World Journal of Pediatric Surgery

Digestive perianastomotic ulcerations after intestinal resection in children

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To cite: Zhang W, Tou J. Digestive perianastomotic ulcerations after intestinal resection in children. *World J Pediatr Surg* 2023;**6**:e000533. doi:10.1136/wjps-2022-000533

► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/wjps-2022-000533).

Received 25 November 2022
Accepted 7 June 2023

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ABSTRACT

Digestive perianastomotic ulceration (DPAU) is a rare complication after intestinal resection and anastomosis occurring at or near the anastomosis site. The purpose of this review is to summarize the characteristics of DPAU, including the etiology, diagnosis and differential diagnosis, clinical manifestations, treatment, and future research. All recent literature on DPAU was searched in PubMed, Embase, and Cochrane and then reviewed. The clinical manifestations of DPAU are mainly gastrointestinal symptoms such as bloody stool and chronic anemia. The diagnosis of DPAU is difficult. Specific diseases, such as Crohn's disease, must be ruled out before a diagnosis can be made. In addition, there are no clear treatment guidelines due to the high degree of heterogeneity in response to drugs and surgery. It is recommended to adjust medication in time and combine various treatment methods. In addition, the mechanism that causes DPAU is not well understood; however, several possible mechanisms have been proposed, such as scar tissue ischemia and underlying diseases. Moreover, there is a high risk of relapses, and a long-term follow-up is necessary. Numerous issues remain to be solved in this area; therefore, more randomized controlled trials and studies should be carried out to further understand this disease.

INTRODUCTION

Digestive perianastomotic ulceration (DPAU) is a long-term complication after intestinal resection. It occurs mainly in children and can be life-threatening in severe cases. In 1988, Parashar *et al* first reported four cases of DPAU.[1] Since then, other cases have been documented by Couper *et al* in 1989,[2] Hamilton *et al* in 1992,[3] Paterson *et al* in 1993,[4] Sondheimer *et al* in 1995,[5] Chari and Keate in 2000,[6] Freeman *et al* in 2015,[7] Charbit-Henrion *et al* in 2014,[8] Frémond *et al* in 2014,[9] Bass *et al* in 2015,[10] Fusaro *et al* in 2018,[11] Lee *et al* in 2018,[12] Barraclough *et al* in 2021,[13] and Madre *et al* in 2021.[14] However, studies related to DPAU remain inadequate, severely limiting our understanding of the disease. The etiology of DPAU remains unclear and there are no specific guidelines for treatment. We performed a literature review (online supplemental material) of the etiology, clinical manifestations, diagnosis, treatment, and prognosis of DPAU to further understand this disease.

ETIOLOGY

The etiology of DPAU remains unclear; however, several possible mechanisms have been proposed. While none of the theories has been confirmed, they are at least somewhat plausible.

Impaired postsurgical vascular supply

The occurrence of DPAU might be secondary to the development of relative ischemia in the scar tissue at the anastomotic site.[8] Scar tissue can damage the vascular supply to the anastomotic site where the intestine grows. However, the long time interval between surgery and the occurrence of DPAU and the location of ulcers, sometimes far away from the anastomosis, do not favor this hypothesis.[9]

Gender

Another vital factor is gender.[8] Of patients with DPAU, 60% are boys.[8 9 14] However, given the small number of patients documented, further research is needed to identify the relationship between gender and the development of DPAU.[8] In addition, many patients with DPAU cannot be definitively diagnosed, leading to bias in the data used for statistical analysis.

Underlying disease

Some authors believe that underlying diseases, such as necrotizing enterocolitis (NEC), are closely associated with the development of DPAU.[3 5 15] Others, however, argue that no underlying disease can be considered a predictive factor for DPAU.[8] According to the latest research, NEC accounts for the largest proportion of DPAU-related underlying diseases at 39%, followed by Hirschsprung disease (22%), intestinal atresia (8%), gastroschisis (8%), and volvulus (6%).[14]

Bacterial overgrowth

The expansion of colonic bacteria can lead to an altered microbiome in the small

intestine, which will activate Toll-like receptors (TLR) and NOD-like receptor (NLR) signals and cause cytokine release, inflammation, and damage to mucosal integrity.[7] However, many patients with DPAU are not sensitive to antibiotic therapy. Furthermore, the microbiome of patients with DPAU has not been fully studied.[8]

Bile acid

Damage to the gut caused by bile acids (BAs) is another potential factor. BAs, derived from cholesterol, are important physiological agents for intestinal nutrient absorption and biliary secretion of lipids.[16] In the distal intestine, the bacteria convert cholic acid and chenodeoxycholic acid into deoxycholic acid and lithocholic acid, which are called secondary BAs. Both primary BA poorly absorbed after extensive resection of the terminal ileum and toxic secondary BA produced by bacterial transformation in the bowel can damage the intestinal mucosa.[8] However, it is not clear how DPAU develops in response to this impairment.

Hyperacidity and hypergastrinemia

Previous studies have also reported the effects of hyperacidity and hypergastrinemia on the development of DPAU.[8 9 11 13] Hyperacidity and hypergastrinemia can be found in the early stage of patients with short bowel syndrome (SBS). The possible mechanism is that the distal small intestine synthesizes molecules that inhibit gastric acid secretion. After intestinal resection, this inhibitory effect will be eliminated, leading to excessive acid synthesis. In addition, small intestine resection can affect gastrin metabolism.[17] The reason why hyperacidity and hypergastrinemia may contribute to DPAU remains unclear. The possible mechanism is that a large amount of gastric acid in patients with SBS enters the small intestine from the stomach, and the intestinal fluid secretion is insufficient, which leads to a significant decrease in intestinal pH, thus leading to DPAU.

Genetic mutation

Genetic mutation is another hypothesis. Some researchers have proposed that DPAU is associated with mutations in NOD2, the intracellular bacterial cell wall peptidoglycan receptor, which is associated with host responses to intestinal bacteria.[9] However, others hold the opposite view.[14] Therefore, it is still a controversial issue.

Other factors

In addition, some researchers have suggested that none of the following factors is a potential cause: the length of the remaining bowel, the existence of the ileocecal valve, or the location of the anastomosis.[8] Patients with DPAU may have genetic susceptibility to intestinal inflammation, and surgery can reveal genetic susceptibility in people at high risk.[9]

CLINICAL MANIFESTATIONS

DPAU mainly occurs in children and teenagers, with a male to female ratio of 1.5.[8 14] Most patients had undergone bowel resection surgery (mean age at surgery was 3.7 months).[7 8 14] Because diagnosis of DPAU is often delayed, the exact onset of the disease may occur months or even years before diagnosis. According to the findings by Madre *et al*[14], DPAU was detected 39 months after surgery on average. Nearly all patients with DPAU present with bloody stools, most of which were concealed bloody stools and only a few were melena and visible rectal bleeding. Other manifestations include chronic anemia (61.2%), which is refractory to iron supplementation, diarrhea (40.4%), abdominal pain (36.4%), abdominal distention (20%), and other symptoms such as growth retardation and hypoproteinemia.[7–9 14]

DIAGNOSIS

Several techniques have been applied to diagnose DPAU with great success. The first step should be laboratory examination, while endoscopy, which is the most important of all the methods, can be used for further confirmation.

Laboratory examination

Fecal occult blood test (FOBT) can be used to detect fecal occult blood loss in patients with DPAU with anemia who have a history of intestinal surgery.[8] The levels of C reactive protein (CRP), fecal calprotectin, anti-*Saccharomyces cerevisiae* antibody (ASCA), and perinuclear antineutrophil cytoplasmic antibody (pANCA) were elevated in most patients.[14]

Imaging

As a non-invasive and highly specific method, technetium-99m red blood cell (^{99m}TC-RBC) radionuclide imaging can detect occult bleeding, which is of great value in the diagnosis of DPAU. Abdominal ultrasonography and CT scans can show non-specific ileal thickening.[9]

Endoscopy

Endoscopy, such as capsule endoscopy and ileocolonoscopy, is often used for diagnosis of DPAU. Capsule endoscopy can not only observe the whole digestive tract, but also offer comfortable and painless inspection. In children with ulcers located in the lower tract, ileocolonoscopy can offer more careful and thorough observation. Under endoscopy, ulcers can be round, radial, and longitudinal in shape and are present at or near the anastomosis site. Ulcers are usually multiple and vary in size, ranging from several millimeters to 4–5 cm in diameter.[8] They can be deep and superficial, with or without active bleeding.[8 9] Ulcers were more common at the proximal end of the anastomosis (68%), but less at the distal end (8%) or on both sides (12%). Few patients have ulcers limited to the anastomosis itself.[14] Biopsy revealed

infiltration of non-specific inflammatory cells and polymorphous cells, including mononuclear cells and granulocytes, in the surrounding tissue. Neither epithelioid gigantocellular granuloma nor ischemic lesions were observed.[8 9 14]

DIFFERENTIAL DIAGNOSIS

A preliminary diagnosis of DPAU can be made based on patients' history of intestinal resection and the corresponding clinical manifestations, such as bloody stool, anemia, abdominal pain, and diarrhea, combined with auxiliary examination: positive result of FOBT, and evaluated CRP and fecal calprotectin. The most valuable diagnostic criterion is to find ulcerations at the anastomosis site under endoscopy. Therefore, clinical history, laboratory results, and endoscopy findings should be comprehensively considered before making a definite diagnosis of DPAU. In addition, other potential diseases, such as Crohn's disease (CD), need to be ruled out.

Crohn's disease

CD is a chronic inflammatory disorder of the gastrointestinal tract. CD shares many similarities with DPAU and must be considered when patients develop bloody stool, fever, and elevated CRP. Patients with CD may also present with abdominal pain, diarrhea, and growth restriction. Fecal calprotectin, ASCA, and pANCA may also be detected.[9 18] Endoscopic findings in patients with CD are similar to those of patients with DPAU, with multiple deep and longitudinal cobblestone-like ulcers and normal mucosal tissues between adjacent ulcerations. Although studies of the European population found no gender difference in patients with CD, studies of Asian populations identified significantly more male patients than female patients, which is consistent with gender differences in patients with DPAU.[17] Anti-inflammatory drugs and immunomodulatory drugs commonly used in the treatment of CD can also be used in the treatment of DPAU, showing good therapeutic efficacy in some patients with DPAU. In terms of prognosis, stable and prolonged endoscopic remission occurs in 10% of patients with CD. Due to intestinal complications, 50% of patients require intestinal resection within 10 years of diagnosis of CD. Furthermore, the risk of relapse remains high.[17–19] Patients with DPAU are also prone to relapse after surgery. The difference between them is that, in terms of clinical manifestation, patients with CD are less likely to have bloody stools, while most patients have parenteral manifestations such as fistula formation and oral ulcers.[18] However, patients with DPAU are closely associated with bloody stools without fistula and other parenteral manifestations. Macroscopic lesions found in CD are deep aphthous erosions (ulcers with diameter less than 5 mm) or ulcers that tend to be longitudinal (with diameter greater than 5 mm) with a cobblestone appearance.[18] However, the manifestations of anastomotic ulcers are varied, which can be deep or superficial, and the shape can be round, longitudinal, radial, etc. Non-caseous granulomas can be found on tissue biopsy of patients with CD. In patients with DPAU, there is no granuloma but a large number of polymorphic cells, such as eosinophils. NOD2 mutation rates are significantly increased in most patients with CD but not in patients with DPAU.[20] In addition, the efficacy of the classic drugs used to treat CD in patients with DPAU remains uncertain.[14] Most patients with CD do not have a history of intestinal surgery, while DPAU is a complication after resection of the intestine. Furthermore, the incidence of DPAU in patients with a history of intestinal resection is much higher than that of CD which occurred by chance alone.[9]

TREATMENT

There are no specific guidelines for treatment of DPAU. Responses to treatments were heterogeneous among patients, making it difficult to elaborate recommendations.[14] Most patients can achieve clinical remission after surgery if they are not sensitive to drugs, but some will relapse several years later. For patients with recurrence, neither surgery nor drug therapy will be effective.[8] Most patients with DPAU require more than two drugs. These include 5-aminosalicylate, glucocorticoids, immunosuppressants, anti-tumor necrotizing factor (TNF) antibodies, antibiotics, probiotics, and cholestyramine.[7 11 14 20] Antibiotics, cholestyramine, anti-inflammatory drugs, and acid-suppressing drugs are the most common and preferentially used in clinical setting. However, the literature indicates that these drugs have limited efficacy. Anti-TNF is quite successful in treating symptoms, but its high cost and the lack of consensus on its use have prevented it from being the primary choice in wards. In conclusion, antibiotics, cholestyramine, anti-inflammatory drugs, and acid-suppressing drugs can be selected according to specific clinical needs. Depending on the financial situation of the patient's family, anti-TNF may be administered if other treatments have not been successful. Surgical resection should be proposed as the last option. It is recommended to adjust the drugs in time and combine various treatment methods.

Anti-inflammatory drugs

Anti-inflammatory drugs include steroidal anti-inflammatory drugs such as glucocorticoids and non-steroidal anti-inflammatory drugs such as mesalamine and 5-aminosalicylic acid (5-ASA). The mechanism of steroidal anti-inflammatory drugs is to promote the synthesis of anti-inflammatory factors and inhibit the synthesis of inflammatory factors to achieve anti-inflammatory effects. The mechanism of non-steroidal anti-inflammatory drugs is inhibiting the synthesis of prostaglandins and the aggregation of leukocytes to reduce the formation of bradykinin and inhibit platelet aggregation. Charbit-Henrion *et al*[8] reported that six patients had a remission period of 2 months to 3 years

after application of anti-inflammatory drugs. Madre *et al*[14] suggested that the response rate of 5-ASA was 53% and that of glucocorticoid budesonide was 50%. Fusaro *et al*[11] revealed that six patients received budesonide and two received mesalamine; their average remission period was 3.3 years.

Anti-TNF antibody

TNF is a proinflammatory cytokine secreted by cells such as macrophages and lymphocytes which plays an important role in some inflammation-related diseases. Anti-TNF antibody can specifically bind TNF and block its proinflammatory effect to achieve therapeutic effect. Freeman *et al*[7] proposed that anti-TNF-α was effective in patients with DPAU and recommended it as part of drug therapy. Madre *et al*[14] reported a response rate of 75% for anti-TNF antibody application. Charbit-Henrion *et al*[8] reported that one patient was treated with infliximab and had a 3-year period of remission.

Endoscopic intervention

Endoscopic intervention is a very effective method for patients with DPAU, especially for those who do not need blood transfusion.[13] It can be considered when drug therapy fails and there is no indication for surgery. Endoscopic interventions include argon plasma coagulation, endoscopic clamp placement (in case of acute massive bleeding), platelet-rich fibrin infusion, and hydrostatic dilation to disentangle stenosis. Barraclough *et al*[13] noted that endoscopic intervention is a very effective way to integrate diagnosis and treatment. Once the location of the DPAU is identified, endoscopic treatment can be performed.[11 13 20]

Antibiotics

The use of antibiotics is based on the etiological hypothesis of DPAU about bacterial overgrowth. Almost all cases have reported it. Charbit-Henrion *et al*[8] preformed antibiotic treatment on six patients, of whom four had a long remission period of 3–5 years, with a remission rate of 66%. A survey conducted by Madre *et al*[14] reported a response rate of 58% for antibiotics. However, some authors argued that the effect of antibiotics on patients with DPAU is not satisfactory.[3 5 11]

Probiotics

The use of probiotics can increase the number and species of intestinal probiotics, effectively inhibit the growth of other abnormal bacteria, and contribute to the establishment of intestinal microecological homeostasis. Its use is also based on the etiological hypothesis of bacterial overgrowth. However, no studies have reported the effectiveness of probiotic treatment in patients with DPAU, and the use of probiotics is rare. Charbit-Henrion *et al*[8] reported that probiotics were used to control flora growth in two patients, but no effect was found.

Cholestyramine

Cholestyramine is a styrene-based, strong quaternary anion exchange resin that binds to BAs through ion exchange in the intestine, impeding the absorption of BAs and cholesterol and promoting their excretion. Under the impact of cholestyramine, the enterohepatic circulation of BAs is impeded, resulting in the reduction of BAs in both blood and the liver. Its use is based on the etiological hypothesis of the mechanism by which BAs cause intestinal damage. Madre *et al*[14] proposed that the response rate of cholestyramine in patients with DPAU was 63%, while Hamilton *et al* argued that cholestyramine had no effect on patients with DPAU.[2–4 21]

Acid-suppressing drugs

The use of acid-suppressing drugs is based on the etiological hypothesis of hyperacidity and hypergastrinemia. These drugs include proton pump inhibitors (PPIs) and H2 receptor antagonists. PPIs can inhibit the hydrogen potassium ATPase (proton pump) on the parietal cells of the gastric mucosa, thus inhibiting the secretion of gastric acid. Ranitidine is a selective H2 receptor antagonist which can competitively block the binding of histamine to the H2 receptor on gastric parietal cells and effectively inhibit basal acid secretion and gastric acid secretion induced by histamine, pentapeptide gastrin, and food stimulation. An investigation reported by Fusaro *et al*[11] found that eight patients with DPAU treated with PPIs and antibiotics achieved clinical remission. However, Bhargava *et al* argued that ranitidine had limited therapeutic effect.[2 3 5 21 22]

Iron supplementation

Iron supplementation is used to treat iron deficiency anemia but has no therapeutic effect on DPAU. In addition, anemia is often refractory to oral iron replacement, leading to parenteral iron therapy or sometimes urgent blood transfusions.[8]

Nutrition support

Many patients with DPAU suffer from malnutrition as a result of bloody stools and diarrhea without proper nutrition support. Therefore, nutrition support, including enteral nutrition and parenteral nutrition, is necessary to correct malnutrition. In addition, it is also an effective therapy. In patients with CD, specialized enteral nutrition leads to high rates of remission and is very successful, especially when used in the early stages of the disease. Madre *et al*[14] reported good tolerance and efficacy of nutrition support in patients with DPAU, with a response rate of 88%. However, a large number of patients with DPAU do not achieve remission. Therefore, intravenous nutrition is required to provide minimum nutritional requirements for growth in these patients.

Surgery

Surgical indications for patients with DPAU are severe life-threatening acute bleeding or failure of drug therapy,

relatively concentrated sites of single or multiple ulcers, and no surgical contraindication.[8 14] If the ulcers spread widely along the intestine, surgical treatments become limited. Combined with ^{99m}TC-RBC radionuclide imaging and endoscopy, the location of the ulcer can be determined to facilitate intraoperative resection. Madre *et al*[14] reported a response rate of 82% for surgery in patients with DPAU. However, it is invasive and carries risks such as excessive blood loss and organ damage during and after surgery. Complications such as SBS, intestinal stenosis, and malnutrition may also occur after surgery. In addition, there is a high possibility of recurrence after surgery. Charbit-Henrion *et al*[8] proposed that 70% of children relapse from 4 months to 7 years after surgery.

PROGNOSIS

Regardless of the treatment, patients may relapse after several years. In general, the prognosis of patients with DPAU is poor, but no deaths have been reported. Madre *et al*[14] found that, of 31 children who underwent endoscopy, 24 (77%) were detected with ulcers or intestinal stenosis. A study by Frémond *et al*[9] showed that 59% of patients still did not achieve clinical remission during an average follow-up period of 2 years. Charbit-Henrion *et al*[8] suggested that the treatment evaluation of DPAU would take at least 5 years. Therefore, for children with a history of intestinal resection, it is strongly recommended to follow up with physical examination, laboratory examination, and imaging every 3–4 months for the first 2–3 years, every 6 months for the following 5 years, and annually thereafter. Laboratory examination should include routine blood tests and FOBT. When patients present with corresponding symptoms or the examination suggests a poor prognosis, it is necessary to properly evaluate the patients with endoscopy to identify DPAU in time. Patients should be informed of the symptoms related to possible recurrence and the importance of prompt medical attention.

CONCLUSIONS

Many problems related to the diagnosis, treatment, and prognosis of DPAU remain to be addressed. No randomized controlled trials (RCTs) have been found in the published literature; therefore, RCTs are needed to determine several crucial issues, such as optimal medications or therapeutic recommendations. Given its complex etiology, more studies should be carried out to determine the etiology of this disease. All of these factors will contribute to a longer lifespan and better quality of life for patients with DPAU.

Acknowledgements The authors would like to thank all the colleagues for their guidance though each stage of the process.

Contributors JT conceptualized and designed the study and critically reviewed and revised the manuscript. WZ summarized the relevant literature, drafted the initial manuscript, and revised it. Both authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data relevant to the study are included in the article or uploaded as supplementary information.

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Search method

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