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Research Progress on Antibiotic-Associated Hemorrhagic Colitis

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Abstract

Antibiotic-Associated Hemorrhagic Colitis (AAHC) is a disease characterized by bloody diarrhea and abdominal pain that occurs after the use of antibiotics. Compared with other diseases that manifest as gastrointestinal bleeding, the prognosis of this disease is still good after discontinuation of antibiotics. In addition, there is insufficient understanding of this disease, so it has been prone to misdiagnosis or missed diagnosis in the past. This article aims to review the research progress on the pathogenesis, clinical manifestations, and other aspects of AAHC, providing a reference for future clinical diagnosis and treatment decisions.

Keywords

Ntibiotic-Associated Hemorrhagic Colitis, *Klebsiella acidophilus*

1. Introduction

The advancement of antibiotics, including penicillin, has markedly enhanced the treatment of bacterial infectious diseases. However, the use of antibiotics can result in various side effects. While some effects may be mild and self-limiting, others can be irreversible. Therefore, it is crucial to monitor these side effects closely and to detect and address them promptly. Diarrhea is a relatively common side effect of antibiotic treatment, affecting 5% to 25% of patients [1]. Its severity can range from mild abdominal cramps and loose stools to colitis, which may progress to life-threatening conditions. Antibiotic-Associated Diarrhea (AAD) is defined as diarrhea that occurs concurrently with antibiotic use, excluding other potential causes [2]. Antibiotic-Associated Colitis (AAC) is characterized by AAD, accompanied by more severe symptoms such as abdominal colic, fever, leukocytosis, fecal leukocytosis, and hypoalbuminemia [3]. The antibiotic-Associated Hemor-

rhagic Colitis (AAHC) discussed in this article represents a specific subtype of AAC. In addition to the clinical manifestations associated with colitis, the primary symptom of AAHC is bloody diarrhea. Symptoms typically emerge within one week of initiating antibiotic therapy and generally resolve within a few days after discontinuation of the antibiotics [4]. Consequently, for patients who initially present with gastrointestinal bleeding, it is essential to consider potential causes such as ischemic bowel disease and inflammatory bowel disease, while also inquiring about their history of antibiotic use to inform future diagnostic and therapeutic strategies.

This article reviews the research on the pathogenesis, clinical and endoscopic manifestations, and treatment of AAHC, with the aim of enhancing the understanding of this condition.

2. Pathogenesis of AAHC

Previous studies have indicated that the mechanism underlying AAHC may be associated with allergic reactions [5], mucosal ischemia resulting from direct antibiotic damage to the mucosa [6], and the excessive proliferation of toxigenic bacteria along with the production of enterotoxins. Currently, it is widely accepted that enterotoxins produced by *Klebsiella acidophilus*, a member of the genus *Klebsiella*, are the primary cause of AAHC [7]-[9].

Klebsiella is a prevalent Gram-negative enterobacterium that commonly inhabits the human respiratory tract and intestines, functioning as a conditional pathogen. This genus comprises several subspecies, including *Klebsiella pneumoniae*, *Klebsiella odoris*, *Klebsiella sclerosus*, and *Klebsiella acidophilus*, and is implicated in a range of diseases, such as nosocomial pneumonia, urinary tract infections, biliary tract infections, surgical wound infections, and deep abscesses [7]. Numerous studies have identified the presence of *Klebsiella acidophilus* in the feces of patients with AAHC [5] [8] [9]. Hogenauer *et al*.'s animal experiments demonstrated that rats infected with *Klebsiella acidophilus* developed AAHC in the right colon following antibiotic exposure, whereas rats without this bacterial infection did not exhibit AAHC. Their research also revealed that *Klebsiella acidophilus* isolated from AAHC patients could induce disease in animal models and could be isolated and purified, thereby further substantiating the role of *Klebsiella acidophilus* in AAHC [10]. Given that *Klebsiella acidophilus* is inherently resistant to para-aminophenylpenicillin, it is predisposed to produce β-lactamase. The frequent administration of antibiotics such as penicillin and amoxicillin may facilitate the extensive proliferation of *Klebsiella acidophilus*. However, it remains uncertain whether the disease in AAHC patients arises from the colonization of *Klebsiella acidophilus*, leading to bacterial proliferation and enterotoxin production following antibiotic treatment, or from an infection with *Klebsiella acidophilus* subsequent to antibiotic application. Future animal experiments are necessary to provide further support for this issue.

Most studies indicate that the enterotoxin produced by *Klebsiella acidophilus*

is the primary mechanism underlying AAHC. The enterotoxin Tilimycin (TM) generated by this bacterium acts as a DNA-damaging agent with gene toxicity, leading to the apoptosis of epithelial cells. Concurrently, it exhibits antibacterial properties, inhibiting the growth of Lactobacillus and Bifidobacterium, thereby further impacting the intestinal microbiota [11] [12]. Animal studies have demonstrated that the transient synthesis of TM in the murine intestine disrupts niche competitors, reduces microbial richness, and alters the taxonomic composition of the microbiota [13]. Excessive secretion of TM may also elevate the mutagenesis rate of opportunistic pathogenic bacteria, facilitating their acquisition of antibiotic resistance. Human feces contain a measurable amount of indole. TM reacts with indole to produce another pathogenic enterotoxin, Tilivalline (TV). Unterhauser *et al.* confirmed the presence of these two toxins in the intestinal tract during the active lesion stage by collecting fecal samples from AAHC patients. Their research further suggests that TV may function as a microtubule stabilizer, preventing the dissociation of already aggregated microtubules, which leads to cell cycle arrest and ultimately results in apoptosis [12]. Additional studies have demonstrated that TV induces apoptotic cell death and disrupts barrier integrity in in vitro polarized human epithelial cells, thereby facilitating the occurrence and progression of AAHC [14]. Although research on the pathogenesis of TM and TV in AAHC remains limited, it is evident that both exhibit cytotoxic effects on human cells [15] [16]. Despite their differing functions, both toxins induce apoptosis in colonic epithelial cells of AAHC patients [10] [14]. Some studies also indicate that TM possesses greater cytotoxicity compared to TV [12] [16].

Further investigations into TM and TV have demonstrated that their biosynthesis is facilitated by enzymes encoded by the aroX and NRPS operons. Relevant studies have established that nucleoidin-like proteins, including Fis, IHF, and Lrp (leucine-responsive regulatory proteins), serve as positive regulatory factors for the aroX and NRPS operons [17] [18]. Conversely, the OmpR protein acts as a negative regulatory factor for these operons [19]. These experiments, which explore the molecular mechanisms underlying enterotoxin production by *Klebsiella acidophilus*, have identified new therapeutic targets for the treatment of AAHC and the restoration of intestinal bacterial homeostasis.

3. Clinical and Diagnostic of AAHC

AAHC was first introduced by Toffler *et al.* in 1978. They examined five patients who had received ampicillin, its derivatives, or penicillin, all of whom presented with bloody diarrhea. However, the clinical manifestations, disease progression, and colonoscopy findings in these patients differed significantly from those associated with known antibiotic-related colitis [20]. As understanding of this condition has evolved, an increasing number of cases have been documented. The affected demographic is broad, encompassing both adults and children, and AAHC typically arises following the administration of penicillin and its derivatives [4]. Additionally, some studies have reported instances of AAHC linked to the use of

quinolones, cephalosporins, and macrolides [9] [21] [22]. The hallmark features of AAHC include the abrupt onset of bloody diarrhea during antibiotic therapy, often accompanied by abdominal cramps and pain. Furthermore, it may present with gastrointestinal symptoms such as nausea and vomiting. These symptoms typically manifest within one week of initiating antibiotic therapy. The prognosis for this condition is generally favorable, with improvement observed within 3 to 7 days following the cessation of antibiotics and the implementation of supportive symptomatic treatment. During the disease's onset, there may be an elevation in white blood cell counts, neutrophils, and C-reactive protein levels, whereas hemoglobin, coagulation function, and other parameters usually remain within normal ranges. Furthermore, the presence of *Klebsiella acidophilus* in stool cultures offers additional support for the diagnosis of AAHC. Real-time Polymerase Chain Reaction (PCR) exhibits greater sensitivity than traditional culture methods. Leitner *et al.* encoded the cytotoxins TM and TV produced by *Klebsiella acidophilus* through the utilization of non-ribosomal peptide synthase genes A (npsA) and B (npsB), respectively. Their findings indicated that the sensitivity of these toxin-specific targets (npsA/npsB) was further improved relative to traditional culture methods. This strategy offers a novel diagnostic tool for AAHC, particularly when clinical and endoscopic manifestations are atypical or when stool cultures yield negative results [23].

In the context of differential diagnosis, AAHC must be distinguished from ischemic bowel disease and inflammatory bowel disease (for differentiation from Clostridioides difficile-associated colitis, please refer to the following text). Regarding the affected population and associated risk factors, AAHC is primarily linked to a history of antibiotic use and can manifest at any age. In contrast, ischemic bowel disease is frequently observed in elderly individuals with mesenteric vascular atherosclerosis. Additional risk factors include diabetes, hypertension, coronary artery disease, peripheral artery disease, and atrial fibrillation. Most patients with inflammatory bowel disease present symptoms in their 20 s and 30 s, although diagnoses can also occur in older adults. Common risk factors for this condition include smoking, childhood antibiotic use, NSAID consumption, and a low-fiber, refined diet. During colonoscopy, the primary endoscopic features of AAHC include segmental mucosal hemorrhage and edema, predominantly observed in the right colon and transverse colon, with comparatively fewer cases reported in the left colon or rectum. This distribution may be attributed to the high water content and significant presence of unabsorbed nutrients in the right colon, which facilitates the colonization of *Klebsiella acidophilus*. Furthermore, the right colon's thin intestinal wall and abundant blood supply enhance the susceptibility to enterotoxin invasion. Pathological manifestations observed in endoscopic biopsies of AAHC reveal mucosal inflammation, primarily characterized by neutrophil infiltration in the lamina propria and epithelial damage [10] [18]. In addition to endoscopic diagnosis, some researchers have identified through ultrasound examination that the intestinal wall is thickened and exhibits congestion. Further-

more, barium enema studies reveal changes consistent with ischemic bowel disease, including spasm, nodularity, and ulceration [20] [24] [25]. Ischemic bowel disease may be observed during endoscopy as pale, edematous mucosa, accompanied by congestion and redness, as well as submucosal petechiae and ecchymosis. The demarcation between the lesion and the normal mucosa is typically distinct, and irregular ulcers may develop along the longitudinal axis of the intestinal tract, primarily affecting the splenic flexure, the left half of the colon, and the sigmoid colon. Inflammatory bowel disease, specifically ulcerative colitis, generally originates in the rectum and presents as continuous, diffuse lesions characterized by irregular, shallow ulcers. Conversely, Crohn's disease can affect the entire colon, with the terminal ileum and ileocecal region being the most frequently involved areas. This condition is marked by segmental and skipping lesions, longitudinal ulcers, slit ulcers, and distinctive cobblestone changes. Therefore, obtaining a thorough history of antibiotic use, in conjunction with the patient's clinical manifestations and endoscopic findings, is crucial for the detection of AAHC.

In a review of seven recently diagnosed cases of AAHC, the age of onset for patients ranged from 13 to 85 years. Five cases were associated with the use of amoxicillin or its derivatives. Specifically, two patients received both amoxicillin and metronidazole orally, one was treated with ampicillin, and another with clarithromycin. Nearly all patients exhibited clinical symptoms of bloody diarrhea and abdominal pain, with one 13-year-old child additionally experiencing nausea and vomiting. Of the seven patients, one declined a colonoscopy, while the remaining six displayed symptoms including colonic mucosal edema and bleeding. Among these patients, one did not test positive for *Klebsiella acidophilus*, whereas the others were confirmed to have this bacterium. All patients experienced resolution of clinical symptoms within one week following the cessation of antibiotics. One patient was administered prednisone due to a prior history of systemic lupus erythematosus.

Author	Publish year	Country	Age (year)	Antibiotics	Antibiotic usage duration (day)	Clinical manifestations	Endoscopic manifestation	Pathology	*Klebsiella acidophilus*	Treatment and prognosis
K. Martin Hoffmann [4]	2010	Austria	15	Amoxicillin and clavulanic acid	3	Bloody diarrhea, abdominal pain	Residual colonic inflammation in the cecum and ascending colon, with mild submucosal hemorrhage.	Excluding chronic intestinal lesions	+	Symptoms disappeared after discontinuing antibiotics for 3 days.
Miyauchi Ryosuke [22]	2013	Japan	67	Clarithromycin	5	Bloody diarrhea, abdominal pain	Mucosal hemorrhagic erosion	Uncertain	+	Improved after the discontinuation of antibiotics.

Continued

Tanaka Kazuyuki [26]	2017	Japan	65	Amoxicillin Metronidazole	1	Bloody diarrhea, abdominal pain	Bleeding and mucosal edema in the transverse colon	Severe swelling of neutrophils and lymphocytes, with hemorrhage in the lamina propria.	+	Oral Administration of 5 mg prednisone led to symptom resolution within 6 days.
Olalekan Akanbi [27]	2017	The United States	85	Amoxicillin and clavulanic acid	5	Bloody diarrhea, abdominal pain	Refuse colonoscopy	None	+	Symptoms disappeared after discontinuing antibiotics for 5 days.
Aaron Fisher [28]	2018	The United States	33	Ampicillin	3	Bloody diarrhea, mild lower abdominal pain	Ulcerated mucosa with erythema and friability throughout the entire colon.	Mucosal congestion and ischemia	+	Symptoms disappeared after discontinuing antibiotics for 4 days.
Youngmin Youn [29]	2018	South Korea	13	Amoxicillin and clavulanic acid	3	Bloody diarrhea, abdominal pain, nausea, and vomiting	Mucosal hemorrhage, erythema, and granular erosion accompanied by edema from the ascending colon to the transverse colon.	Red blood cell fibrinoid changes with superficial mucosal damage, with no glandular deformation or cryptitis.	+	Symptoms disappeared after discontinuing antibiotics for 3 days.
Yasuhiko Hamada [30]	2020	Japan	53	Amoxicillin, Metronidazole	3	Bloody diarrhea, abdominal pain	Bleeding and edema of the ascending colon mucosa	No specific changes	untested	Improved after the discontinuation of antibiotics.
Yusaku Kajihara [31]	2020	Japan	55	Amoxicillin	4	Bloody diarrhea, abdominal pain	Mucosal hemorrhage and edema from the transverse colon to the splenic region	No specific changes	+	Symptoms disappeared after discontinuing antibiotics for 2 days.

4. The Difference from Clostridioides Difficile-Associated Colitis

Clostridioides difficile-associated colitis, commonly referred to as pseudomembranous colitis, represents a distinct form of antibiotic-associated colitis. Following antibiotic treatment, an imbalance in the intestinal microbiota occurs, resulting in the proliferation of *Clostridium difficile* (CD) [32]. The extracellular toxins produced by this bacterium can induce neutrophil infiltration and damage to intestinal epithelial tissue [33]. Pseudomembranous colitis is typically regarded as a condition that arises post-antibiotic treatment, leading to the prevailing belief that

Clostridium difficile is the primary causative agent of antibiotic-associated colitis. However, it is important to note that 60% - 75% of cases of antibiotic-associated colitis are attributable to *Clostridium difficile*, while *Klebsiella acidophilus* can also contribute to Antibiotic-Associated Hemorrhagic Colitis (AAHC). Additionally, other pathogens, including Salmonella, Clostridium perfringens type A, Staphylococcus aureus, and Candida albicans, may also be implicated [3]. Regarding onset time, AAHC typically manifests acutely, usually within one week following antibiotic use. In contrast, pseudomembranous enteritis may develop during the acute phase of antibiotic treatment or emerge within a few weeks after the cessation of antibiotics. Clinically, while pseudomembranous enteritis can also present with watery diarrhea, abdominal cramps, and occasionally bloody diarrhea, it is characterized by more severe systemic manifestations, such as toxic megacolon, intestinal obstruction, septic shock, and potentially death [34] [35]. Consequently, the prognosis for severe cases is poor, whereas the prognosis for AAHC remains acceptable following the discontinuation of antibiotic therapy. Finally, in terms of endoscopic findings, pseudomembranous enteritis is identified by a distinctive plate-like pseudomembrane composed of fibrin, mucus, inflammatory cell exudates, and necrotic cells observed during colonoscopy. This condition is most frequently located in the rectum, sigmoid colon, and left colon, whereas AAHC primarily exhibits mucosal edema and bleeding, predominantly affecting the right colon.

5. AAHC Treatment

The most critical intervention for this disease is the early identification of affected patients. In cases where bloody diarrhea is suspected to result from antibiotic use, it is essential to discontinue antibiotic treatment. This should be accompanied by fluid replacement, maintenance of electrolyte balance, nutritional support, and other symptomatic and supportive therapies. As previously noted, the prognosis for this condition remains favorable following the cessation of antibiotics. Although AAHC rarely progresses to a chronic state, Granger *et al*. documented the first case of AAHC that developed into chronic diarrhea. In this instance, Fecal Microbiota Transplantation (FMT) was conducted using feces from the patient's 11-year-old son, resulting in a six-year period without recurrence [36]. In the presence of *Klebsiella acidophilus*, the relative abundance of Enterobacteriaceae in this patient was notably low. However, fecal microbiota transplantation (FMT) restored microbiota diversity, leading to increased resource competition among bacteria. This outcome inhibited the growth of pathogenic bacteria and suggests that enhancing beneficial intestinal flora may offer novel approaches for the future treatment of AAHC.

6. Summary

Few reports on AAHC exist, primarily due to a limited understanding of the side effects associated with antibiotic use and the generally favorable prognosis of this

condition. This lack of awareness often results in missed diagnoses and misdiagnoses. Furthermore, AAHC is predominantly characterized by gastrointestinal bleeding and abdominal pain, symptoms that can easily be mistaken for other disorders, such as ischemic bowel disease and inflammatory bowel disease. Colonoscopy undoubtedly plays a critical role in diagnosing this condition. However, it is important to acknowledge that discontinuing antibiotic treatment can significantly contribute to disease recovery and reduce the likelihood of recurrence. In recent years, Japanese researchers have reported cases of AAHC following amoxicillin treatment aimed at eradicating Helicobacter pylori. Notably, patients who developed AAHC were not exclusively those who had previously received amoxicillin; some exhibited symptoms after an initial unsuccessful eradication attempt followed by subsequent amoxicillin treatment. These findings underscore the necessity of not only considering the clinical application of antibiotics but also being vigilant about the adverse reactions they may provoke.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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