			$1968	Kamdeu[215]	$28404	Despande[169]	$3427-$33055	Kwon[10]
					$31957	Nylund[14]	$3427-9960[1]	Dubberke[216]
							$7179	Dubberke[217]
							$11631[2]	Dubberke[216]
							$11353[3]	Lawrence[124]
							$23643	Tabak[117]
Length of stay (days additional stay)	NR		8.5 d	Elseviers[37]	4 d	Despande[169]	3 d	Lawrence[124]
					4 d	Nylund[14]	4 d	Dubberke[217]
					6 d	Sammons[44]	6 d	Vesteinsdottir[73]
					23d	de Blank[69]	10 d	Abdelsattar[218]
							13 d	Tabak[117]
							14 d	Crabtree[184]
							16 d	Zerey[193]
							24 d	McFarland[121]
Re-admissions	NR		8%	Pozzoni[160]	NR		21%	McFarland[121]
							39%	Abdelsattar[218]
							52%	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.

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

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%	Wenisch[102]
							66%	Kallen[220]
Probiotics	*S. boulardii* (pRR = 0.43)	McFarland[19]	*S. boulardii* (pRR = 0.47)	McFarland[131]	*S. boulardii* (pRR = 0.25)	McFarland[138]	*La+Lc+Lr* (pRR = 0.21)	Johnson[137]
	L. rhamnosus GG (pRR = 0.36)	McFarland[19]	*S. boulardii* (pRR = 0.49)	Szajewska[132]	*S. boulardii* (pRR = 0.25)	Szajewska[132]	*La+Lc+Lr* (pRR = 0.21)	McFarland[138]
	S. boulardii (pRR = 0.43)	Szajewska[132]	*La+Lc+Lr* (pRR = 0.51)	Hempel[129]			*L. casei* DN114001 (pRR = 0.08)	McFarland[138]
	L. rhamnosus GG (pRR = 0.48)	Szajewska[132]	*L. rhamnosus* GG (no)	Szajewska[132]			*S. boulardii* (no)	Szajewska[132]
Treatment								
Initial episode[1]								
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		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		NR		93% (*P* = 0.07)	Lowy[146]
Recurrent disease[1]								
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	NR		NR		NR		86%	Cornely[147]

(% no further recurrences)					
Probiotics	NR	NR	NR	*S. boulardii* (65%)	McFarland[111]
(% no further recurrences)				*S. boulardii* with high dose vanco (83%)	Surawicz[142]
Fecal replacement therapy	NR	NR	NR	81%	van Nood[224]
(% no further recurrences)				90%	Cammatora[225]

[1]Studies 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*.

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 (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 per day), followed by oral vancomycin (40 mg/kg per day) 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 *vs* 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 *vs* 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 delineation 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.

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