Incidence and Risk Factors for Antibiotic-associated Diarrhea Among Hospitalized Children

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Background: We aimed to evaluate the incidence, clinical findings, and risk factors of antibiotic-associated diarrhea (AAD) in hospitalized children without known comorbid diseases.

Methods: All hospitalized children during the 1-year period that fulfilled the inclusion criteria were included in this study (n = 358). AAD was defined as; ≥2 loose or watery stools per day for a minimum of 24 hours during antibiotic treatment caused by Clostridioides difficile or negative stool tests for identifiable infectious agents.

Results: During hospitalization, diarrhea developed in 32 (8.93%) of the 358 patients. C. difficile toxin B was positive for 1 case. No infectious agents were detected in 21 patients. Overall, AAD was observed in 22 patients (6.14%, 95% CI: 4.09–9.13). Male sex ($P = 0.027$, OR: 3.36), age between 1 month and <3 years ($P = 0.01$, OR: 4.23), ibuprofen use ($P = 0.044$, OR: 2.63) and late administration of antibiotics ($P = 0.001$, OR: 9.5) were associated with the development of AAD.

Conclusion: The incidence of AAD is low among hospitalized children without comorbid diseases, and most diarrheal episodes are mild and self-limiting. The use of probiotics in this patient group may be limited to certain specific situations.

Key Words: risk factors, ibuprofen, antibiotic-associated diarrhea

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Antibiotic-associated diarrhea (AAD) is defined as unexplained diarrhea that occurs in association with antibiotic therapy. It may occur just a few hours after antibiotic administration or up to 8 weeks after the discontinuation of antibiotics. Many cases of AAD are mild and self-limiting, but they may cause severe electrolyte/fluid imbalance, hospital readmissions and pseudomembranous colitis in a minority of cases.[1] Most guidelines recommend preventing AAD in high-risk patients by using specific strains of probiotics along with antibiotic treatment.[2–4]

Some mechanisms have been suggested for AAD: (1) alterations in the gut microbiota composition and overgrowth of pathogenic microorganisms, especially Clostridioides difficile (C. difficile) and Staphylococcus, Clostridium perfringens type A, Klebsiella oxytoca and Candida in a minority of cases; (2) disturbance of normal colonic microbiota leading to alterations in the bacterial metabolome, such as reduced carbohydrate metabolism (alterations in the degradation of nonabsorbed carbohydrates) that leads to osmotic diarrhea and decreased bile salt deconjugation by bacteria that leads to secretory diarrhea; (3) allergic and toxic effects of antibiotics on the intestinal mucosa and (4) stimulation of intestinal motility through the motilin-like effect of some types of antibiotics.[5]

The incidence of AAD varies depending on the (1) criteria used to diagnose it, (2) study population (outpatient vs. inpatient), (3) route of antibiotic administration (intravenous vs. oral), (4) type of antibiotics used and (5) presence of comorbid diseases.[2,6,7]

No prospective study has evaluated the incidence and risk factors of AAD among hospitalized children without any comorbid diseases. Most studies were based on file records, and the definition of AAD and patient inclusion criteria were not clearly defined. Therefore, we aimed to evaluate the incidence, clinical findings, and risk factors of AAD in hospitalized children without known comorbid diseases.

PATIENTS AND METHODS

This was a prospective observational study performed in inpatient clinics [infant clinics (aged children between 1 month and <5 years old), adolescent clinics (aged children between ≥5 years old and ≤18 years old) and pediatric infectious disease clinics (aged children between 1 month and ≤18 years old)] of Karadeniz Technical University, Farabi Hospital for 1-year period between December 1, 2018, and November 30, 2019. All children hospitalized during the 1-year period that fulfilled the inclusion criteria were included in the study. Inclusion criteria for the study were; (1) >1 month and ≤18 years old; (2) receiving antibiotics during hospitalization; (3) having no comorbid diseases such as cystic fibrosis, inflammatory bowel disease, celiac disease, allergic diseases, immunodeficiencies, chronic renal failure, diabetes, intestinal parasites and other chronic diseases that may be associated with increased risk of diarrhea and (4) absence of acute gastroenteritis at initial admission; and no usage of drugs such as probiotics, prebiotics, laxatives, and anti-diarrheal drugs within the previous 2 weeks.

Patients included in the study were evaluated daily for the presence of diarrhea (number and consistency of stools) by a member of the study team (D.U.). Diarrhea was defined according to the criteria of the Amsterdam Infant Stool Scale (A-consistency) in children younger than 1 year and Bristol Stool Form (scores 5–7) in children older than 1 year.[8,9] In the presence of diarrhea for a minimum of 24 hours, stool samples were analyzed with immunochromatographic tests for the presence of rotavirus, adenovirus (rapid Adeno/Rota Virus test, Boson Biotech, Netherlands), and norovirus (ichroma Noro, Boditech Med, S. Korea), with bacterial culture methods for Salmonella spp., Shigella spp., Campylobacter spp. and Yersinia spp. using specific media, and with microscopic examination for parasitic pathogens. For the detection of toxigenic C. difficile, samples were evaluated using an immunochromatographic test (Clostridium difficile toxin A+B, CerTest Biotec, Spain) and an anaerobic culture method using a specific medium (Cycloserine-Cefoxitin-Fructose Agar, CCFA, Becton Dickinson, USA).

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Three definitions were used for the AAD. We used the less strict method: ≥2 loose or watery stools per day for a minimum of 24 hours during antibiotic treatment. AAD was diagnosed in cases of diarrhea, defined clinically as above, caused by C. difficile or negative laboratory stool tests for identifiable infectious agents. In all cases, loose or watery stool corresponded to a score of 5–7 on the Bristol Stool Form scale or A-consistency on the Amsterdam Infant Stool Scale.[10]

The study was conducted in accordance with the Helsinki Declaration, and ethical approval was obtained from the Ethics Committee of the Karadeniz Technical University Institutional Ethics Committee (study number: 2018/61). According to the study protocol, informed consent, which included the content and aims of the study, was signed by the parents of the patients before inclusion in the study.

Statistical analysis was performed using SPSS version 16.0 software (SPSS Inc., Chicago, IL). Continuous variables were expressed as mean ± standard deviation (SD), and categorical variables were expressed as number (n) and percentage (%). Comparison of continuous variables between the groups was performed using Student's *t*-test for the normally distributed variables, and the Mann–Whitney U test for non-normally distributed variables. Categorical variables were compared using the $\chi\chi^2$ test (or Fisher exact test when needed). The Shapiro-Wilk test was used to assess normal distribution. Statistical significance was set at $P \leq 0.05$. Logistic regression analysis was performed to determine significant parameters for the presence of ADD.

RESULTS

During the 1-year period; 1042 children were hospitalized in 3 pediatric clinics, and 358 children were included in the study (Fig. 1).

The demographic and clinical characteristics of the children in this study are shown in Table 1. The mean ± SD age of the patients was 55.03 ± 54.91 months (median: 36 months, range 1–215 months, 49.7%, <3 years).

During hospitalization, diarrhea developed in 32 (8.93%) of the 358 patients. Six patients were positive for rotavirus, 3 patients were positive for norovirus and 1 patient was positive for adenovirus. *C. difficile* toxin B was positive for 1 case. No infectious agents were detected in 21 patients. Overall, AAD was observed in 22 patients (6.14%, 95% CI: 4.09–9.13) with a median of 3.5 days after antibiotic treatment (Fig. 2). The median duration of AAD was 3 days, and the median number of loose stools in patients with AAD was 4/day. All AAD episodes were mild clinically.

Table 1 shows a comparison of the demographic and clinical findings of patients with (n = 22) and without AAD (n = 336). Male patients (77.3% vs. 48.2%, $P = 0.01$, OR: 3.6, 95% CI: 1.3–10.1) and patients aged between 1 month and <3 years were more common in the AAD (+) group (77.3% vs. 47.9%, $P = 0.01$, OR: 3.6, 95% CI: 1.3–10.2). Carbapenem (13.6% vs. 3.8%, $P = 0.04$, OR: 3.9, 95% CI: 1–14.9) and ibuprofen (54.5% vs. 29.4%, $P = 0.01$, OR: 2.8, 95% CI: 1.2–6.8) usage was more common in AAD (+) group. Late administration of antibiotics (after 24 hours) increased the development of AAD (27.2% vs. 3.5%, $P \leq 0.0001$, OR: 10.1, 95% CI: 3.3–30.4). The length of hospitalization was longer in AAD (+) patients (12 ± 5.35 days vs. 9.25 ± 6.15 days, $P = 0.039$).

The multivariate regression analysis of the risk factors for the development of AAD is shown in Table 2. Male sex ($P = 0.027$, OR: 3.36), age between 1 month and <3 years ($P = 0.01$, OR: 4.23), ibuprofen use ($P = 0.044$, OR: 2.63) and late administration of antibiotics ($P = 0.001$, OR: 9.5) were associated with the development of AAD.

DISCUSSION

The incidence of AAD was low in the present study. Due to differences in the selection criteria of the study populations and differences in the definition of AAD, it is difficult to compare our results with those of previous studies. In a recent study, Bau et al[7]

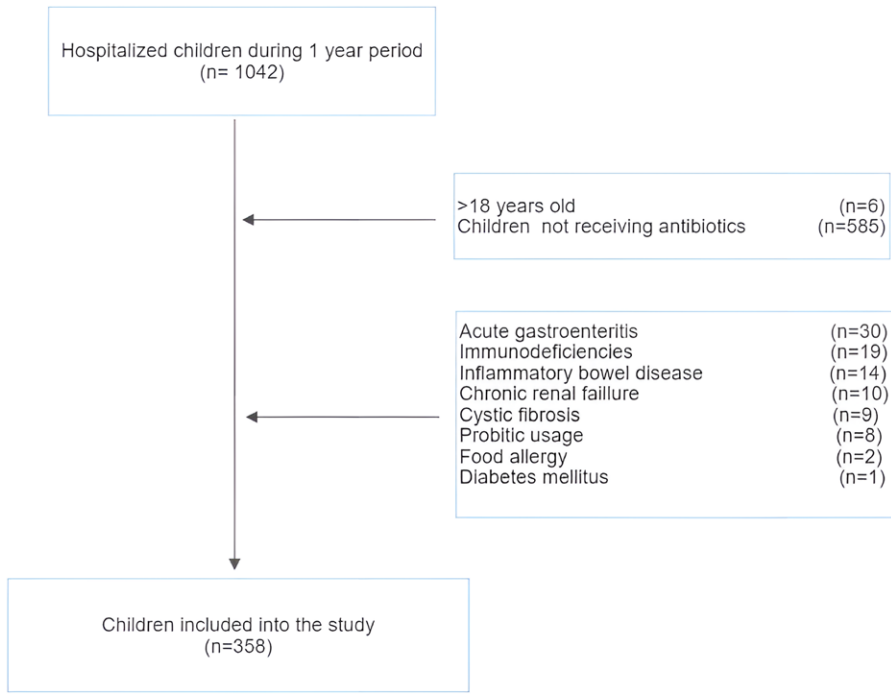


FIGURE 1. Flow chart of the patient enrollment into the study.

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TABLE 1. Demographic and Clinical Findings of the Patients, and Comparison of the Patients With and Without AAD

Parameters	Overall (n = 358)	AAD (+) (n = 22)	AAD (-) (n = 336)	OR (95% CI)	*P*
Gender, male, n (%)	179 (50)	17 (77.3)	162 (48.2)	3.6 (1.3–10.1)	**0.01**
Age, mean ± SD, months	55.03 ± 54.92	33.65 ± 43.23	56.43 ± 55.35	0.4	0.059
Age group, n (%)					
1 month–<3 years	178 (49.7)	17 (77.3)	161 (47.9)	3.6 (1.3–10.2)	**0.01**
≥3 years–<6 years	71 (19.8)	2 (9.1)	69 (20.6)	0.3 (0.08–1.6)	0.2
≥6 years–≤18 years	109 (30.4)	3 (13.6)	106 (31.5)	0.3 (0.09–1.1)	0.09
Indications of antibiotics, n (%)					
Respiratory tract infections	95 (26.5)	7 (31.8)	88 (26.1)	1.3 (0.5–3.3)	0.55
Urinary tract infections	87 (24.3)	8 (36.3)	79 (23.5)	1.8 (0.7–4.5)	0.17
Fever of unknown origin	39 (10.9)	2 (9.1)	37 (11)	0.8 (0.1–3.5)	0.77
Bacterial meningitis	40 (11.2)	2 (9.1)	38 (11.3)	0.7 (0.1–3.4)	0.74
Soft tissue infections	36 (10.1)	1 (4.5)	35 (10.4)	0.4 (0.05–3.1)	0.39
Preseptal cellulitis	20 (5.6)	0	20 (5.9)	0.34 (0.02–5.8)	0.46
Septic arthritis	12 (3.4)	0	12 (3.5)	0.57 (0.03–10)	0.7
Lymphadenitis	12 (3.4)	1 (4.5)	11 (3.2)	1.4 (0.17–11.4)	0.7
Bacterial septicemia	12 (3.4)	1 (4.5)	10 (2.9)	1.5 (0.18–12.7)	0.68
Cholangitis	11 (3.1)	0	11 (3.2)	0.6 (0.03–11)	0.75
Antibiotic classes, n (%)					
Cephalosporins	232 (50.8)	17 (77.3)	215 (63.9)	1.9 (0.6–5.3)	0.2
Penicillins	85 (18.6)	6 (27.2)	84 (25)	1.1 (0.4–2.9)	0.8
Glycopeptides	45 (9.8)	1 (4.5)	44 (13)	0.3 (0.04–2.4)	0.2
Macrolides	42 (9.2)	4 (18.1)	43 (12.7)	1.5 (0.4–4.6)	0.4
Clindamycin	21 (4.6)	2 (9.1)	25 (7.4)	1.2 (0.2–5.6)	0.7
Aminoglycosides	16 (3.5)	0	16 (4.7)	0.4 (0.02–7.4)	0.5
Carbapenems	16 (3.5)	3 (13.6)	13 (3.8)	3.9 (1–14.9)	**0.04**
Time of antibiotic administration, after the 24 hours, n (%)	18 (5)	6 (27.2)	12 (3.5)	10.1 (3.3–30.4)	**<0.0001**
Number of antibiotics, single, n (%)	270 (75.4)	13 (59)	257 (76.4)	0.44 (0.1–1)	0.07
Route of administration, intravenous, n (%)	343 (95.8)	22 (100)	321 (95.5)	2.1 (0.12–37)	0.5
Additional drug, n (%)					
Proton pump inhibitors	80 (18.1)	6 (27.7)	74 (22)	1.3 (0.5–3.5)	0.6
Ibuprofen	111 (25.1)	12 (54.5)	99 (29.4)	2.8 (1.2–6.8)	**0.01**
Paracetamol	107 (24.2)	6 (27.7)	101 (30)	0.8 (0.3–2.2)	0.78
Salbutamol	61 (13.8)	4 (18.1)	57 (14.8)	1 (0.3–3.3)	0.88
Length of hospitalization, mean ± SD, days	9.5 ± 6.1	12 ± 5.35	9.25 ± 6.15	3.59	**0.039**

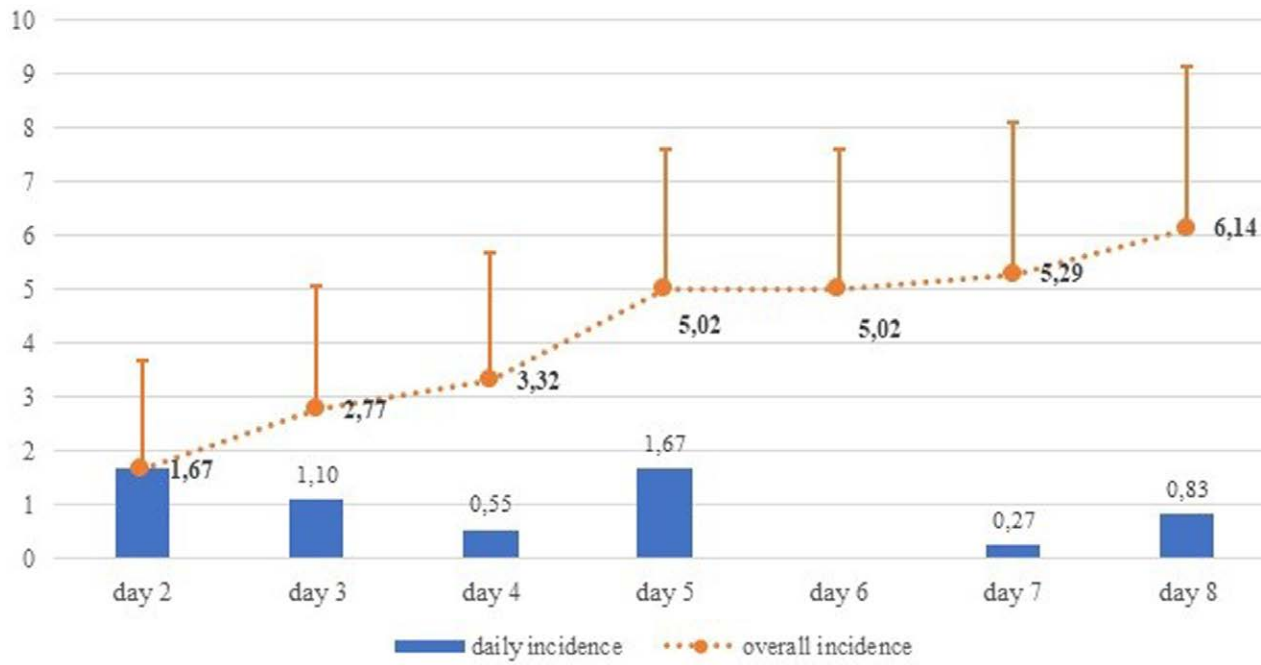


FIGURE 2. Daily and overall incidence of antibiotic-associated diarrhea.

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TABLE 2. Multivariate Regression Analysis of the Risk Factors for the Development of AAD

Parameters	*P*	OR	95% CI
Male gender	**0.027**	3.36	1.14–9.85
1 month–<3 years	**0.01**	4.23	1.3–12.5
Carbapenems	0.107	0.33	0.06–1.76
Ibuprofen	**0.044**	2.63	1.02–6.77
Late antibiotic administartion (after 24 hours)	**0.001**	9.5	2.68–33.6

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analyzed the frequency of AAD for a 1-year period and found that AAD occurred in 20.4% of the patients. Similar to our study, they tried to exclude children with comorbid diseases, but unlike our study, their study also included patients who were not hospitalized. In a meta-analysis, the incidence of AAD ranged from 4.3% to 80% (median incidence of 22%).[6] Despite having more severe infections requiring hospitalization and aggressive and broad-spectrum antibiotic treatments, the low incidence of AAD in our patient group may be related to (1) exclusion of patients with comorbid disease, (2) extensive analysis of all cases with diarrhea and (3) the fact that the majority of the children received intravenous antibiotics.

In our study, male sex was associated with AAD development. In previous studies, no significant gender-based differences were reported in children, but female sex was found to be associated with an increased risk of AAD in some adult studies.[6] In a recent study, Hasan et al[11] found a higher rate of *C. difficile* positivity among males with AAD compared to females in a pediatric study, but the results were not significant. Gender-dependent differences in gut microbiota composition, such as differences in alpha diversity and richness or differences in phylum levels after antibiotic treatment, have been reported in human and animal studies.[12] But further studies are needed to analyze the effects of these differences on the development of AAD in children.

Age is another risk factor for the development of AAD. Turck et al[13] analyzed the risk factors for AAD in an outpatient pediatric population and found that young age (<2 years) was one of the major risk factors for the development of AAD. Similarly, Bau et al[7] found the highest rate of AAD in children aged less than 3 years. The gastrointestinal tract is unstable, immature and more susceptible to alterations caused by antibiotics until 2–3 years of age than in older children.

The association between nonsteroidal anti-inflammatory drug use and the development of AAD is well-defined in adult patients. In a meta-analysis, an association between nonsteroidal anti-inflammatory drug usage and *C. difficile*-associated diarrhea was found, but further studies are suggested to analyze the effect of specific subtypes of nonsteroidal anti-inflammatory drugs.[14] Data on children were lacking; in only 1 study, Guo et al[15] analyzed the risk factors *C. difficile*-associated diarrhea in children, and they found an increased risk of nonsteroidal anti-inflammatory drug usage. Nonsteroidal anti-inflammatory drugs may cause dysbiosis by antibacterial activity, as reported in vitro for indomethacin, diclofenac, ibuprofen, aspirin and celecoxib. In human studies, ibuprofen has been shown to increase the abundance of Acidaminococcaceae and Enterobacteriaceae. Additionally, ibuprofen causes enrichment in Propionibacteriaceae, Pseudomonadaceae, Punicei-coccaceae and Rikenellaceae species compared with nonusers or naproxen users.[16]

One of the interesting findings of our study was that the late administration of antibiotics increased the risk of AAD. All the children in our study group were hospitalized for a suspected infection, but antibiotic treatment was initiated late (after 24 hours) in a subgroup of patients for the late documentation of infection. Prolonged cytokine exposure due to bacterial infections in these subgroups of patients may increase the likelihood of developing AAD in addition to antibiotic treatment.

We observed a low rate of *C. difficile* infection among patients with AAD. It was reported that 42.6% of hospitalized children had AAD in a previous pediatric study, and in multivariate analysis, the major risk factor was the length of hospitalization ≥10 days before diarrhea when compared to children without non-*C. difficile*-associated AAD. Other risk factors include prolonged duration of antibiotic treatment and gastrointestinal tract operation.[17] Additionally, epidemiological studies among hospitalized children have shown an increased incidence of *C. difficile*-associated diarrhea in recent years. We used a toxin detection test for the diagnosis of *C. difficile* as suggested by the protocols.[10] As mentioned above, it may be related to the selection criteria of the study population in our study.

The major limitations of our study were as follows: (1) We did not interview patients with AAD after hospital discharge. If we continue to study after hospital discharge, the incidence of AAD might increase. However, the findings will be based on parent reports (not physician findings), and we will not be able to exclude infectious diarrhea, which may decrease the reliability of our results. (2) It may be better to perform a *C. difficile* polymerase chain reaction test in patients with toxin-negative noninfectious AAD.

According to our study, the incidence of AAD is low among hospitalized children without comorbid diseases, and most of the diarrheal episodes are mild and self-limiting. The aim of probiotic usage should be reconsidered in AAD, not only for prevention but also for the restoration of intestinal microbiota after antibiotic treatment.

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