Hirschsprung-Associated Enterocolitis 71

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Abstract

Hirschsprung-associated enterocolitis (HAEC) is a common and sometimes life-threatening complication of Hirschsprung's disease (HD). Presenting either before or after definitive surgery for HD, HAEC may manifest clinically as abdominal distension and explosive diarrhea, along with emesis, fever, lethargy, and even shock. The pathogenesis of HAEC, the subject of ongoing research, likely involves a complex interplay between a dysfunctional enteric nervous system, abnormal mucin production, insufficient immunoglobulin secretion, and unbalanced intestinal microflora. Early recognition of HAEC and preventative practices, such as rectal washouts following a pull-through, can lead to improved outcomes. Treatment strategies for acute HAEC include timely resuscitation, colonic decompression, and antibiotics. Recurrent or persistent HAEC requires evaluation for mechanical obstruction

Daniel H. Teitelbaum passed away in 2016

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or residual aganglionosis and may require surgical treatment with posterior myotomy/myectomy (POMM) or redo pull-through. This chapter describes the incidence, pathogenesis, treatment, and preventative strategies in the management of HAEC.

Keywords
Hirschsprung's disease · Enterocolitis · HAEC · Pathogenesis · Prevention · Treatment

Introduction

Hirschsprung-associated enterocolitis (HAEC) is a serious, life-threatening complication of Hirschsprung's disease (HD). Harald Hirschsprung, a Danish pediatrician, is credited with the first description of congenital megacolon in 1886 based on his observations of two children who died at 7 and 11 months of age, likely from repeated bouts of HAEC. His description of one of these children is shown here (Corman 1981):

> ". . .bowel movements became copious, watery and involuntary. He vomited only once, but the emaciated youngster was crying and manifestly suffering. . .Rectal temperature was 38.4 °C. No stool was felt in the rectum, but evacuation followed with withdrawal of the finger. During the stay in the hospital, which lasted four or five weeks, diarrhea alternated with inability to evacuate. The abdominal girth varied between 56 and 41 cm; he died with emaciation. . .Microscopic examination of the stool showed. . . epithelial and pus cells."

His description of this unfortunate child covers all of the classic signs and symptoms of enterocolitis, including the classic fever, distention, and watery stools, as well as the expulsion of stool with removal of the examiner's finger. The association between HD and HAEC was recognized by Swenson and Fisher in 1956, and the process was later described in detail by Bill and Chapman in 1962 (Bill and Chapman 1962). Significant advances in the treatment of HD disease have been made in the past 50 years, starting with Swenson and Bill in 1948 and later operations by Duhamel, Soave, and others. The success of these procedures, along with better understanding of the etiology, pathophysiology, and complexity of HD, has led to improved outcomes for patients with this disease. Despite these advancements, HAEC remains a frequent complication of HD with real morbidity and mortality, and its etiology and pathophysiology remain poorly understood. This paper provides an up-to-date review of the epidemiology, pathophysiology, and treatment of HAEC, including pre- and postoperative preventive strategies (Demehri et al. 2013).

Incidence/Diagnosis

Review of modern literature shows that HAEC occurs preoperatively or at the time of HD diagnosis in 6–26% of cases and post-pull-through surgery in 5–42% (Teitelbaum et al. 1988; Imamura et al. 1992; Rescorla et al. 1992; Elhalaby et al. 1995b; Pastor et al. 2009; Teitelbaum and Coran 2013). In a retrospective review by Haricharan, of 52 children who underwent pull-through surgery, HAEC admissions decreased by 30% with each doubling of age at diagnosis and increased ninefold when postoperative stricture was present (Haricharan et al. 2008). Whether this older age at diagnosis means a different type of HD or lesser length of aganglionosis is uncertain; however, this finding is in contradistinction to others who have found that a delay in diagnosing HD beyond the first month of life actually predisposes children to a higher incidence of HAEC (Teitelbaum et al. 1988).This may be due to the fact that the incidence of HAEC has varied considerably between different surgical groups, most likely secondary to lack of a standard definition of HAEC. Pastor et al. developed a scoring system for diagnosis of HAEC through a consensus approach using the Delphi method (i.e., panel of experts in the area of Hirschsprung evaluating a progressively more refined list of characteristics) by identifying clinical diagnostic criteria for HAEC from a larger pool of potential items (Pastor et al. 2009). Eighteen items were included in the score with the following criteria receiving the highest scores: diarrhea, explosive stools, abdominal distension, and radiologic evidence of bowel obstruction or

mucosal edema (Table 1). The frequencies of major presenting features of HAEC are listed in Fig. 1.

Table 1 HAEC score (Adapted from Pastor et al. 2009)

History	
Diarrhea with explosive stool	2
Diarrhea with foul-smelling stool	2
Diarrhea with bloody stool	1
History of enterocolitis	1
Physical examination	
Explosive discharge of gas and stool on rectal examination	2
Distended abdomen	2
Decreased peripheral perfusion	1
Lethargy	1
Fever	1
Radiologic examination	
Multiple air fluid levels	1
Dilated loops of bowel	1
Sawtooth appearance with irregular mucosal lining	1
Cutoff sign in rectosigmoid with the absence of distal air	1
Pneumatosis	1
Laboratory	
Leukocytosis	1
Shift to left	1
Total	20
	HAEC ≥10

Radiologic Imaging

Plain abdominal radiographs will likely demonstrate colonic dilation (90% sensitivity), but this is nonspecific (24% specificity). Gaseous intestinal distension with abrupt cutoff at the level of the pelvic brim – the "intestinal cutoff sign" (Fig. 2) – is both sensitive (74%) and specific (86%) for HAEC (Elhalaby et al. 1995a). If a radiographic contrast enema study is performed, it would demonstrate a spastic distal colon with spiculations of the mucosal lining, consistent with the presence of mucosal inflammation and erosions (Fig. 2c). It is important to note that such enema studies should be avoid in the presence of HAEC due to the great risk of perforation with the application of intraluminal pressure. Chronic HAEC symptoms typically include persistent diarrhea, soiling, intermittent abdominal distension, and failure to thrive. In patients that present repeatedly with these symptoms, mechanical obstruction from aganglionosis should be ruled out in the neorectum or a residual proximal segment. The role of rectal biopsy in the diagnosis of HAEC is controversial and not recommended during the acute phase given the high risk of perforation, unless a diagnosis of HD has yet been obtained. However, as will be discussed below, a strong consideration for retained or recurrent aganglionosis must be pursued in a child with recurrent HAEC.

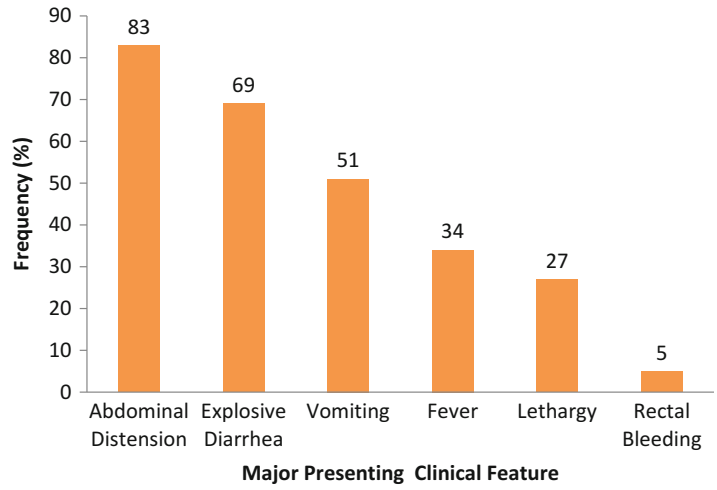

Fig. 1 Frequency of the major presenting clinical features among patients with HAEC (Adapted from Elhalaby et al. 1995)

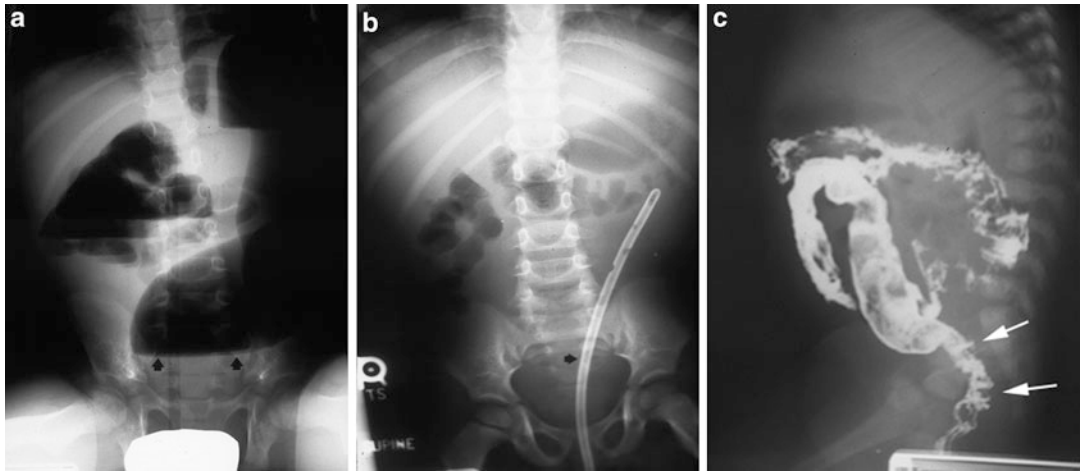

Fig. 2 Plain radiograph findings of HAEC. (**a**) Marked gaseous distension of the colon, with abrupt cutoff at the level of the pelvic brim (intestinal cutoff sign, *arrows*) in a patient with postoperative HAEC. (**b**) A plain film of the same patient after insertion of a rectal tube (*arrow*), with marked decrease in amount of colonic gaseous distension (Reprinted from Elhalaby et al. 1995, copyright, with permission from Elsevier). (**c**) Contrast enema performed during an unrecognized enterocolitis episode. Note the spastic distal nature of the bowel, with spiculations of the mucosal lining, consistent with mucosal inflammation and erosions (*arrows*)

Differential Diagnosis

Certainly the diagnosis of viral enteritis is common in infancy and, as such, must be entertained whenever a child presents with diarrhea and fever. The use of the Delphi scoring system as mentioned above has proven useful in ruling out viral enteritis, but not uncommonly one may opt to treat for HAEC in such cases, as the consequences of not treating, and the subsequent advancement of mucosal inflammation, outweigh the risk of enteral antibiotics and rectal washout therapy.

Anatomic factors such as an anastomotic narrowing may result in frequent bowel movements and abdominal distension. Importantly, a careful physical examination is always important in helping to sort out the etiology of an infant's symptomatology after a pull-through procedure.

Another diagnosis that should be considered is the finding that a subgroup of patients with HD has pronounced hypermotility, without HAEC (Kaul et al. 2011). Such children may manifest with over 15 bowel movements per day (often squirting and small in volume as seen in children with HAEC), and such symptoms may persist for several years. While advanced colonic manometry studies might be needed, certainly frequent stooling, without other findings of HAEC should help with this diagnosis. Typically, these infants will not respond to classic treatment approaches used in enterocolitis (e.g., antimicrobials, washouts, and Botox injections). Interestingly, use of antidepressant medication, with associated anticholinergic activity, such as amitriptyline, has proven useful in reducing the number of bowel movements in these HD patients.

Pathogenesis

Despite being the leading cause of morbidity and mortality in Hirschsprung's disease, the pathophysiology of HAEC remains poorly understood. Historically, Swenson and Fisher in 1956 first postulated that this disorder was caused by a defect in water and electrolyte metabolism (Fisher and Swenson 1956). Later theories included partial mechanical obstruction leading to colitis (Swenson et al. 1960). Subsequent experience with the disorder has implicated a variety of causes, including mucosal immunity defects,

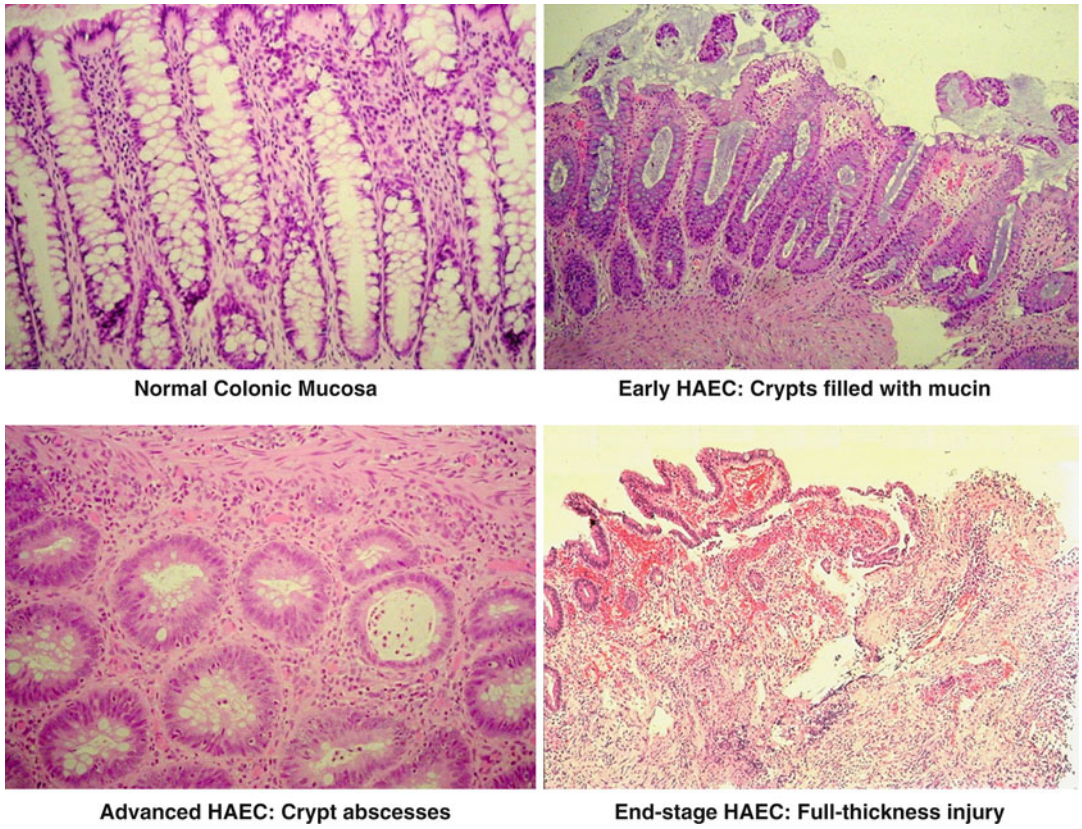

Fig. 3 Histopathologic findings of HAEC. *Top left* panel – normal mucosa. *Top right* panel – crypt dilation and retained mucin. *Bottom left* panel – multiple crypt abscesses per high-power filed (HPF). *Bottom right* panel – intraluminal fibrinopurulent debris or mucosal ulcerations (Reprinted from Elhalaby et al. (1995), with permission from Elsevier)

disordered motility, abnormal mucin production, and infection (Austin 2012). As no single etiology has been identified, the clinical entity of HAEC likely represents a common result of various dysfunctions of intestinal homeostasis.

An understanding of the histopathologic changes associated with HAEC may provide insight into its pathophysiology. Similar to other inflammatory processes of the colon, HAEC is histologically characterized by cryptitis, the appearance of neutrophils in intestinal crypts (Teitelbaum et al. 1989). Early episodes of HAEC, often captured during a rectal biopsy during the initial work-up for Hirschsprung's disease is associated with crypt dilation and retained mucus. Such mucin retention is unique to only two diseases, Hirschsprung's disease and cystic fibrosis. This histologic process progresses to the development of crypt abscesses. If untreated, more advanced stages of HAEC demonstrate mucosal ulceration and fibrinopurulent debris. In severe cases, ischemia, transmural necrosis, and perforation may occur, leading to shock and systemic hypoperfusion. A histological grading system is shown in Fig. 3 and represents a progression of pathologic changes with increasing severity (Teitelbaum et al. 1989; Elhalaby et al. 1995b). Interestingly, these pathologic findings have been found in aganglionic as well as ganglionic segments. This suggests that the contributing mechanisms go beyond the simple mechanism of distension of the bowel (see below) or the absence of ganglia (Murphy and Puri 2005).

Another proposed mechanism of HAEC is partial obstruction, which may lead to stasis, bacterial overgrowth, and translocation. The finding of an

anastomotic stricture or narrowing has been consistently observed by a number of investigators as a risk factor for developing HAEC, and this may well relate to its pathogenesis (Hackam et al. 1998). The successful treatment of patients with recurrent HAEC with internal sphincterotomy (Polley et al. 1985), or a posterior myotomy, lends support to functional obstruction as an etiology in some patients. As HAEC also occurs in infants without evidence of obstruction, including patients with diverting stomas, other factors must play a role.

The increased risk of HAEC in patients with trisomy 21 potentially suggests a genetic role in the etiology of HAEC (Teitelbaum et al. 1988). The etiology of this predisposition is not understood. However, infants with trisomy 21 have immune deficiencies that span both T cell and B cell lineages, as well as dysfunction in their neutrophils. All these may greatly contribute to the predisposition this subgroup of Hirschsprung's children have to develop HAEC. No genetic abnormality has been shown to cause HAEC; however some genetic variations do correlate with more severe disease. For example, intestinal autonomic dysfunction has been associated with mutation in the RET proto-oncogene (Staiano et al. 1999), which is known to be associated with HD. In addition, variations in the ITGB2 immunomodulatory gene (CD18) have been found in 66% of patients with HD, with 59% of these patients developing HAEC (Moore et al. 2008). More than one variation in the ITGB2 gene was associated with more severe HAEC. Continued work on the role of genetic variation in HAEC may shed more light on its pathogenesis.

As the primary defect in HD is the congenital lack of intestinal ganglia, an abnormal enteric nervous system (ENS) remains a culprit in the pathogenesis of HAEC. The ENS has a role in intestinal homeostasis, including motility, epithelial barrier function, mucosal immunity, epithelial transport, and regulation of the gut microbiome. Dysfunction of the ENS may lead to the initiation or propagation of the inflammatory cycle of HAEC. Miyahara et al. (2009) demonstrated markers of neuronal immaturity in the proximal, normal ganglionic bowel of Hirschsprung's patients, and this suggests dysfunction of the ENS beyond the aganglionic segment. Such an abnormal ENS may create an abnormal intestinal equilibrium, where perturbations such as partial obstruction or bacterial overgrowth may lead to enterocolitis.

A fundamental component of intestinal homeostasis is epithelial barrier function (EBF), a composite function of factors including mucin production, intraluminal immunoglobulins, epithelial tight junctions, and the enteric nervous system. Dysfunctional EBF may result in adherence of pathologic organisms to enterocytes. Most interesting is the finding of the development of enteroadhesive behavior in organisms during episodes of HAEC (i.e., microbial penetration of the mucin layer with subsequent adherence of bacteria to the lining epithelial cells). This phenomenon is demonstrated with the adherence of *C. difficile*, *Cryptosporidium*, and *E. coli* in up to 39% of patients with HAEC in some reports (Teitelbaum et al. 1989).

One of the more intriguing histologic manifestations of HAEC is the outpouring of mucins which fill the crypt cells. This led to an early investigation of nature of these mucins. Akkary et al. demonstrated that the nature of these mucins shifted toward the production of neutral mucins (Akkary et al. 1981). Abnormalities in the amount and composition of mucin, a key component of the mucosal barrier function, may contribute to this dysfunction. Further investigation of these changes confirmed this shift in neutral mucins (Teitelbaum et al. 1989) and a decline in acidic sulfomucins. This shift (increase in neutral mucins and a decrease in acidic sulfomucins) was subsequently correlated to a loss of barrier function using an in vitro approach (Aslam et al. 1999). A key component of mucins is the MUC family of proteins. The production of MUC-2, the predominant mucin expressed in humans, is markedly depressed in patients with HD, and for those samples examined during an episode of HAEC, production of MUC-2 was virtually undetectable at the protein level (Mattar et al. 2003). In addition, reduced total colonic mucin turnover correlates with an increased risk of HAEC development (Aslam et al. 1998). Such

changes in mucin production and composition may be secondary to abnormalities in the ENS described above, as the goblet cells that secrete mucus are regulated by submucosal neuroendocrine cells, which are reduced in patients with HAEC (Soeda et al. 1993). Other regulators of intestinal epithelial barrier function, such as mast cells and enteric glial cells, are abnormal in HD, but have yet to be fully investigated in HAEC (Austin 2012). Finally, it is intriguing to speculate that the altered production of mucins may actually be a nutrient source to selected bacteria in patients with enterocolitis. Recently, a relatively unknown organism, Akkermansia spp., particularly, *Verrucomicrobia* thrive on mucins and have recently been implicated in the development of inflammatory conditions, including inflammatory bowel disease (Belzer and de Vos 2012). While an extensive examination of the microbial populations of children with HAEC has not yet been done, it will be intriguing to examine for the expansion of such populations in the setting of HD.

As deficiencies in epithelial barrier function lead to loss of mucosal integrity, the mucosa of patients with HAEC may exhibit diminished recovery. Reduced expression of caudal type homeobox (CDX) gene-1 and gene-2 has been found in the mucosa of patients with HAEC (Lui et al. 2001). As these genes are involved in mucosal proliferation and differentiation, this suggests a deficiency in mucosal healing, which may contribute to prolonged mucosal damage and subsequent enterocolitis.

Another component of intestinal epithelial defense that has been implicated in HAEC is the mucosal immune system. Secretory IgA, the predominant immunoglobulin in the intestinal tract, plays a role in preventing bacterial translocation in healthy intestine. Wilson-Storey and Scobie in 1989 demonstrated that, in patients with HD, secretory IgA was undetectable in saliva while it was increased in buccal mucosa (Wilson-Storey and Scobie 1989). For those with HAEC, however, secretory IgA was absent from the buccal mucosa altogether. Similarly, colonic resection specimens studied by Imamura et al. in 1992 showed elevated IgA, IgM, and IgG chain plasma cells in the lamina propria of bowel from patients with HAEC, with decreased luminal IgA in the aganglionic segment of these same patients (Imamura et al. 1992). Similar findings have been seen in a mouse model of HAEC using piebald-lethal mice, whereby an initial elevation of immunoglobulins was measured early in the life followed by a precipitous fall near the death of these animals (Fujimoto et al. 1988; Caniano et al. 1989). Other immune changes noted in patients with HAEC included increased distribution of CD57+ natural killer cells, CD68+ monocytes/macrophages, and CD45RO+ leukocytes in the bowel of patients with HAEC (Imamura et al. 1992). To determine whether these changes are primary defects predisposing to HAEC, or whether they are secondary to enterocolitis, Turnock et al. in 1992 evaluated suction rectal biopsies of infants with HD and found similar levels of mucosal immunoglobulins regardless of the presence of HAEC (Turnock et al. 1992). This suggests that in patients with HAEC, mucosal IgA production is intact but intraluminal transfer is deficient, limiting the role of IgA in mucosal defense (Murphy and Puri 2005). These findings implicate an intrinsic immune deficiency in the development of HAEC, which may explain the increased risk in patients with trisomy 21, who are known to have abnormal cytotoxic T cell and humoral function.

The factors described above may create a dysfunctional environment in which the gut microbiome is susceptible to a pathologic change in composition leading to HAEC. A microbial etiology of HAEC has been investigated since the first reports of high *C. difficile* toxin titers in patients with HAEC compared to those with HD only and normal controls (Thomas et al. 1982). These findings were not substantiated in later studies, which found variable *C. difficile* carriage rates (Wilson-Storey et al. 1990; Hardy et al. 1993). While not currently thought to be causative, *C. difficile* may flourish in the setting of HAEC (Murphy and Puri 2005), with an associated mortality rate of 50% if pseudomembranous colitis develops (Bagwell et al. 1992). Changes in the composition of the gut microbiome were evaluated by Shen et al. in 2009, who found decreased colonization of

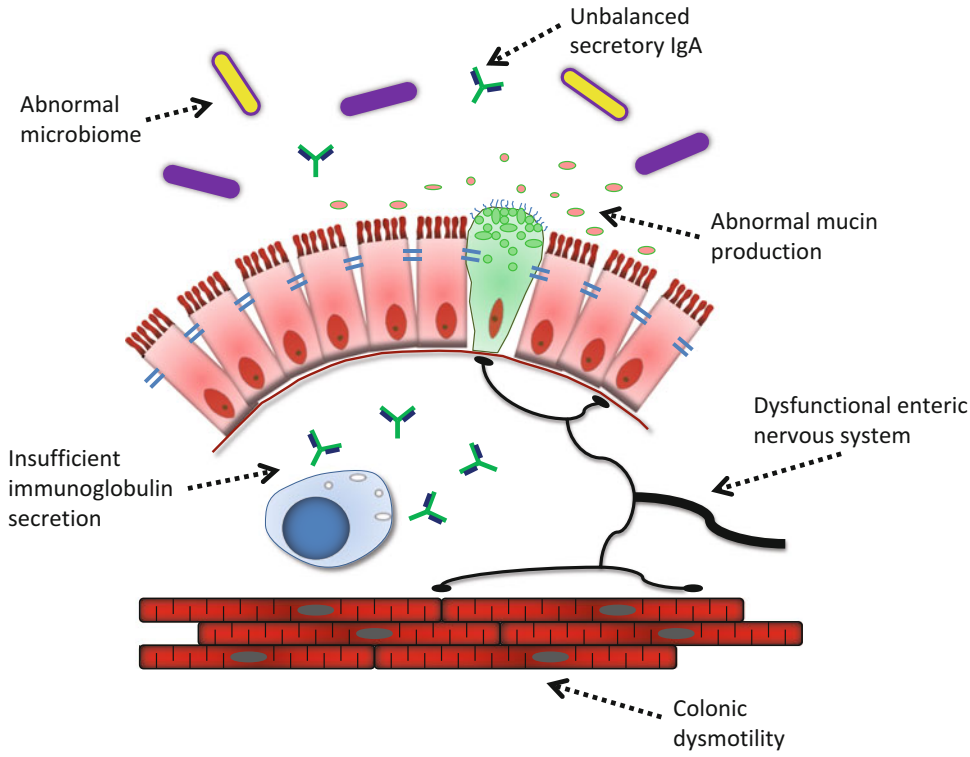

Fig. 4 Schematic representation of the potential pathophysiologic mechanisms contributing to HAEC. Note multiple changes occurring in patients with HAEC. This includes an abnormal microbial population (microbiome), insufficient and unbalanced immunoglobulin production, abnormal mucins, and a dysfunctional enteric nervous system which may contribute to colonic dysmotility

bifidobacteria and *lactobacilli*, probiotic organisms, in patients with HD versus controls, and even lower colonization in those with HAEC (Shen et al. 2009). This finding of altered microbial equilibrium is supported by a recent study evaluating the stool microflora of a child with HD during HAEC episodes and during remission, finding a clustering of microbial diversity with HAEC episodes (De Filippo et al. 2010). These studies suggest that disequilibrium of the gut microbiome may result in dominance of a predisposing bacterial community for HAEC development, though further investigation must be done to establish the specific organisms involved (Li et al. 2016; Frykman et al. 2015).

While the elements contributing to HAEC are increasingly well described, much work remains in elucidating its pathophysiology. There is increasing evidence that several factors, including a dysfunctional enteric nervous system, abnormal mucin production, insufficient immunoglobulin secretion, and unbalanced intestinal microflora, contribute to the development of the common clinical entity of HAEC. A summary of the potential pathophysiologic mechanisms contributing to HAEC is shown in Fig. 4.

Treatment

The treatment of children presenting with suspected HAEC is resuscitation, decompression of the gastrointestinal tract, and antibiotics. The severity of the episode dictates antibiotic choice; mild episodes of HAEC can be treated with oral metronidazole alone, while more severe episodes should be treated with intravenous, broad-spectrum therapy including ampicillin, gentamicin, and metronidazole. Unfortunately, there are few studies comparing antimicrobials for the

treatment of HAEC. Classically, the colon is under considerable pressure, potentially a strong causative factor for the HAEC episode. Decompression of the colon is essential and can generally be done with rectal washouts. Rectal washouts with saline (10–20 mL/kg) using a large bore soft tube should be initiated immediately and repeated anywhere from two to four times per day until proper decompression as determined by clinical examination. In the case of fulminant disease, washouts should be avoided due to risk of perforation, but gentle passage of a rectal tube to decompress the bowel is critical. Bowel rest is indicated with parenteral nutrition in cases of prolonged disease (Vieten and Spicer 2004; Levitt et al. 2010). Inability to adequately decompress the bowel or cases of sepsis with HAEC maybe an indication for diversion with a leveling colostomy just proximal to the transition zone. The use of intraoperative frozen section histology is essential in cases where a child initially presenting with HD has HAEC, in order to level the colon at a site with ganglion cells.

Current surgical treatments for HD, including one-stage endorectal pull-through (ERPT), have become standard of care (Coran and Teitelbaum 2000). Although pull-through operations relieve the obstructive symptoms of HD, there is a persistent risk of the development of enterocolitis, occurring in up to 42% of patients (Hackam et al. 1998; Teitelbaum et al. 2000; Vieten and Spicer 2004). Compared to patients undergoing a two-stage approach, recent data shows a trend toward a higher incidence of enterocolitis in the primary ERPT group compared with those with a two-stage approach (42.0% vs. 22.0%). Although this is thought to be primarily due to a lower threshold in diagnosing HAEC in more recent years (Teitelbaum et al. 2000), it is possible that a tighter anastomosis in these younger infants undergoing a primary pull-through may be a contributing factor. Risk factors for post-pull-through enterocolitis include anastomotic leak or stricture and postoperative intestinal obstruction due to adhesions; such factors increase the relative risk of subsequent enterocolitis by approximately threefold (Hackam et al. 1998). Ruling out a mechanical cause of partial bowel obstruction should be undertaken in infants that present with repeated episodes of enterocolitis following a pull-through procedure. If a contrast enema is normal, full-thickness rectal biopsy is warranted to rule out aganglionosis in the pull-through segment (Moore et al. 1994; Levitt et al. 2010). While a rare cause of HAEC, in cases of retained or secondary aganglionosis associated with enterocolitis, such patients will need a redo pull-through (Lawal et al. 2011). In cases of anastomotic strictures, a trial of dilation is recommended with the possibility of a redo pull-through being reserved if dilations are unsuccessful.

Medical approaches for treatment of HAEC include antibiotics and sodium cromoglycate. Although there is no data to support prophylactic antibiotic therapy post-pull-through, the authors have recommended its use with the first signs and symptoms of HAEC. Sodium cromoglycate, a mast cell stabilizer, is not absorbed in the gastrointestinal tract. A nonrandomized study by Rintala and Lindahl in 2001 showed a favorable response in three out of five patients with decrease in number of bowel movements and abdominal distention (Rintala and Lindahl 2001). Unfortunately, there have been no follow-up studies to verify these results.

Surgical or interventional approaches for treatment of HAEC include botulinum toxin injections, sphincterotomy, and posterior myotomy/myectomy (POMM) (Fig. 5). With the observation that post-pull-through patients often have tight rectal sphincters, Swenson and coworkers initially proposed that sphincterotomy prevents enterocolitis. However, a follow-up evaluation did not show significant improvement with such procedures (Swenson et al. 1975).

In children with recurrent HAEC over 1–2 years following their pull-through, the use of a POMM should be considered. The use of this approach has been tempered by some series showing poor functional outcomes. A study using the transanal POMM approach showed adulthood incontinence in 4 out of 14 patients who underwent POMM procedures as children (Heikkinen et al. 2005). Small reports from various groups have shown mixed results (Polley et al. 1985; Marty et al. 1995a). It is possible that the

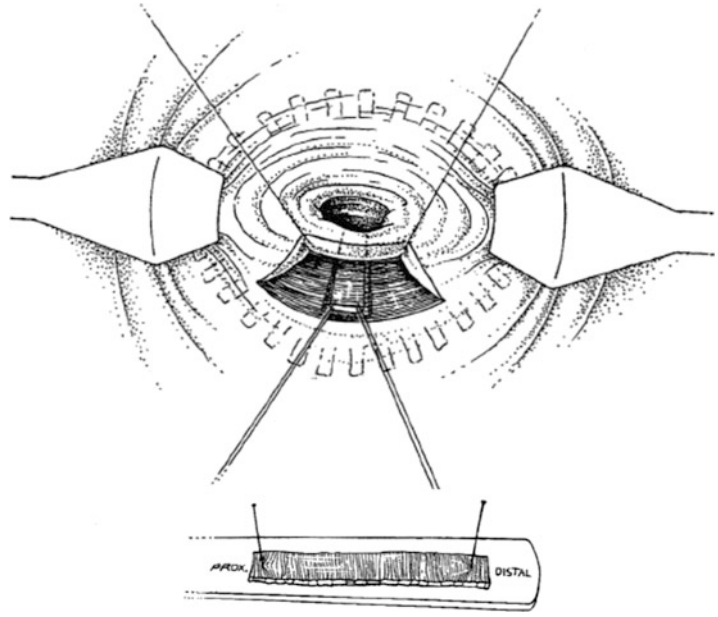

Fig. 5 Operative approach to a posterior myectomy (POMM). Note a flap of mucosa and submucosa are raised posteriorly about 0.5–1 cm above the dentate line. The muscularis is incised and a one-half centimeter wide segment is carried as far cephalad as possible. It is critical to keep the segments oriented for pathologic review (Reproduced with permission from Teitelbaum et al. 2013)

etiology of incontinence in these patients is the transection of part, or all, of the internal anal sphincter. If the performance of a POMM is started above the level of the dentate line, damage to the internal anal sphincter can be avoided. Wildhaber et al. in 2004 reported excellent continence rates with this approach for recurrent HAEC (Wildhaber et al. 2004). An additional advantage to the use of a POMM is that a redo pull-through operation can still be performed in case myectomy is not successful.

The use of botulinum injections for treatment of recurrent HAEC post-pull-through has shown promise in recent studies (Minkes and Langer 2000) with improvement in symptoms and number of hospitalizations; however, long-term results have been mixed with difficulty predicting response in patients. Finally, in rare cases of recalcitrant HAEC not responsive to medical and surgical intervention, end ileostomy or colostomy is a last resort (Estevao-Costa et al. 1999).

Preventive Strategies

Some authors have noted preoperative enterocolitis increases the risk of post-pull-through enterocolitis (Engum and Grosfeld 2004). Ideally, the best treatment for enterocolitis is its prevention. Rectal washouts limit colonic distention and fecal stasis and should be performed when surgical management is delayed (Vieten and Spicer 2004). It has been noted that a histologic grade of III or higher on rectal biopsy, regardless of the patient's clinical history, indicates high risk for potential development of clinical enterocolitis and may be an indication for prophylactic antibiotics (Teitelbaum et al. 1989).

Postoperatively, scheduled rectal washouts have been shown to reduce the incidence of postoperative HAEC. In a review by Marty et al. in 1995a, 36% of patients in the nonirrigation cohort developed postoperative enterocolitis compared with 8% of patients in the rectal irrigation cohort (Marty et al. 1995b). Traditionally, routine anal dilations where thought to prevent stricture formation with most pediatric surgeons recommending daily dilations by parents. However, recent data has challenged this assertion. In a retrospective review by Temple et al. in 2012, children undergoing repair of HD or anorectal malformation had either routine dilatation by parents or weekly calibration of the anastomosis by the surgeon, with daily dilation reserved for children with concern for anastomotic narrowing. There was no significant difference in the

development of enterocolitis in children with HD (Temple et al. 2012). Despite these latter findings, it has been our practice to start such anal dilations at 3 weeks post-pull-through and typically send the infant home with a prophylactic course of metronidazole for the first 2 months after surgery.

Topical isosorbide dinitrate or nitroglycerin applied to the anal canal has been shown to relax the smooth muscle of the anal sphincter. Some authors have shown that anal application of topical isosorbide dinitrate paste leads to improvement in recurrent HAEC and "internal sphincter achalasia"; although small patient numbers limit the interpretation of the outcomes of these studies, this approach should be studied further in the future (Messina et al. 2007).

Because of the potential for an altered microbiome/epithelial cell interaction in children with HAEC, many have thought that probiotics may confer a prophylactic benefit to such patients. El-Sawaf et al. recently reported on a multicenter, prospective, randomized, controlled trial of probiotics versus placebo in infants undergoing a pull-through for HD to determine if the use of probiotics could decrease the incidence and frequency of HAEC (El-Sawaf et al. 2013). Unfortunately, the use of a high dose of orally delivered probiotics failed to offer any prophylactic benefit to this group of patients. Multivariate analysis, adjusting for length of aganglionosis and age of child, also failed to demonstrate any benefit of probiotics to a subgroup of HD children. This certainly emphasizes the multifaceted aspect of the etiology and the complexity of this disorder.

Conclusion and Future Directions

HAEC remains a substantial source of morbidity for children with HD. Its clinical characteristics have become increasingly well defined over the past several decades, aiding in the early recognition and treatment of children who are at risk of developing this complication. Through considerable research into its pathophysiology, a multifaceted picture has begun to emerge where several dysfunctions of intestinal homeostasis create a fragile environment where perturbation leads to HAEC. Intestinal decompression, antibiotics, and rectal washouts remain the cornerstones of treatment for acute HAEC, with surgical intervention such as POMM an effective option for patients with recurrent HAEC.

Future goals in the management of HAEC include identification of patients at high risk and the development of patient-specific measures to prevent its onset. Further understanding of the pathophysiology of HAEC may provide targets for treatment and prevention. For example, given the likely role of alterations of gut microbiology, the identification of a high-risk intestinal microbiome in a patient may allow for early modulation of this bacterial profile to prevent HAEC. In addition, further research into the role of immune dysfunction in HAEC may lead to the development of strategies to modulate the enteric immune system to create a lower-risk intestinal environment. Finally, as the outcomes of surgical intervention for HAEC continue to be assessed, the optimal timing of surgical intervention (i.e., POMM) is yet to be defined. Much knowledge has been gained over the past three decades in the diagnosis, treatment, and prevention of HAEC, with more progress on the horizon in the understanding of its pathophysiology and use of this understanding to develop better therapeutic and preventive strategies.

Cross-References

- ▶ Anorectal Malformations
- ▶ Colonic and Rectal Atresias
- ▶ Embryology of Congenital Malformations
- ▶ Hirschsprung's Disease
- ▶ Sepsis
- ▶ Variants of Hirschsprung Disease

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