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Hirschsprung-associated enterocolitis: a comprehensive review

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ABSTRACT

Hirschsprung-associated enterocolitis (HAEC) is an important cause of morbidity and the leading cause of mortality in patients with Hirschsprung disease. The pathophysiology of disease includes dysmotility of the enteric nervous system, dysbiosis of the microbiota, failure of the intestinal barrier, and impaired immunity. Common manifestations include fever, abdominal distension, lethargy, vomiting, and diarrhea. Given the non-specific signs and symptoms of HAEC, high clinical suspicion is warranted, especially in patients with risk factors. Diagnosis and management of HAEC depend on the severity of disease presentation. Several preoperative and postoperative modalities have been explored to prevent HAEC. The current review elaborates on the risk factors, pathogenesis, diagnosis, treatment, and prevention of HAEC.

INTRODUCTION

Initially described by Harald Hirschsprung in 1886, Hirschsprung disease (HSCR) is a common cause of bowel obstruction in neonates.[1] Hirschsprung-associated enterocolitis (HAEC) is the main cause of morbidity and mortality in HSCR and typically presents with fever, abdominal distension, lethargy, vomiting, and diarrhea.[2] In fact, the initial report from Hirschsprung described two children with constipation since birth who died after developing marked abdominal distension and loose stools,[1] consistent with what was later more clearly defined as HAEC.[3–6]

Establishing a definitive diagnosis of HAEC poses a significant challenge for clinicians. Therefore, there is a highly variable reported incidence ranging from 6% to 60% before definitive pull-through surgery and ranging from 25% to 42% postoperatively, with most prospective series reporting an incidence of over 40%.[7–9] It can present acutely at any time between the birth and adulthood, yet it presents more commonly within the first 2 years of age.[10]

The aim of this review article is to provide an up-to-date synopsis of the risk factors, pathogenesis, diagnosis, treatment, and prevention of HAEC.

RISK FACTORS AND RECURRENCE

The most well-established risk factor for the development of HAEC is that of trisomy 21.[11–13] The incidence of HAEC in patients with HSCR and trisomy 21 is around 50% when compared with 29% in the non-trisomy 21 patients.[10 11 13 14] It is thought that the intrinsic immune defects in cytotoxic T-lymphocytes and derangements in humoral response in infants with trisomy 21 may explain their higher HAEC risk.[15] Current evidence suggests that patients with trisomy 21 experience more severe HAEC episodes.[16]

Additional risk factors implicated in the development of HAEC include male sex, delay in HSCR diagnosis, family history of HSCR, and other congenital abnormalities.[10 17] Moreover, Elhalaby *et al*. postulated that a single HAEC episode can lead to alterations in the intrinsic intestinal immunity via chronic mucosal changes that lead to an increased risk for future episodes.[17] Although longer HSCR is also postulated to be associated with recurrent HAEC, current evidence has been conflicting, yet HAEC appears to be more common in patients with aganglionic segments longer than the sigmoid.[6 17 18] In fact, a recent meta-analysis showed that preoperative enterocolitis, malnutrition, hypoproteinemia, and respiratory infection were risk factors for both postoperative HAEC and for recurrent HAEC.[19] In addition, it reported that length of aganglionic segment greater than 30 cm was associated with postoperative HAEC, while short-segment HSCR was a protective factor against both postoperative and recurrent HAEC.[19] Additional data have shown that the length of resection is associated with the postoperative risk of HAEC, across all HSCR variants, as well as with long-term outcomes and quality of life in patients with HSCR.[20] In a 28-year experience with total colonic HSCR, the type of pull-through was not associated with the incidence of HAEC,[21] which has been noted in other studies as well.[22 23] Risk factors associated with postoperative HAEC include anastomotic leak, stricture, fistula, and bowel obstruction

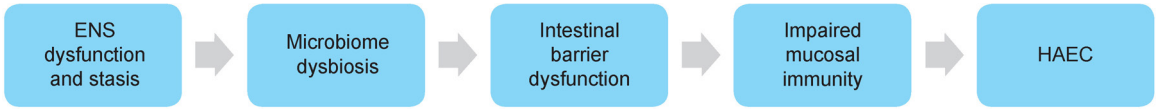

Figure 1 Working model for Hirschsprung-associated enterocolitis (HAEC) pathogenesis. Enteric nervous system (ENS) dysfunction can result in dysmotility and stasis, as well as microbiome dysbiosis, impaired intestinal barrier function, and abnormal immune response leading to the development of HAEC.

or ileus.[9 19 24] Interestingly, older age at surgery has been associated with shorter HAEC-free interval postoperatively, but not with a higher incidence.[25]

PATHOGENESIS

Thanks to significant scientific advancements that have taken place over the last decade, there is currently a working model for the pathogenesis of HAEC. This model involves dysfunction of the enteric nervous system (ENS) causing dysmotility and stasis, which leads to microbiome dysbiosis, followed by intestinal barrier failure, which ultimately via impaired mucosal immune response is believed to lead to HAEC (figure 1). Each of these steps in the sequence may be a potential target for preventive or therapeutic modalities.

Enteric nervous system dysfunction causing dysmotility and stasis

The earliest suggested mechanism of HAEC was thought to be associated with an impairment in intestinal motility causing functional obstruction with either subsequent bacterial stasis, overgrowth and translocation, or distension and ischemia.[6 26 27] The initial theory that HAEC pathogenesis was due to partial mechanical obstruction leading to proximal bowel dilatation, fecal stasis, and bacterial invasion could not explain the enterocolitis seen in the distal colon or in the aganglionic bowel or even in the postoperative setting.[28 29]

The ENS plays a critical role in intestinal homeostasis due to its ability to dilute and purge pathogens via propulsion of intestinal contents and modulation of secretory function.[30 31] A growing body of evidence has shown the decreased neuronal density in the ganglionated bowel using the *EdnrB*$^{NCC-/-}$ HSCR mouse model, and the shift in neurotransmitter phenotypes with underrepresentation of cholinergic (contractility) neurons and over-representation of nitrergic (relaxation) neurons.[32] Additional data using both *Ednrb*$^{-/-}$ mice and tissue from patients with HSCR indicated that a greater proportion of nitrergic neurons in the proximal resection margin was associated with a higher incidence of constipation and/or HAEC postoperatively.[33] Another recent pilot study from China reported that the histopathologic grade of ganglion cells from the proximal resected margin was significantly related to issues with postoperative constipation and HAEC.[34] Notably, similar data in patients with HSCR showed that smaller ganglion size and higher percentage of nitric oxide synthase neurons in the proximal resection margin correlated with decreased patient-reported quality of life.[35] Overall, the data are compelling regarding the fact that the remaining ganglionated bowel may not support normal bowel function after pull-through surgery for HSCR and that the prospect of a more detailed pathologic analysis, including neurotransmitter analysis, may pave the way toward more prognostic tools for counseling patients with HSCR and their families.[35]

Dysbiosis of the microbiota

The microbiota of the gut exhibits dynamic diversity over time and in response to stimuli, such as diet and other host-associated factors. The gut microbiota starts to develop at birth and evolve rapidly until the age of 3 years, at which point they approach the adult composition.[36] The microbiome of the gut is determined by multiple factors including gestational age, mode of delivery, antibiotic exposure, race, diet, and environment.[37 38]

Ward *et al.* reported increasing alpha diversity of the microbiome in *EdnrB*$^{-/-}$ mice, with a greater increase in mutant mice compared with wild type, as well as that the differences in alpha diversity between groups increased with age.[39] The same research team was also able to show a significant difference in beta diversity between colonic and fecal microbiota.[39] Specifically, the authors demonstrated increases in *Bacteroidetes* and decreases in *Firmicutes* in mutant colon and feces at the phylum level, while they showed increases in *Coprobacillus* and *Bacteroides* in mutant colon, which may indicate their implication in the development of HAEC.[39] Another study by Pierre *et al.*[40] showed similar profiles of microbiota between mutant and control mice in the early neonatal period with eventual divergence prior to the onset of HAEC. Notably, both studies showed a decrease in *Lactobacillus* over time in mutant mice.[39 40] Of note, Li *et al.*[41] demonstrated the abundance of *Veillonella parvula* in patients with HAEC when compared with patients with HSCR without HAEC, as well as the similarities in microbiota between patients with HAEC and patients with HAEC in remission in different intestinal sites and their divergence from those in patients with HSCR. On the other hand, Parker *et al.*[42] reported longitudinal changes in the fecal microbiota of patients with HSCR with active enterocolitis, as well as composition similarity in patients who were able to achieve remission, while patients with recurrent HAEC experienced ongoing substantial variability in the composition of microbiota. Another pilot study showed changes in microbiota of a patient as he progressed from his pre-HAEC, acute HAEC episode, and remission states

using amplified ribosomal DNA restriction analysis.[43] Neuvonen *et al.* reported decreased overall microbial richness in patients with HSCR compared with healthy controls, as well as higher abundance of *Proteobacteria* and *Lactobacillus* and decreased levels of *Clostridia* and *Prevotella* with 16S rDNA amplicon sequencing in patients with recurrent HAEC.[44] Together, these studies indicate that dynamic changes in the intestinal and colonic microbiota contribute to the pathogenesis of HAEC.

Intestinal barrier dysfunction

The intestinal barrier plays an important role in preserving host homeostasis and the epithelial integrity is primarily maintained via production of mucin from goblet cells, which serves as a scaffold for bacteriostatic and bactericidal proteins.

A growing body of evidence has suggested alterations in the volume and composition of mucin produced in the colon of patients with HSCR.[45] Data suggest that patients with HSCR, who developed HAEC, had lower rates of mucin turnover compared with patients with HSCR who did not experience HAEC.[46] In fact, a study using *EdnrB*$^{-/-}$ mice showed significantly reduced passive and active transport rates compared with wild type in both the ganglionic and aganglionic colon segments.[47] Another study using the same mouse model demonstrated increased goblet cell number and size and increased cell proliferation when compared with wild-type mice in aganglionic segments, but notably reduced goblet cell size and number in ganglionic segments.[48] Additionally, data from in vitro studies have shown that MUC-2, the predominant mucin expressed in the human colon, can prevent bacterial translocation across the intestinal wall.[49 50] Studies have also shown that patients with HSCR have decreased MUC-2 levels with patients with HAEC even having undetectable levels.[51] All things considered, alterations in mucus production and function appear to be implicated in the development of HAEC. Additional components of the intestinal barrier that have been implicated as contributing to pathogenesis in other inflammatory bowel diseases, such as tight junctions and permeability, remain understudied in HAEC pathogenesis.

Impaired mucosal immunity

Secretory immunoglobulin A (IgA) is the predominant immunoglobulin in the intestinal tract, both in the lumen and within the wall, and provides a major immunological barrier. Secretory IgA is known to bind to bacteria and to prevent bacterial translocation across a morphologically intact segment of viable intestinal tissue.[52] Data have also suggested that patients with HSCR experience impaired transfer of secretory IgA across the gastrointestinal mucosa since they have been found to have significantly decreased secretory IgA in the saliva despite increased IgA levels in buccal mucosal tissue.[53 54] Moreover, plasma cells in the lamina propria of HAEC bowel were found to have increased levels of IgA, IgM and IgG when compared with non-HAEC bowel, as well as decreased luminal IgA, which may suggest decreased production or impaired transport into the lumen.[55] Data from *EdnrB*$^{NCC-/-}$ mice have shown reduced levels of IgA secretion in the gut compared with *EdnrB*$^{NCC+/-}$ mice, while the nasal and bronchial secretory IgA levels were unchanged, suggesting a gut-specific defect in either IgA production or secretion that may be a potential therapeutic target.[56] Additionally, transport of IgA into the intestinal lumen is an active process mediated by the polymeric immunoglobulin receptor (pIgR), and levels of pIgR have been identified as being suppressed in HSCR/HAEC, with resultant accumulation of IgA in the lamina propria of the intestine, suggesting both impaired IgA production and transport as potential factors in HAEC pathogenesis.[57]

Immune cells are also known to play a pivotal role in the pathogenesis of HAEC. During the early stages of inflammation, macrophages are predominantly of the classically activated (M1) type and facilitate the development of inflammation, while the alternatively activated (M2) macrophages facilitate tissue stabilization and maturation.[58] There is evidence to suggest the infiltration of the proximal dilated colon with proinflammatory M1 macrophages of both *EdnrB*$^{-/-}$ mice and patients with HAEC, while the population of M2-type macrophages is found to be higher in the distal when compared with the proximal segment.[59] At the same time, the function of the interstitial cells of Cajal appears impaired in the dilated, aganglionic colon and appears to be caused by proinflammatory cytokines produced by macrophages, resulting in suppression of C-KIT expression and pacemaker currents.[59] This suggests that M1 macrophages may play an important role in the development of HAEC through disruption of the phenotype and function of the interstitial cells of Cajal and as a result their pacemaker function, leading to intestinal dysmotility.[60] In addition, mucosal neuroendocrine cells participate in the synthesis and storage of neuropeptides and biogenic amines, which act as chemical messengers.[61] Data have shown an increased number of neuroendocrine cells in the aganglionic segment of bowel in patients with HSCR when compared with ganglionated bowel and normal controls, as well as a decreased number of neuroendocrine cells in ganglionated bowel in patients with HAEC versus those without.[62 63] It is also worth mentioning that *EdnrB*$^{NCC-/-}$ mice have shown decreased B lymphocyte numbers and defects in maturation.[56] Another study showed that colonic tissue with low cholinergic fibers from patients with HSCR was associated with higher HAEC incidence and showed decreased number of Treg cells and increased number of Th17 cells.[64] Notably, another group used the *EdnrB*$^{-/-}$ mouse model and demonstrated that splenic lymphopenia and abnormal splenic architecture may contribute to impaired immune response.[65] The same group also reported that enterocolitis in *EdnrB*$^{-/-}$ mice and Edn3 ligand-knockout (Edn3$^{-/-}$) mice leads to thymic involution, suppression of B lymphopoiesis, and splenic

lymphopenia as a consequence of colonic aganglionosis, and not from a direct effect of a defect in intrinsic Edn3-Ednrb signaling to the lymphoid organs.[66]

DIAGNOSIS

The most common clinical manifestations of HAEC are fever, abdominal distention, and diarrhea, yet the presentation can be highly variable and also include lethargy, vomiting, obstipation, and rectal bleeding.[2] Due to the non-specificity of HAEC presentation and the increased risk of morbidity and mortality associated with a delayed or missed HAEC diagnosis, many pediatric surgeons prefer to presumptively diagnose and treat suspected HAEC cases. Therefore, the possibility of HAEC should be suspected in all patients with HSCR and in neonates presenting with distal bowel obstruction.[10] It is important to note that even patients with HSCR after a pull-through operation or those with diverting stoma will still present in a similar way. Bowel perforation can also be seen but reportedly only in 2%–3% of the patients.[17] Rectal examination by either digit or soft catheter can be both diagnostic and therapeutic and results in characteristically explosive foul smelly stool and gaseous decompression. Additionally, it is important to exclude other causes of colitis, like necrotizing enterocolitis in infants and infectious colitis in older children.

In a Delphi analysis published in 2009, an expert panel of 27 surgeons and gastroenterologists started with 38 features (history, patient characteristics, physical examination signs, laboratory findings, radiology findings, and pathology findings) and iteratively refined this list to 16 features that led to the development of the HAEC score.[67] More recently, the HAEC score was critically evaluated in a multicenter study, and according to the findings a HAEC score of 4 maximized the sum of sensitivity (83.7%) and specificity (98.6%) compared with the previously established cut-off of 10 that demonstrated lower sensitivity (41.9%) with perfect specificity.[68] Therefore, the authors concluded that a cut-off of 4 should be used rather than 10 to avoid underdiagnosis of HAEC, or alternatively the new HAEC risk score should be used that included only the four variables of diarrhea with explosive stool, decreased peripheral perfusion, lethargy, and dilated loops of bowel.[68] A study from 2013 described the 'clinical grade' of HAEC for use in a prospective trial and this system grades the degree of diarrhea, abdominal distention, and systemic manifestations into mild, moderate, and severe to assign an overall clinical grade.[8] A study from the American Pediatric Surgical Association Hirschsprung Disease Interest Group published in 2017 followed a system similar to that described by Bell for necrotizing enterocolitis[69] and categorized the clinical suspicion and severity of HAEC into three grades according to history, physical examination, and imaging studies (table 1).[2] Most recently in 2021, a retrospective multicenter study evaluated the existing HAEC and new HAEC risk scores and developed a novel scoring system that included the six variables of fever, bloody diarrhea, obstipation, distention, dilated loops of bowel on X-ray, and leukocytosis, and showed its improved sensitivity of 67.8% and specificity of 87.9%.[70] A summary of the previous HAEC scoring systems is depicted in table 2.

TREATMENT

Initial episode

Unfortunately, there is no current algorithm or guideline based on high-level evidence regarding the management of HAEC. Most therapies aim to treat symptoms rather than a specific cause. Important pillars of management involve fluid resuscitation, electrolyte replacement, dietary changes, antibiotics, rectal irrigations, and, in advanced HAEC, even surgery. The 2017 study by the American Pediatric Surgical Association Hirschsprung Disease Interest Group described the appropriate treatment options according to HAEC grade (table 3).[2] Patients with grade I HAEC can be safely managed with oral metronidazole and hydration in the outpatient setting. Rectal irrigations may be considered for these

Table 1 American Pediatric Surgical Association Hirschsprung Disease Interest Group guideline for the diagnosis of HAEC

Grade	Description	Clinical history	Physical examination	Radiographic findings
I	Possible HAEC	► Anorexia ► Diarrhea	► Mild abdominal distention	► Normal ► Mild ileus gas pattern
II	Definite HAEC	► Previous HAEC episode ► Explosive diarrhea ► Fevers ► Lethargy	► Fever ► Tachycardia ► Abdominal distention ► Abdominal tenderness ► Explosive gas/stool on digital rectal examination	► Ileus gas pattern ► Air/fluid levels ► Dilated loops of bowel ► Rectosigmoid cut-off
III	Severe HAEC	► Obstipation ► Obtunded	► Decreased peripheral perfusion ► Hypotension ► Altered mentation ► Marked abdominal distention ► Peritonitis	► Pneumatosis ► Pneumoperitoneum

HAEC, Hirschsprung-associated enterocolitis.

Table 2 HAEC scoring systems

Variables	Pastor score	Frykman score	Lewit score
History			
Diarrhea with explosive stool	2	5	–
Diarrhea with foul-smelling stool	2	–	–
Diarrhea with bloody stool	1	–	2
Obstipation	–	–	1
History of enterocolitis	1	–	–
Physical examination			
Explosive discharge of gas and stool on rectal examination	2	–	–
Distended abdomen	2	–	1
Decreased peripheral perfusion	1	5	–
Lethargy	1	5	–
Fever	1	–	2
Radiologic examination			
Multiple air fluid levels	1	–	–
Dilated loops of bowel	1	4	1
Sawtooth appearance with irregular mucosal lining	1	–	–
Cut-off sign in rectosigmoid with absence of distal air	1	–	–
Pneumatosis	1	–	–
Laboratory			
Leukocytosis	1	–	2
Shift to left	1	–	–
Total	20	19	9

HAEC, Hirschsprung-associated enterocolitis.

patients, especially in case of abdominal distention or incomplete evacuation. They are performed using a large-bore soft catheter with several side holes that is first lubricated, advanced in the colon, and then gentle washouts with 10 mL/kg aliquots of warm or room temperature normal saline are performed. Notably, patients with

Table 3 American Pediatric Surgical Association Hirschsprung Disease Interest Group guideline for the management of HAEC

Grade	Disposition	Diet	Antibiotics	Irrigations	Surgery
I	Outpatient	► Oral hydration	► Oral metronidazole	► Consider rectal irrigations.	–
II	Outpatient or inpatient	► Clear liquids or nothing by mouth	► Oral or intravenous metronidazole ► Consider intravenous ampicillin plus gentamicin or intravenous piperacillin/tazobactam.	► Rectal irrigations	–
III	Inpatient, possible intensive care unit	► Nothing by mouth ► Intravenous fluid hydration	► Intravenous metronidazole ► Intravenous ampicillin plus gentamicin or intravenous piperacillin/tazobactam	► Rectal irrigations	► Proximal diversion for failure of non-operative management ► Exploration for pneumoperitoneum

HAEC, Hirschsprung-associated enterocolitis.

HAEC who have not undergone surgery yet should have the tube passed into the transition zone preferably. This can be ensured clinically either via review of previous radiographic studies or by monitoring the patient for any resistance or discomfort. Patients with grade II HAEC may be managed either in an outpatient or inpatient fashion with dietary restriction to clear liquids or nothing by mouth, rectal irrigations, and oral or intravenous antibiotics. On the other hand, patients with grade III HAEC are in many cases managed in the intensive care unit with bowel rest, intravenous antibiotics, and rectal irrigations. Surgical proximal bowel diversion may be required if non-operative management fails, while laparotomy is recommended in case of bowel perforation.

Recurrent Hirschsprung-associated enterocolitis

Recurrent HAEC episodes should be worked up for identification of possible causes, such as anatomic or pathologic causes of obstruction. Contrast water-soluble enema studies (not during acute HAEC episodes due to risk of perforation), examination under anesthesia, or even rectal biopsy to confirm presence of ganglionated bowel can be employed. Surgical intervention is required for anatomic abnormalities, such as anastomotic stricture, Duhamel kink or spur, tight Yancey-Soave cuff, retained aganglionosis, or transition zone pull-through.[2 10] Data suggest that the injection of *Clostridium botulinum* toxin into the intrasphincteric groove has been shown to decrease obstruction-related hospital admissions in children who had undergone pull-through surgery for HSCR.[71] However, a more recent study has questioned its efficacy and emphasized the need to evaluate this modality for longer duration of follow-up, as well as the use of repeated injections.[72]

PREVENTION

Some studies have advocated for prophylactic interventions such as routine rectal washouts, especially in young infants at higher risk of HAEC and in case of anticipated delays in surgical treatment, since reduction of fecal stasis and bacterial load limits colonic distention.[73] A systematic review and meta-analysis reported a reduced incidence of HAEC with routine postoperative irrigations but no difference in the incidence of HAEC with the use of prophylactic probiotics.[74] A Cochrane systematic review also showed no difference in the recurrence of HAEC with probiotics when compared with placebo but emphasized the need for well-designed and sufficiently powered randomized clinical trials to clarify the true efficacy of probiotics.[75] A study of 34 consecutive children undergoing primary transanal rectosigmoidectomy showed that the incidence of HAEC postoperatively was only 6% with the use of routine anal dilations for 3 months postoperatively.[76] Another study compared postoperative weekly calibrations by the surgeon versus daily dilations by the parents and found no difference in outcomes.[77] On the contrary, a study from Ireland reported no reduction in the development of HAEC with the prescription of routine anal dilations.[78] Similarly, a study from China showed no difference in the risk of developing HAEC with anal dilations preoperatively, but it reported a shorter operative time in short-segment (aganglionosis limited to the proximal rectum) or typical-segment disease (aganglionosis from anus to the rectosigmoid junction or distal sigmoid)[79]; of note, the American Pediatric Surgical Association has recently defined short-segment HSCR as aganglionosis up to the sigmoid colon-descending colon junction and long-segment HSCR as aganglionosis from sigmoid colon-descending colon junction up to the cecum.[80] Diverting stoma can be considered for patients with HSCR with severe congenital heart disease due to their compromised physiology and impaired tolerance to HAEC episodes.[81] Modalities for prevention of HAEC remain elusive and would contribute greatly to reducing the morbidity that patients with HSCR and their families experience.

CONCLUSION

HAEC is a major cause of morbidity and the leading cause of mortality in patients with HSCR. Despite several advancements in explaining the pathophysiology of disease, it still poses a significant diagnostic and therapeutic challenge. Further improvement in diagnosis and management, as well as their standardization across institutions, is of paramount importance. Future potential areas of research include personalized therapies using analysis of the intestinal microbiota, targeted pre/probiotic therapies, therapies targeting the mucus barrier, and stem cell administration to restore bowel function.

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Contributors IAZ contributes to conceptualization, methodology, visualization, validation, investigation, resources, writing—original draft. KPK and MF contribute to investigation, resources, writing—review and editing. AG (guarantor) contributes to conceptualization, methodology, visualization, validation, investigation, resources, writing—review and editing, supervision, project administration.

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