Antibiotic-associated Bloody Diarrhea in Infants: Clinical, Endoscopic, and Histopathologic Profiles

Maha Barakat, Zeinab El-Kady, Mohamed Mostafa, Naglaa Ibrahim, and Hamdy Ghazaly

ABSTRACT

Objective: Antibiotic-associated diarrhea constitutes 1 of the most frequent side effects of antimicrobial therapy with widely varying clinical presentations; however, little is known about its antibiotic-associated bloody diarrhea (AABD) form, particularly in very young children. The aim of this study was to describe the clinical, endoscopic, and histopathologic profiles of community-acquired AABD in infants.

Patients and Methods: The study included 23 infants referred with bloody diarrhea that developed a few days after receiving antibiotics on an outpatient basis for watery diarrhea (18), respiratory tract infections (4), or urinary tract infection (1). Detailed clinical assessment, videosigmoidoscopy, and histopathologic examination of endoscopic biopsies were performed for all.

Results: Clinically, on presentation, bloody diarrhea was acute in all except 1 patient with a prolonged course (for 25 days) and stopped in all 2 to 6 days after discontinuation of antibiotics. Fever and/or leukocytosis were present only in 8 (34.8%). Sigmoidoscopy revealed varying types of erythema (papul, ring, diffuse) and ulcers (aphthoid, diffuse) in 18 and pseudomembranes in 5. Histopathologically, only 3 showed the characteristic mushroom-like pseudomembranes, whereas all of the other infants had nonspecific colitis.

Conclusions: Community-acquired AABD is not uncommon in infants presenting with acute or chronic forms even without fever or leukocytosis. When suspected, discontinuation of antibiotics is a good policy if facilities for bacterial culture with cytotoxin assays are limited. The characteristic endoscopic or histopathologic pseudomembranes are encountered only in a small percentage (26%). Rational use of antibiotics should be adhered to particularly in cases of watery diarrhea that is mostly of viral origin.

Key Words: antibiotic-associated diarrhea, bloody diarrhea, infants, pediatric endoscopy

(JPGN 2010;00: 00–00)

Antibiotic-associated diarrhea (AAD) has been recognized worldwide as 1 of the most frequent side effects of antimicrobial therapy, with an incidence ranging from 5% to 35% particularly in hospitalized patients (1,2). The diagnosis of AAD starts primarily with history taking and should be suspected in any patient who develops diarrhea during antibiotic therapy or within 6 to 8 weeks of treatment (3). Interestingly, this iatrogenic problem can be induced by almost all of the antibiotics, even after a single dose (4).

Clinically, AAD may manifest through a spectrum extending from mild to fulminant life-threatening colitis, with patterns varying from watery to bloody diarrhea and hemorrhagic colitis (5). Pathogenetically, various mechanisms have been proposed to explain the occurrence of AAD. Following an antibiotic-induced disturbance of the normal gut flora profile, Clostridium difficile contributes to about 20%, whereas several other organisms including Clostridium perfringens, Staphylococcus aureus, Candida albicans, and Klebsiella oxytoca can be collectively responsible for about 2% to 3% of AAD cases. Also, a direct antibiotic effect on the intestinal mucosa shares as another mechanism in a minority of cases. Otherwise, about 75% of AAD cases have been described as “nonspecific” with no defined mechanism. Of all of the mechanisms, C difficile infection has received much attention mainly as a nosocomial infection for which advanced age and hospitalization are the major risk factors (6,7).

Few data are available regarding the occurrence of AAD in the infancy period in a nonhospital ambulatory setting, particularly when presented as antibiotic-associated bloody diarrhea (AABD), the form that generally seems to be underdiagnosed. Although diarrheal illnesses in infancy constitute a common clinical problem, especially in developing countries (8), bloody diarrhea in particular represents an alarming event to the physician and causes much anxiety and fright in the child’s parents.

The aim of this study was to provide a detailed description of the clinical, endoscopic, and histopathologic profiles of AABD in infants in a community-acquired non-nosocomial setting.

PATIENTS AND METHODS

This study included 23 infants admitted to the Gastroenterology and Hepatology Unit, Department of Pediatrics, Assiut University Hospital, with a history highly suspicious of AABD between April 2004 and November 2008. They were 14 boys and 9 girls with an age range of 2 to 11 months (mean ± SD 6.6 ± 2.6 months). All of them developed bloody diarrhea a few days after receiving antibiotic therapy for various illnesses on an outpatient basis through other hospitals or pediatrics clinics. Of the 23 patients, 18 were receiving antibiotics for watery diarrhea, 4 for respiratory tract infections, and 1 for urinary tract infection. The study protocol was approved by the Assiut Faculty of Medicine ethics committee.

Full clinical assessment was performed for all of the infants, including a detailed history taken from the parents about the bloody diarrhea (eg, its onset, frequency, duration, presence of colic, fever, convulsions, or vomiting) and all of the antibiotics given to the infant before the occurrence of bloody diarrhea, with a thorough clinical examination including temperature and signs of...
dehydration on admission. None of the infants included had any other serious illnesses, for example, cardiac, hepatic, renal, and cerebral diseases or malignancies. Also, none had a history of hospitalization before the admission for bloody diarrhea.

For all of them, the following routine tests were done: complete blood count, stool examination for parasites, red blood cells or leukocytes, and a routine bacteriologic stool culture for enteric pathogens (eg, Shigella, Salmonella).

Written informed consent was obtained from the parents to perform a short colonoscopic examination; the procedure was explained, and 1 of the parents (usually the mother) was allowed to attend. The examination was performed using a videocolonoscope (Pentax EC-3440F, Tokyo, Japan) with a distal diameter of 11.5 mm. No prior bowel preparation was done. Intravenous light sedation was applied using incremental doses of midazolam; an initial dose of 0.05 mg/kg body weight was given and increased if necessary according to the child’s response after 2 minutes until an adequate level of sedation was achieved. Sigmodoscopic examination was arranged to be simple for a duration not exceeding 3 minutes with image recording. The maximum length of tube insertion was 8 to 15 cm. All of the examinations were performed by the same endoscopist (M.B.). No complications were reported, and recovery from sedation was uneventful.

Using the standard biopsy forceps, 2 biopsies were obtained from the recorded lesions in each patient. The specimens were fixed in vials containing 10% neutral buffered formalin solution, labeled, and sent to the histopathology laboratory to be processed, stained by hematoxylin and eosin (H&E), and examined by the same histopathologist (M.M.).

Once admitted with a suspected diagnosis of AABD, the following lines were applied as a management strategy with follow-up for clinical signs of improvement particularly during the next 24 to 72 hours:

1. **Line 1:** stoppage of all antibiotics + supportive and fluid therapy (in cases of dehydration or vomiting)
2. **Line 2:** as in line 1 + oral metronidazole suspension (7.5 mg/kg 3 times daily for 10 days) if at least 1 of the following criteria of severity was present: fever, abdominal colic, leukocytosis, endoscopic or histologic pseudomembranous colitis (PMC) (9)

**Data Analysis**

Most of the data were descriptive, expressed as direct numbers, percentages, or mean ± SD. Differences between groups were compared using Student t test. Probability values (P) less than 0.05 were considered significant.

**RESULTS**

Clinically, on admission, the reported duration of bloody diarrhea was less than 1 week in all of the children (range 1–4; mean 2.5 days), except 1 who had a prolonged course with bloody diarrhea lasting for 25 days, during which the child received repeated and changing courses of antibiotic combinations on repeated medical consultations.

The onset of bloody diarrhea was 2 to 5 days (mean 2.8 days) after intake of antibiotics either as a single (in 16 patients; 69.6%) or as combined therapy (in 7 patients; 30.4%) including cotrimoxazole in 12, penicillin derivatives in 10, cephalosporins in 7, and aminoglycosides in 4.

Abdominal colic was reported in 4, fever in 5 (one 2-month-old infant had febrile convulsions), and vomiting in 2, with signs of mild dehydration on admission in 3. Leukocytosis (with a white blood cell count of more than 11,000/mm³) was reported in 6. None of the patients had any serious complications, for example, toxic megacolon, toxic shock, and perforation.

In all, the microscopic stool analysis was negative for parasites. Microscopic red blood cells were detected in all patients (>10 per high-power field), and fecal leukocytes (>5 per high-power field) denoting inflammatory diarrhea were seen in 13 (56.5%) patients. Routine stool culture revealed no growth of enteropathogens (eg, Shigella, Salmonella) in all.

On endoscopic examination, the rectal mucosa was involved in all of the children and various lesions were revealed (Fig. 1) including patchy erythema in 4 patients, ring erythema in 2, diffuse erythema with blood ooze in 1, scattered aphthoid ulcers in 2, diffuse ulcerations in 7, mixed lesions (erythema and ulcerations) in 2, and ulcerations with pseudomembranes in 5 (interestingly, only 1 of them had fever, 3 had leukocytosis, and 1 had no fever or leukocytosis).

On histopathologic examination of the biopsy specimens, only 3 patients (13%) had the characteristic mushroom-like mass of mucus and neutrophils at the surface epithelium (Fig. 2) as a pathognomonic feature of *C. difficile* antibiotic-associated PMC (1 of them without endoscopic PMC). In the rest of the patients,
features of nonspecific colitis were detected in their biopsy specimens.

According to the management strategy applied, the criteria of severity indicating metronidazole therapy were fulfilled in 12 patients in various combinations as shown in Table 1. In response to the management strategy, the bloody diarrhea stopped with improvement of the general condition within 2 to 6 days (mean 2.5 days) in all of the patients of both groups, those on line 1 (11 patients), and those who received oral metronidazole (11 patients). Interestingly, metronidazole was not given to the infant who had only histopathologic PMC with a prolonged AABD for 25 days, because by the time the histopathology report came up (after 4 days), the child had already improved with stoppage of bloody diarrhea after discontinuation of all antibiotics. None of the patients developed any complications along the period of hospitalization until discharged.

Although patients having the severity criteria (receiving line 2 therapy) tended to be younger than the other group (receiving line 1), the difference did not reach statistical significance (5.9 ± 2.5 vs 7.3 ± 2.8 months, respectively; \( P > 0.05 \)). Also, there was no statistically significant difference regarding the time needed for improvement between both groups (2.6 ± 1.2 vs 2.3 ± 0.7 days, respectively; \( P > 0.05 \)).

**DISCUSSION**

In extension to the body of literature examining various aspects of AAD, this study is the first to describe its endoscopic and histopathologic profiles in infants with bloody diarrhea. The diagnosis of AABD has been primarily based on 3 pieces of evidence: (1) the strong circumstantial clinical evidence of occurrence shortly after intake of antibiotics, and resolution shortly after their discontinuation in all 23 patients (3,10); (2) the solid evidence of the presence of PMC (endoscopic or histopathologic) in 26% of cases (6/23) as a criterion for defining *C. difficile* AAD, which is responsible for almost all of the PMC cases (11–13); and (3) exclusion of other possible parasitic or bacterial infections on routine stool examination and culture and other colonic lesions (eg, polyps or other inflammatory lesions) on endoscopy and histopathology.

Through this study, varying clinical presentations of AABD were noted. For example, fever was absent in most of them (78%), and 1 presented by a long course of AABD extending for 25 days. It should be noted that there are no characteristic diagnostic features for AABD; the pattern of diarrhea together with the accompanying symptoms (eg, fever) is nonspecific and shared by other diseases such as bacterial infections, inflammatory bowel disease, and ischemic colitis (14). Furthermore, there is no relation between the pattern of AAD and its inducing mechanism with no reported differences between *C. difficile*–positive and –negative children (15). Also, AAD shows no relation to the duration of antibiotic therapy, and symptoms may start even on the first day of intake (3).

Thus, the diagnosis of AAD rests primarily on a high suspicion index, and empirical therapy (with cessation of antibiotics or addition of metronidazole for *C. difficile* when suspected) is often started even before having the stool culture results and continued even after receiving negative culture results (16).

In the present study, fortunately, all of the infants responded to treatment either by discontinuation of antibiotics plus supportive measures alone or with addition of oral metronidazole in the presence of fever, colic, leukocytosis, or PMC; this response was itself supportive evidence of the AABD diagnosis. Various treatment regimens have been proposed in severe and recurrent cases including vancomycin and various alternative antimicrobials, probiotics, bile acid sequestrants, and intravenous immunoglobulin, extending to colectomy for fulminant cases (17).

Endoscopically, the characteristic PMC pattern was recorded in 21.7% (5/23) of infants in this study; however, widely varying incidences of PMC have been reported in adults having *C. difficile* AAD, with figures reaching 35.5% (9), 40.6% (18), 55.2% (19), and up to 89% (20), probably owing to differences in selection criteria and disease severity. This means that a definite evidence of AAD cannot be obtained endoscopically in all of those affected, which makes endoscopy of poor sensitivity for the identification of AAD. Apart from PMC, varying patterns of erythema and ulcers have been demonstrated in other infants with AABD (78.3%). Varying lesions also have been described in cases of "antibiotic-associated hemorrhagic colitis" in adults (21,22). Perhaps this variation is related to the severity and extent of mucosal affection in AABD cases. Similarly, the variation extends to the histopathologic pictures from that of nonspecific colitis to the pathognomonic mushroom (also called volcano or summit)-like pattern (3,23). Interestingly, mushroom-like histologic PMC may be detected in the absence of an endoscopic PMC.

**TABLE 1. Distribution of the severity criteria in 12 patients with AABD**

<table>
<thead>
<tr>
<th>Case</th>
<th>Fever</th>
<th>Leukocytosis</th>
<th>Colic</th>
<th>PMC (E)</th>
<th>PMC (H)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>√</td>
<td>√</td>
<td>√</td>
<td>√</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>√</td>
<td>√</td>
<td>√</td>
<td></td>
<td>√</td>
</tr>
<tr>
<td>3*</td>
<td>√</td>
<td>√</td>
<td>√</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>√</td>
<td>√</td>
<td>√</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>√</td>
<td>√</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>√</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>√</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>√</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>√</td>
<td>√</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>√</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>√</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>5</td>
<td>6</td>
<td>4</td>
<td>5</td>
<td>3</td>
</tr>
</tbody>
</table>

**Notes:** AABD = antibiotic-associated bloody diarrhea; E = endoscopic; H = histologic; PMC = pseudomembranous colitis.

*Presented with AABD for 25 days.*
It should be noted that in all of the infants examined through this study, the descending colon was involved; however, in *K. oxytoca* AABD, the lesions may occur predominantly in the right colon or may be segmental with rectal sparing (24). Also, in early cases of *C. difficile* infection, the lesions may be restricted to the right colon (5), and recognition of such lesions, then, requires longer intubations of the endoscope. On the contrary, the lesions may involve the whole colon in severe cases with fulminant colitis (25).

Concerning the possible etiologies of AABD in this study, several infectious and noninfectious mechanisms could be responsible. *C. difficile*, the most common infectious etiology, causes bloody diarrhea as a part of its clinical spectrum (26), possibly through gross mucosal damage by its enterotoxin as demonstrated experimentally (27); however, the bleeding may be occult with erythrocytes seen only on stool examination (18,26). Also, *K. oxytoca* has been shown to cause AABD particularly on using penicillin derivatives leading to cytotoxin-induced mucosal damage and hemorrhage, resulting in “antibiotic-associated hemorrhagic colitis,” which resolves spontaneously on cessation of antibiotic therapy (24.28.29). Other organisms have been reported in AAD as *C. perfringens, S. aureus* (30), and *Candida* infections even in immunocompromised patients (31). Moreover, various antibiotics can directly or indirectly cause microcirculatory disturbances and tissue damage leading to hemorrhagic colitis with no organisms detected on stool culture (21).

The presence of several possible incriminated organisms in AAD increases considerably the costs on trying to determine the causative pathogen with application of several culture media and cytotoxin assays. The cost issue is of significant concern particularly in cases of limited resources where a more practical, less costly approach is increasingly required to be adopted. For example, the gold standard tissue culture–stool cytotoxin assay for *C. difficile* (to detect the cytopathic effect on a cell culture) is expensive especially if a small number of specimens is to be examined, and is not routinely available in all of the hospital laboratories even in developed countries because it necessitates a maintained cell line (32). Stool culture alone or stool toxin detection alone by enzyme immunoassays cannot be relied upon, particularly in our study group, because of the normal high carriage rate of *C. difficile* approaching 52% of healthy children younger than the first year of age, contrary to 0% to 3% carriage rate in healthy adults (33), and the presence of toxin at a high frequency in infants in the absence of clinical manifestations (34). Thus, awareness of the AAD problem with all of its forms, particularly the bloody diarrhea form, is critically important for avoiding the diagnostic dilemma of performing several tests, and also avoiding the therapeutic dilemma of adding more antibiotics or changing the currently received antibiotics after being labeled as “noneffective” leading to a vicious circle complicating and aggravating the problem.

Unfortunately, in most of the cases of AABD included in this study, the inciting antibiotics were prescribed on inappropriate basis for infants experiencing watery diarrhea (18/23; 78%). The latter is almost of viral etiology because rotavirus infection represents the most common cause of infantile diarrhea particularly in developing countries (8,35). Even in developed countries, it has been estimated that up to 50% of antibiotic usage is inappropriate (36). Therefore, AAD control depends on adherence to evidence-based antibiotics prescription, and improving decision making by junior doctors about whether or not to start antibiotics (37), taking into consideration that the AAD problem has been augmented by the recent identification of a hypervirulent *C. difficile* strain causing a more serious illness and showing relative refractoriness to standard therapy (38).

Most of the studies on AAD have been conducted on hospitalized patients, and *C. difficile* infection has been regarded primarily as a nosocomial infection (6). The present study points to the community-acquired AABD in infants who are receiving antibiotics on an outpatient basis. The occurrence of the bloody diarrhea form of AAD may be related to the vulnerability of the colon mucosa, to bacterial toxins, or directly to antibiotics, in this very young age group of patients. Only a few data are available about the incidence of community-acquired AAD, with figures reaching 6.2% in children receiving antibiotics on an ambulatory basis (39).

**CONCLUSIONS**

AABD is not uncommon in infants presenting as acute or chronic forms even without fever or leukocytosis. When suspected, discontinuation of antibiotics is a good policy, particularly if facilities for bacterial culture with cytotoxic assays are limited. The characteristic endoscopic or histopathologic pseudodemembranes are encountered only in a small percentage (26%). Rational use of antibiotics should be adhered to particularly in cases of watery diarrhea that is mostly of viral origin.

**REFERENCES**


