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Clinical and Laboratory Features of Antibiotic-Associated Diarrhea in Young Children

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Abstract Antibiotic-associated diarrhea (AAD) is one of the most frequent complications of antibacterial therapy in early childhood. Due to the morphofunctional immaturity of the gastrointestinal tract and the immune system, its clinical course is highly variable, requiring a differentiated diagnostic and therapeutic approach. The incidence of AAD in young children ranges from 5% to 30%, with the highest rates observed in preterm infants and those under one year of age. This is largely explained by the immaturity of the intestinal microbiota and immune system. In the post-COVID period, the irrational use of antibiotics has further increased the prevalence of AAD, emphasizing the need for improved methods of diagnosis, severity assessment, and treatment.

Keywords Antibiotic-associated diarrhea, Clostridioides difficile, Fecal calprotectin, Young children

1. Introduction

Antibiotic-associated diarrhea (AAD) is one of the most frequent complications of antibacterial therapy in early childhood, with an incidence ranging from 5% to 30%, reaching the highest rates in preterm infants and children under one year of age [1]. According to WHO, AAD is defined as the occurrence of ≥3 unformed stools per day during or within 8 weeks after antibiotic treatment, in the absence of other causes [1].

The role of *Clostridioides difficile* in pediatric AAD remains controversial, as many infants and young children are asymptomatic carriers [2,3]. Globally, the irrational use of antibiotics—particularly in outpatient pediatric practice—contributes to both antibiotic resistance and the growing prevalence of AAD [3].

AAD not only worsens the clinical course of underlying diseases but also increases healthcare costs due to prolonged hospitalization and the need for additional therapy. Current challenges include the limited availability of diagnostic methods, lack of validated severity assessment tools, and insufficient evidence-based approaches for management in young children.

Recent studies highlight the importance of gut microbiota disturbances, the pathogenic role of *C. difficile*, and the potential of early diagnostic markers such as fecal calprotectin and *C. difficile* toxins [4]. Personalized antibiotic strategies and adjunctive therapies, including lactoferrin, are being actively investigated, but standardized management protocols in pediatrics remain to be developed [5].

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2. Methodology of the Study

A single-center observational (prospective–retrospective) study was conducted during 2023–2025. The analysis included 140 young children (aged 1 month to 3 years) who underwent inpatient treatment with clinically confirmed antibiotic-associated diarrhea (AAD).

Definition of AAD

A case of antibiotic-associated diarrhea (AAD) was established in the presence of the following:

- ✓ use of systemic antibacterial agents within the preceding **2–8 weeks**;
- ✓ occurrence of **liquid or watery stools ≥3 times per day**;
- ✓ confirmation by laboratory and/or instrumental methods.

Diagnostic approaches followed the **ESPGHAN guidelines (2020)**.

Inclusion criteria

- ✓ Age 1 month to 3 years;
- ✓ Hospitalization for treatment;
- ✓ Fulfillment of the AAD case definition.
- ✓ Exclusion criteria

Congenital gastrointestinal pathology:

1. Severe somatic comorbidities;
2. Viral or parasitic intestinal infections.

Patient stratification

Patients were allocated into two main groups:
- **Infectious AAD**, subdivided into:
- **Confirmed** *Clostridioides difficile* **infection**;

Predominance of opportunistic flora (*Enterobacter spp.*, *Klebsiella spp.*, *Proteus spp.*, and others).

Non-infectious AAD, defined as the absence of significant infectious etiology based on coprological and microbiological findings.

Age stratification

For analytical purposes, patients were grouped into three age intervals:

- ✓ **0–6 months,**
- ✓ **7–12 months,**
- ✓ **1–3 years.**

Data Collection and Examination

Clinical and anamnestic data: age, sex, type of feeding, information on current/previous antibiotic therapy (class, route of administration, duration, repeated courses), comorbidities, signs of dehydration and intoxication, and duration of diarrhea.

Laboratory methods: complete blood count (leukocytosis, hemoglobin), C-reactive protein (CRP), coprological examination, bacteriological stool culture, and verification of *Clostridioides difficile* (toxin testing/PCR according to the local protocol).

Severity assessment: a standardized clinical–laboratory severity scoring scale, adapted for inpatient settings, was applied to ensure comparability between subgroups.

Outcomes and Indicators

Primary outcomes:

1. Distribution of AAD by etiology (infectious vs. non-infectious) and clinical subtypes;
2. Age distribution of cases within each subtype.

Secondary outcomes:

- ✓ Intensity of clinical and laboratory inflammatory response;
- ✓ Severity by the standardized scale;
- ✓ Duration of diarrheal syndrome;
- ✓ Requirement for etiotropic therapy in infectious forms.

3. Analysis and Results

Age distribution

In patients with *Clostridioides difficile* (Cl+), the peak incidence of AAD was observed at **6–12 months (37.1%)** and **1–3 years (40.3%)**, with statistically significant differences compared to the non-infectious group at these ages ($p < 0.05$). In cases associated with other opportunistic flora (*Enterobacter*, *Klebsiella*, *Proteus* spp.), the highest prevalence was recorded at **3–6 months** and **6–12 months**, although significant differences were confirmed only in the youngest subgroup ($p < 0.05$).

In the combined infectious group, incidence was also maximal at 6–12 months and 1–3 years, while in the non-infectious group AAD was most common in infants <3 months, with a decline in frequency at older ages.

Temperature profile

- ✓ **Normal (36–37 ℃):** less frequent in Cl+ (11.3%) vs. non-infectious (25.7%), showing a trend toward higher inflammatory activity ($p = 0.067$).
- ✓ **Subfebrile (37–38 ℃):** most common across all groups, especially non-infectious AAD (57.1%). A significant difference was found only in the subgroup with other flora (30.4% vs. 57.1%, $p = 0.047$).
- ✓ **Febrile (38–39 ℃):** markedly higher in infectious AAD (35.5–39.1%) vs. non-infectious (17.1%), significant in the combined group ($p = 0.038$).
- ✓ **Hyperpyrexia (>39 ℃):** paradoxically more frequent in non-infectious AAD (25.7%) vs. Cl+ (6.45%), $p = 0.008$, likely reflecting severe comorbid conditions rather than infectious activity.

Clinical symptomatology

Comparative χ^2-analysis revealed significant intergroup differences:

- ✓ **Abdominal pain:** $\chi^2 = 7.071$, $p = 0.029$
- ✓ **Abdominal distension:** $\chi^2 = 22.042$, $p < 0.001$
- ✓ **Loss of appetite:** $\chi^2 = 19.180$, $p < 0.001$
- ✓ **Irritability:** $\chi^2 = 11.120$, $p = 0.004$

The most frequent symptoms in Cl+ were **abdominal distension (82.3%)**, **loss of appetite (67.7%)**, and **abdominal pain (53.2%)**, while in non-infectious AAD, **dry skin (42.8%)** was predominant, with lower frequency of other symptoms.

Interpretation

These findings highlight:

1. The **age-specific distribution** of AAD subtypes;
2. The **higher inflammatory response** in infectious forms, especially Cl+;
3. The diagnostic relevance of **abdominal distension, anorexia, and abdominal pain** as clinical indicators of infectious AAD in early childhood.

Table 1. Frequency of clinical symptoms in children with AAD of different etiology

Symptom	Cl+ (n=62)	Other bacteria (n=2)	Non-infectious (n=35)	χ^2	*p*-value
Abdominal pain	33	7	10	7.071	0.029
Abdominal distension	51	11	13	22.042	0.001
Loss of appetite	42	9	8	19.180	0.001
Irritability	32	6	7	11.120	0.004
Dry skin	30	8	15	1.294	0.524
Decreased skin turgor	28	10	9	2.020	0.365
Reduced diuresis	25	8	11	0.992	0.609

Interpretation:

1. Statistically significant intergroup differences were observed for **abdominal pain, distension, loss of appetite, and irritability**, which were most pronounced in the *Clostridioides difficile*-positive group ($p < 0.05$).
2. Signs of **dehydration (dry skin, reduced turgor, reduced diuresis)** did not differ significantly between groups ($p > 0.05$).

The analysis of dehydration severity in children with AAD revealed distinct differences between infectious and non-infectious etiologies.

- ✓ **Mild dehydration** was significantly more frequent in the non-infectious group (**38.9%**) compared with *Clostridioides difficile* (**8.1%**) and the combined infectious group (**8.2%**). Although the differences did not reach strict statistical significance ($p = 0.087$ and $p = 0.069$, respectively), a clear trend was observed, suggesting that mild dehydration is more common in non-infectious AAD, possibly due to lower fluid losses and the absence of pronounced intoxication.
- ✓ **Moderate dehydration** was observed in **44.4%** of children with non-infectious AAD versus **21.0%** in the *C. difficile* group ($p = 0.044$). In the combined infectious group, however, the difference was not statistically significant. This may reflect the longer duration of diarrhea or insufficient correction of fluid-electrolyte imbalance prior to hospitalization in the non-infectious subgroup.
- ✓ **Severe dehydration** occurred more frequently in infectious AAD (**22.6% in Cl+** and **20.0% in the combined group**) compared to **16.7%** in non-infectious cases. Despite higher relative rates (e.g., OR = 3.111 for the *C. difficile* group), statistical significance was not reached ($p > 0.05$), likely due to limited sample size and variability of clinical presentation.

Table 2. Severity of dehydration in children with AAD by etiology

Severity of dehydration	*Clostridioides difficile* (%)	Other flora (%)	Infectious total (%)	Non-infectious (%)	*p*-value
Mild	8.1	11.0	8.2	38.9	0.069–0.087 (ns)
Moderate	21.0	26.0	24.0	44.4	0.044 (Cl+ vs non-inf.)
Severe	22.6	18.0	20.0	16.7	>0.05 (ns)

Interpretation

- ✓ **Infectious AAD (especially *C. difficile*)** was associated with a tendency toward **more severe dehydration**, reflecting the impact of inflammatory-mediated fluid loss and intoxication.
- ✓ **Non-infectious AAD** was characterized by a predominance of **mild-to-moderate dehydration**, consistent with slower disease progression and less systemic involvement.

These findings emphasize the importance of **early differential diagnosis** and **timely fluid correction**, particularly in children with suspected infectious AAD.

In the comparative analysis of coprological parameters in children with antibiotic-associated diarrhea (AAD) of infectious and non-infectious origin, both common features and statistically significant differences were identified, reflecting the underlying nature of the pathological process.

Table 3. Comparative coprological findings in children with AAD of infectious and non-infectious etiology

Parameter	Infectious AAD (%)	Non-infectious AAD (%)	χ^2	OR (95% CI)	*p*-value
Undigested plant fiber	24.7	57.1	10.45	4.06 (1.77–9.33)	0.001
Starch	4.7	45.7	28.62	17.05 (5.12–56.85)	0.001
Undigested food residues	11.8	42.9	12.27	5.64 (2.01–15.85)	0.001
Leukocytes (↑)	38.2	21.4	3.94	2.26 (1.01–5.05)	0.047
Erythrocytes/mucus admixtures	26.4	9.5	4.81	3.41 (1.07–10.86)	0.028

Interpretation:

Non-infectious AAD was characterized by significantly higher frequency of starch, undigested fiber, and food residues, reflecting fermentative dyspepsia and malabsorption due to enzymatic insufficiency.

Infectious AAD, particularly *Clostridioides difficile*, was associated with higher rates of leukocytes and erythrocyte/mucus admixtures, indicating an inflammatory-destructive process.

Fecal Calprotectin Analysis

Calprotectin is a specific marker of intestinal inflammation belonging to the family of calcium-binding proteins, with a molecular weight of 36.5 kDa, composed of one light and two heavy polypeptide chains. It is released from neutrophils and possesses bacteriostatic and fungicidal properties [6–7]. In patients with intestinal infections, fecal calprotectin remains elevated even after a short course of anti-inflammatory therapy, exceeding the normal values by

5–7 times. Increased levels reflect mucosal inflammation of the gastrointestinal tract, typical of conditions with active inflammatory processes [8–9].

In healthy children older than one year, fecal calprotectin levels are usually below 50 μg/g. In neonates, however, values may be up to ten times higher due to anatomical and physiological characteristics of the intestinal mucosa, antigen exposure, and immaturity of the immune system [10]. In most cases, fecal calprotectin correlates with disease severity, and in moderate forms of intestinal infections levels are higher than in mild forms [11].

In the present study, fecal calprotectin levels were determined in children with antibiotic-associated diarrhea (AAD) of different etiologies, as well as in healthy controls. The analysis demonstrated significant differences between the groups.

- ✓ **Clostridioides difficile-associated AAD (Cl+):** 393.65 ± 39.23 μg/g — the highest values, consistent with pronounced neutrophil-mediated intestinal inflammation.
- ✓ **Bacterial AAD (other flora):** 195.45 ± 24.49 μg/g — elevated above normal, but significantly lower compared with Cl+ (p_1 = 0.0001).
- ✓ **Non-infectious AAD:** 85.2 ± 11.7 μg/g — markedly lower than Cl+ (p_2 = 0.0001) and bacterial AAD (p_4 = 0.0003).
- ✓ **Healthy controls:** 31.6 ± 3.82 μg/g — within the normal range and significantly different from all AAD groups (p_3 and p_5 < 0.001).

Interpretation

Fecal calprotectin reliably reflects the degree of intestinal inflammation and serves as a sensitive **differential diagnostic marker** for stratifying forms of AAD in early childhood.

Table 4. Fecal calprotectin levels in children with AAD and in the control group

Group	*n*	Calprotectin (μg/g ± SE)	Statistical comparison (*p*-value)
Clostridioides difficile (Cl+)	62	393.65 ± 39.23	p_1 = 0.0001 vs. other bacteria
Other bacteria	23	195.45 ± 24.49	p_4 = 0.0003 vs. non-infectious
Non-infectious AAD	35	85.2 ± 11.7	p_2 = 0.0001 vs. Cl+; p_5 = 0.0001 vs. control
Control group	20	31.6 ± 3.82	p_3 = 0.0001 vs. Cl+

Interpretation:

The **highest calprotectin values** were detected in the *C. difficile*-positive group (≈394 μg/g), confirming active neutrophilic inflammation.

Children with AAD due to other bacteria also had **elevated levels**, but significantly lower than Cl+ cases.

Non-infectious AAD showed moderately increased levels, significantly lower than both infectious subgroups.

The **control group** remained within the physiological range (<50 μg/g), with highly significant differences compared to all AAD subgroups.

4. Conclusions

Coprological profile clearly differed depending on the etiology of AAD:

In **infectious AAD**, inflammatory signs predominated: leukocytes were present in 100% of cases versus 42.9% in non-infectious AAD (p < 0.001), consistent with a more pronounced neutrophilic response. In **non-infectious AAD**, markers of maldigestion and accelerated transit prevailed: significantly more frequent detection of fiber (57.1% vs. 24.7%; p = 0.001; OR = 4.06), starch (45.7% vs. 4.7%; p = 0.001; OR = 17.05), undigested residues (42.9% vs. 11.8%; p = 0.001; OR = 5.63), and crystals (94.3% vs. 72.9%; p = 0.009; OR = 6.12). Mushy stools were more frequent in non-infectious AAD (28.6% vs. 15.3%), but the difference did not reach statistical significance (p = 0.094). Yeast-like fungi were detected in 29.4% of infectious cases and were absent in non-infectious AAD (p = 0.001), reflecting possible secondary colonization under dysbiosis and antibiotic therapy.

Fecal calprotectin proved to be a sensitive differential diagnostic marker of intestinal inflammation:

- ✓ Highest levels were found in *Clostridioides difficile*–associated AAD (393.65 ± 39.23 μg/g);
- ✓ Moderately elevated levels were recorded in AAD caused by other bacteria (195.45 ± 24.49 μg/g);
- ✓ Levels were substantially lower in non-infectious AAD (85.2 ± 11.7 μg/g);
- ✓ Healthy controls remained within normal limits (31.6 ± 3.82 μg/g);
- ✓ All intergroup differences were statistically significant ($p \leq 0.001$), confirming the gradient of inflammation: **Cl+ → other bacteria → non-infectious → control**.

Severity of AAD was not linearly dependent on the severity of the underlying disease. Severe forms of AAD, including toxigenic *C. difficile* colitis, developed even in children with relatively mild primary diagnoses (e.g., community -acquired pneumonia, tonsillopharyngitis). Conversely, in children with severe underlying conditions (e.g., sepsis, severe pneumonia, neuroinfection), AAD often presented with only mild to moderate severity. This highlights the necessity of independent risk and severity stratification for AAD, rather than extrapolation from the severity of the underlying illness.

5. Recommendations

Diagnostic algorithm for stratification of AAD in children aged 1 month–3 years:

- **Step 1:** Confirm antibiotic exposure (2–8 weeks) and ≥3 unformed stools/day.
- **Step 2:** Perform baseline laboratory and coprological evaluation:

Leukocytes → marker of inflammation.

Fiber, starch, undigested residues, crystals → markers of maldigestion/accelerated transit.

- **Step 3:** Fecal calprotectin as a triage test of inflammation:

High values (e.g., >250 μg/g, per protocol) → priority exclusion of CDI (toxin/PCR testing) and other bacterial causes.

Relatively low values in the presence of excess fiber/ starch/residues → focus on maldigestion/accelerated transit (non-infectious etiology).

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