



# Hirschsprung-associated enterocolitis: prevention and therapy

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Hirschsprung-associated enterocolitis remains the greatest cause of morbidity and mortality in children with Hirschsprung disease. This chapter details the various approaches used to treat and prevent this disease process. This includes prevention of complications, such as stricture formation, prophylaxis with rectal washouts, and identification of high-risk individuals. The chapter also details approaches to diagnose Hirschsprung-associated enterocolitis as well as to exclude other etiologies.

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Hirschsprung-associated enterocolitis (HAEC) was first recognized in the late 19th century by Härald Hirschsprung who included it in his hallmark description of congenital megacolon.<sup>1</sup> HAEC is a condition of intestinal inflammation characterized clinically by fever, abdominal distention, diarrhea, and sepsis.<sup>2</sup> Hirschsprung also noted key pathologic findings of HAEC at autopsy, including crypt abscesses, mucosal ulceration, and transmural necrosis.<sup>3</sup> Today, HAEC is the leading cause of morbidity and is responsible for half of the deaths associated with Hirschsprung disease (HD).<sup>4</sup> Despite many proposed etiologies, the biological mechanisms underlying HAEC are poorly understood.

This article focuses on early identification of high-risk patients and reviews the evidence supporting preventative strategies to reduce the likelihood of patients developing HAEC. It also reviews diagnostic criteria for HAEC and current presurgical and postsurgical management approaches. In addition, we also describe a strategy to work up postsurgical patients with chronic or recurrent HAEC and discuss the management options to treat each underlying cause.

## Early diagnosis

### Recognition

One of the keys to prevention of HAEC is early diagnosis of HD in the perinatal period. HD occurs in approximately 1 in 5000 live births<sup>5</sup> and should be considered in infants who fail to pass meconium in the first 24 hours of life.<sup>6</sup> Failure to recognize HD in the early perinatal period places children at greater risk of HAEC,<sup>7</sup> with HAEC complicating 18% to as many as 50% of these children in the preoperative period.<sup>8</sup> One study showed that the incidence of HAEC was 24% for infants diagnosed with HD after the first week of life compared with 11% if diagnosed within the first week.<sup>9</sup> Further supporting this finding, another study found a greater delay in passage of meconium (53 vs 44 hours) and a much more significant delay in HD diagnosis (16.6 vs 4.6 days) in children who developed HAEC.<sup>10</sup> Paradoxically, children who are diagnosed with HD outside the neonatal period may actually be resistant to the development of HAEC.<sup>11</sup> Decreased rates of HAEC in this group of children may be secondary to improved mucosal defenses<sup>12</sup> or may represent a different disease phenotype. It is important to note that not all studies have found association between increased incidence of HAEC and delayed diagnosis of HD.<sup>13</sup>

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Conversely, establishing a diagnosis of HAEC can be challenging before the diagnosis of HD being made. HAEC can be the presenting symptom in some HD patients, and HAEC may not be immediately recognized because of the relative rarity of HD.<sup>14</sup> These factors may potentially lead to a delay in diagnosis. Hence, evaluating physicians and surgeons should keep HAEC in mind as a potential diagnosis, especially when assessing a newborn with possible necrotizing enterocolitis or distal bowel obstruction with loose stools.

### Identification of high-risk Hirschsprung patients

Although any patient with HD is theoretically at risk for developing HAEC, there appears to be a number of factors that contribute to increased risk of HAEC development. These include family history, trisomy 21, long-segment disease, and previous episodes of HAEC. HD is heritable with 2.8%-12% of patients with a family history of HD,<sup>15-18</sup> and development of HAEC may also be influenced by heritable factors. Engum et al<sup>19</sup> demonstrated a 35% incidence of HAEC in patients with a family history of HD compared with a 16% incidence among those without a family history of HD. Similarly, HD and trisomy 21 have a known association with 2.9%-8.2% of HD patients also having trisomy 21.<sup>4,20-22</sup> Children with Down syndrome and HD are at significantly higher risk of developing HAEC with an incidence as high as 50%.<sup>6,23</sup> An incidence of HAEC as high as 48% has been identified in HD patients with trisomy 21 compared with a 25% incidence in those without trisomy 21.<sup>10,24</sup> Similar risk of HAEC may exist in patients who concomitantly have intestinal neuronal dysplasia and trisomy 21.<sup>25</sup> Although most studies support the association of HAEC and HD-trisomy 21, not all studies found this associated risk. Haricharan et al<sup>11</sup> reported that trisomy 21 may be protective against HAEC, with a hazard ratio of 0.1 ( $P = 0.09$ ) among a cohort of 52 patients.

Long-segment disease, that is aganglionosis proximal to the splenic flexure, may confer increased risk of HAEC because of dysmotility of the residual segment leading to stasis of luminal contents. In 1995, Elhalaby et al<sup>26</sup> showed significantly higher rates of HAEC in patients with long-segment disease compared with those with short-aganglionic segment disease, 49% vs 31%, respectively. Similar data from Reding et al<sup>27</sup> report a 56% incidence of HAEC in the preoperative period among children with long-segment disease compared with a 16% incidence among children with short-segment disease ( $P < 0.01$ ). More recent data from Lacher et al showed a lower overall incidence of HAEC, but demonstrated continued increase in prevalence of HAEC in the long-segment cohort (17.6% vs 11.4%) in both the pre- or postoperative periods.<sup>28</sup>

### Other factors

Most authors believe that some children have a predisposition toward development of HAEC, and that one episode of

HAEC may increase risk of future HAEC regardless of therapy.<sup>2,10</sup> Reding and colleagues<sup>27</sup> reported 12 cases of preoperative HAEC, 4 of which redeveloped HAEC in the postoperative period. A retrospective study of 168 patients with HD found that 57 patients developed 119 episodes of HAEC. Twenty-one children (37%) developed HAEC preoperatively with 8 recurring in the postoperative period. The remaining 36 children (63%) developed only postsurgical HAEC.<sup>29</sup> Other authors have suggested that HAEC may be associated with female gender,<sup>30</sup> and although increased incidence of HAEC has been reported in girls (42% vs 30%,  $P = 0.16$ ), the observation did not reach significance.<sup>29</sup>

## Preoperative prevention

### Prophylactic interventions

For prophylactic prevention of HAEC, some have advocated for routine rectal washouts or diverting enterostomy in select populations. Because of an immature immune system, young infants are thought to be at higher risk of HAEC and, therefore, require frequent assessment. Hence, this group may benefit from routine rectal washout, which reduces fecal stasis and bacterial load, thereby limiting colonic distension.<sup>8</sup> Routine washouts should be performed, especially if there are anticipated delays in surgical management. Although certainly not needed in most cases, diversion should be considered for those HD patients with severe congenital heart disease because of their compromised physiology and impaired tolerance to insult.<sup>4</sup>

### Probiotics

Probiotics have been used to prevent colitis in a number of pediatric conditions and may be beneficial in the prevention of HAEC. Use of *Lactobacillus*, *Bifidobacterium*, *Saccharomyces*, and *Streptococcus species* has been reported in children. These organisms have been evaluated for treatment of infectious diarrhea, antibiotic associated diarrhea, atopic dermatitis, necrotizing enterocolitis, *Helicobacter pylori* infection, Crohn disease, and ulcerative colitis.<sup>31-33</sup> Shen et al<sup>34</sup> reported markedly decreased *Lactobacillus species* and *Bifidobacteria species* in children with HAEC. Proponents suggest that replacement of these commensal strains may restore bacterial equilibria and thereby play a preventive role against HAEC. Further, Herek<sup>35</sup> proposed that probiotic therapy with *Saccharomyces boulardii* may be beneficial against HAEC associated with *Clostridium difficile* (*C diff*) because of its ability to stimulate secretion of immunoglobulin A and its production of a protease that inactivates *C diff* endotoxin; however, currently this remains speculative. To date, we are not aware of published studies that have evaluated probiotics as preventive therapy in HAEC.

## Diagnosis

### Clinical diagnosis

Bill and Chapman<sup>36</sup> described HAEC as a clinical syndrome of abdominal distension, pain, explosive watery diarrhea, fever, and prostration. Elhalaby et al<sup>29</sup> characterized the incidence of presenting symptoms in children with HAEC: abdominal distension in 99% of cases, explosive diarrhea in 82%, vomiting in 61%, fever in 40%, lethargy, in 32%, rectal bleeding in 6%, and shock in 6%. In addition to these “classic” diagnostic criteria, many patients will present with less specific symptoms, such as loose stool or perianal excoriation.<sup>2</sup> Because of lack of clearly defined diagnostic criteria for HAEC, the reported incidence of HAEC has wide variation in the literature. As an attempt to standardize the diagnostic criteria for HAEC, Pastor et al<sup>2</sup> developed and validated a scoring system using a Delphi analysis to gain consensus from a panel of experts. The HAEC scoring system serves as a standardized and reproducible outcome measure for future studies, rather than an aid to clinicians for establishing a diagnosis of HAEC.

### Diagnostic imaging

Diagnostic imaging for HAEC consists mostly of plain abdominal radiographs. Several radiographic findings are associated with HAEC and were included in the recent Delphi analysis.<sup>2</sup> These include the “cutoff” sign in the rectosigmoid colon with absent distal air, dilated loops of bowel, air fluid levels, pneumatosis intestinalis, “sawtooth” appearance with irregular intestinal lining, and even free intra-abdominal air from intestinal perforation proximal to an aganglionic segment. Although these findings may aid in the diagnosis of HAEC in an appropriate clinical setting, taken in isolation, they are highly nonspecific. Elhalaby et al<sup>29</sup> reviewed clinical-radiologic correlations and found colonic dilatation on plain radiography to have a sensitivity (90%) but low specificity (24%). Use of barium enema was found to be of little clinical use and could be dangerous should the child develop a perforation. Others have suggested adjunctive use of ultrasonography, which may identify peritoneal ascites or internal septations that are suggestive of peritonitis or intestinal inflammation.<sup>14</sup> In one unusual case, Sheth et al<sup>37</sup> reported the diagnosis of HAEC in a 3-month-old infant using computed tomography. However, the routine use of computed tomography is not recommended because of increased radiation exposure and addition of little value to the diagnosis or treatment of HAEC.<sup>38</sup>

### Other diagnostic modalities

When the diagnosis of HAEC may be unclear in a clinically stable patient, other procedures, such as colonoscopy or capsule endoscopy, have been described to evaluate for

HAEC.<sup>39</sup> If HD is complicated by pseudomembranous colitis secondary to *C diff*, endoscopy may show typical plaque-like lesions.<sup>40</sup> Endoscopic evaluation should be approached with caution, and it is relatively contraindicated to perform endoscopy in the setting of suspected moderate-to-severe HAEC because of risk of intestinal perforation.<sup>41</sup>

## Therapy

### Acute presentation

Children presenting with a suspected diagnosis of HAEC require broad-spectrum antibiotics and intravenous fluid resuscitation. At our institution, we provide a 20-mL/kg bolus of isotonic fluids followed by continued fluid replacement at one and one-half times the maintenance rate. Children who appear ill are immediately started on ampicillin, gentamicin, and metronidazole and require close hemodynamic monitoring. Patients presenting with severe HAEC and sepsis will need admission to the intensive care unit, aggressive fluid resuscitation, and in some severe cases, require vasopressors and ventilatory support.<sup>14</sup> Other less ill children are started on metronidazole alone to empirically treat for anaerobes, including *C diff*, an organism that can be associated with HAEC.<sup>42</sup> Rectal washouts with warm saline should be instituted as soon as possible. Most authors recommend use of a “large bore” rubber catheter (depending on the size of the child) and saline washouts at 10-20 mL/kg<sup>8,43</sup> Washouts may be performed 2-4 times daily, and cutting additional holes in the catheter will assist with instillation and drainage.<sup>44,45</sup> On initial presentation, we perform washouts until the effluent is clear and then continue twice daily until symptoms resolve. Alternate methods have been described, including a continuous irrigation method.<sup>46</sup> Regardless of approach chosen, it is critically important to distinguish these “rectal washouts” from retention enemata, in which fluid is instilled and retained. Retention of a large volume of fluid can cause further bowel distention, leading to increased risk of perforation.

### Role for diversion

Immediate diversion should be strongly considered for all patients presenting with sepsis and severe HAEC, especially in newborns when this is the initial presentation. Although recently, there is a trend toward managing stable neonates who have been treated for HAEC with a single stage procedure without creation of an enterostomy. Nonetheless, risk factors, such as delayed presentation, comorbid conditions, presence of HAEC, or multiple risk factors for HAEC in the preoperative period, warrant consideration of diversion when determining operative strategy. It has been suggested that stable children with delayed presentation of HD and HAEC may benefit from prolonged decompression with rectal irrigations and delayed pull through to allow the

bowel to resume a more normal caliber. A 2011 survey of pediatric surgeons in the United Kingdom and Ireland found that 19 of 34 would change to a staged operation in the setting of HAEC and 7 of 34 would do so in the setting of Down syndrome.<sup>47</sup> It is important to note that diversion will virtually always improve a patient's condition, but may not resolve HAEC in all cases.<sup>48</sup>

## Postoperative prevention

### Anal dilations and nitrates

In one study, Gao and colleagues<sup>49</sup> reported routine anal dilations for a period of 3 months after transanal pull-through procedure to prevent stricture. They found postoperative development of HAEC in only 2/34 (6%) patients, which is significantly lower than most published series. However, more recent data has questioned the need for daily dilation. A study by Temple et al<sup>50</sup> found daily dilation by family members to have similar efficacy to weekly dilations by medical staff with similar rates of HAEC, 18% and 12%, respectively. A separate study showed that weekly dilations by medical staff diminish negative psychological and social effects that families experience from routine anal dilations.<sup>51</sup> Because many pediatric surgeons do not routinely perform anal dilations after primary or staged pull-through operations, the value of routine anal dilatation as a potential means of HAEC prevention is uncertain at best.

Others have explored a less invasive method to relax the internal anal sphincter termed "chemical sphincterotomy" with use of topical isosorbide dinitrate or nitroglycerin applied to the anal canal. Topical nitrates serve as exogenous nitric oxide "donors," which are known to relax the smooth muscle of the anal sphincter. Tiryaki et al<sup>52</sup> treated a series of 6 children and demonstrated resolution of obstructive symptoms and recurrent episodes of HAEC. These authors advocate for the routine use of topical nitrates as a preventative measure against postpull-through HAEC.

### Prophylactic washouts

In addition to preoperative prevention, rectal washout is also effective for prevention of postoperative HAEC. Irrigations are performed with 10- to 20-mL/kg aliquots 1-2 times daily. Marty and colleagues<sup>53</sup> reported decreased incidence (7.5% vs 35.8%) and severity of HAEC in children receiving scheduled rectal washouts. Irrigations were started 1-2 weeks postoperatively and continued twice daily for 3 months, then once daily for 3 months. Similar results were found in a Spanish study of 37 children with HD.<sup>45</sup>

### Antibiotics and antimicrobials

Antibiotics are a mainstay of therapy for HAEC. Clinical suspicion of HAEC should prompt early antibiotic admin-

istration to prevent advancement of disease.<sup>54</sup> In addition to bacterial overgrowth, it is thought that alterations in bacterial composition<sup>55</sup> and certain pathogens (*C diff*, *Candida species*, *Rotavirus*) may increase risk of HAEC.<sup>54,56</sup> To avoid morbidity from septicemia, it is not only imperative to recognize HAEC but also to institute appropriate antimicrobial therapy. Metronidazole is the most commonly used agent for treatment of both simple and complicated disease and should be instituted even if patients are manifesting mild symptoms.<sup>54</sup> Alternatively, one may empirically use metronidazole and norfloxacin for antibiotic therapy as described by Rintala and Lindahl.<sup>57</sup> Stool cultures should be sent to identify causal organisms and also to rule out other infectious etiologies (such as, *Shigella*). Significant candidal infections should be treated with antifungals, such as fluconazole. Interestingly, microbial genomics offer a potentially powerful tool to evaluate the intestinal microbiota and may provide insight into pathogenesis of HAEC. One study analyzed changes in stool bacterial composition of a single patient with multiple episodes of HAEC and multiple courses of antibiotics. The authors suggest that application of this approach to additional patients may help guide antibiotic therapy in the future.<sup>55</sup>

As previously mentioned, for complicated or advanced cases of HAEC, we implement broad spectrum antibiotic therapy (ampicillin, gentamicin, and metronidazole). Those patients found to have *C diff*. in the setting of severe HAEC may benefit from addition of oral or rectal vancomycin.<sup>58</sup> Overall, studies comparing antimicrobial agents or regimens for the treatment of HAEC are lacking.

## Recurrent or refractory HAEC

Much has been written regarding the management of challenging Hirschsprung patients with "recurrent," "chronic," "chronic recurrent," or "refractory" HAEC. Not surprisingly, the number of episodes, or duration of symptoms that constitutes each term, is not agreed on among authors, thus making it difficult to compare studies and their results. Despite this lack of consensus, most authors describe patients who have failed antibiotic/washout regimens and "medical" therapy constituting multiple courses of antibiotics, and possibly trials of cromoglycate with continued recurrence of HAEC. For the purposes of this article, these terms may be used interchangeably, unless otherwise stated.

### Identifying underlying causes

When postpull-through patients present with recurrent HAEC, the pediatric surgeon must diligently use a strategy to evaluate these patients for potential anatomic and pathologic causes, and then have a rational approach to treat each cause.<sup>43,59-61</sup> A first step is to obtain a detailed history of enterocolitis, abdominal distention, failure to thrive, including dilations, washouts, laxatives, or antimotility medica-

tions. It is also helpful to review operative reports of the pull-through operation and pathology specimens from the original operation, if available. A physical examination should be performed specifically focused on presence of an anastomotic stricture. Water-soluble contrast enema is necessary to evaluate the anatomy of the pull through with attention given to the presence of stricture, massively enlarged post-Duhamel pouch, obstructing Soave cuff, dilated retained aganglionic segment, and kink or twist of the pull-through segment. Next, an anorectal examination under anesthesia should be performed to carefully evaluate the anal canal, and rectal biopsies taken to evaluate for ganglion cells and the presence of nerve trunk hypertrophy. Suction rectal biopsies are reported to be adequate to provide sufficient tissue in children 3 years and younger. It is recommended older children undergo full-thickness open biopsy. The primary goal is to evaluate for a retained aganglionic segment, aganglionic or transition zone pull-through, all of which can lead to obstructive symptoms, fecal stasis, and enterocolitis. Intestinal neuronal dysplasia has also been reported by multiple authors in the pull-through segment of patients with recurrent enterocolitis;<sup>59,60,62</sup> however, these findings have been questioned by others, suggesting that many of these may be the transition zone.<sup>43</sup> Anorectal manometry can be helpful as an adjunctive diagnostic test in selected patients in whom either an anatomic or pathologic abnormality has not been identified, or in patients with suspected internal anal sphincter achalasia or colonic dysmotility. Most authors have not found value in its routine use for work up of patients with recurrent HAEC.

## Approaches to manage patients with recurrent post pull-through HAEC

For patients presenting with anastomotic strictures, most authors recommend a trial of dilatations. If dilatations are unsuccessful in achieving clinical response, then redo pull through is recommended. One group advocates redo pull-through operations for retained aganglionic segment, aganglionic or transition zone pull-through, stricture, dilated Duhamel pouches, and obstructing Soave cuff. Their preferred strategy is a transanal Swenson approach with selective use of either laparoscopy or laparotomy.<sup>43</sup> In patients with a rectum frozen in scar, this group uses the posterior sagittal approach. Other authors have reported managing anastomotic stricture and Soave cuff obstruction with conversion to a Duhamel approach.<sup>60</sup> In cases of a dilated Duhamel "spur," the author has resected the spur with good response.<sup>63</sup> In patients that have had a Soave-type pull through (endorectal pull-through either minimally invasive transanal approach or traditional transabdominal approach), other authors prefer redo endorectal pull-through procedure.<sup>59,64</sup>

There is no consensus regarding the best approach for remedial procedures for patients with an identifiable pathologic or anatomic cause of enterocolitis. Furthermore, redo pull-

through operations are relatively uncommon procedures and are best performed by an experienced team. For a more extensive discussion regarding operative strategy for redo pull-through operations, please view the cited references.

In patients with recurrent or refractory HAEC in which no anatomic or pathologic etiology has been identified, a number of therapeutic approaches are described below.

## Medical approaches

### Antibiotics and antimicrobials

Despite the appeal of prophylactic antibiotic therapy to prevent recurrent episodes of HAEC, there is no supportive evidence to show efficacy, and furthermore, it may increase the risk of selecting resistant organisms. However, because of the potential morbidity of early HAEC becoming advanced, many practitioners have a low threshold for starting antibiotics at the first signs and symptoms of HAEC.

### Sodium cromoglycate

Sodium cromoglycate is a mast cell stabilizer frequently used in the management of asthma. Rintala and Lindahl<sup>56</sup> were the first to report using sodium cromoglycate to treat 8 patients with either chronic or recurrent HAEC (as described by the authors). Six of 8 patients had a favorable response to the treatment with a median follow-up of 14 months. Three of the 5 patients with chronic HAEC improved with a median decrease in daily bowel movements from 6 to 3 and more solid stools. Two of the patients did not respond to sodium cromoglycate after 4 months of treatment at which point it was discontinued. Two of the 3 patients with recurrent HAEC had an excellent response with complete resolution of symptoms. One patient developed an episode of HAEC after a rotavirus infection. No side effects of sodium cromoglycate were reported. This study found that sodium cromoglycate is an effective treatment modality of patients with chronic or recurrent HAEC. Although sodium cromoglycate is used to treat HAEC patients in some centers, to date, we can find no follow-up studies on the use of these agents.

## Surgical approaches

### Botulinum toxin therapy

Minkes and Langer<sup>65</sup> evaluated 18 postsurgical HD patients with persistent constipation, obstructive symptoms, or recurrent HAEC, and internal anal sphincter hypertonicity. They treated each patient with intrasphincteric botulinum toxin injections and followed the group prospectively for a 4-year period. In their study, they found 14 patients showed improvement in bowel function, 12 of these >1 month, and

5 >6 months, although they did not specify the number of patients with enterocolitis or which symptoms improved. Four patients developed transient encopresis that resolved within 3 weeks of treatment, and there were no adverse side effects. The authors concluded that this therapy was safe and a less invasive alternative to myectomy in these patients, and also showed that repeat injections are necessary for recurrent symptoms.

Koivusalo et al,<sup>66</sup> treated a series of 8 postsurgical HD patients with botulinum toxin injections with a median follow-up of 19 months. The major presenting symptoms of these patients were as follows: 3 with obstructive symptoms alone, 3 with obstructive symptoms and recurring enterocolitis, 2 with recurring enterocolitis. When focused on only the 5 patients with enterocolitis, one patient had complete resolution of symptoms, two others had significant improvement of enterocolitis but soiling was not eliminated, whereas the remaining 2 patients had little or no improvement. The authors concluded that although intrasphincteric botox injections were successful in some patients, it was difficult to predict which patients would benefit from this therapy.

Chumpitazi et al<sup>67</sup> studied a mixed population of 73 children with either surgically repaired HD or internal anal sphincter (IAS) achalasia, all of whom developed obstructive symptoms and/or enterocolitis because of inability of the IAS to relax. All the patients were treated with intrasphincteric botulinum toxin injections with a mean follow-up of 32 months. Within the HD group ( $n = 30$ ), there were 13 patients with enterocolitis requiring hospitalization. When the authors studied this subgroup of patients with HAEC, they found a decrease from  $2.3 \pm 0.6$  hospitalizations per year to  $1.0 \pm 0.3$  hospitalizations per year ( $P = 0.06$ ). The authors did not report on specific symptom improvement in this group. However, they found that the long-term response to botox varied according to the underlying diagnosis because children with IAS responded better than those with HD. Their study showed that the factors predicting a favorable long-term outcome were initial short-term improvement after the first botox injection and having internal anal sphincter achalasia rather than HD.

In summary, intrasphincteric botox injection for the treatment of recurrent HAEC appears to be safe and can be used for multiple injections if symptoms recur. This treatment reduces the number hospitalizations for enterocolitis and can be effective in improving symptoms in some patients; however, it is difficult to predict which patients will respond. Some authors have suggested that improvement of symptoms after botox injection predicts favorable response to myectomy/myotomy,<sup>65</sup> whereas others have reported data contradicting this relationship.<sup>67</sup>

### Posterior myotomy/myectomy

The transanal posterior myotomy/myectomy procedure was originally described for the definitive treatment of short-segment HD by Lynn<sup>68</sup> in 1966. Although uncommonly used today for the original purpose, it has been applied to patients

with recurrent HAEC after pull-through operation with moderate success. Weber et al<sup>69</sup> reported 14 patients with recurrent HAEC (10 Soave and 4 Duhamel) who all underwent myectomy as initial treatment, 11 (78%) responded with cessation of diarrhea, improved appetite and weight gain, and normal stool pattern. Two of the patients in the Soave group required additional procedures, one required sphincterotomy and the other underwent conversion to a Duhamel procedure; both responded and were deemed "cured." One patient in the Duhamel group subsequently required colostomy and eventually died of HAEC. The authors did not report long-term continence data in this group of patients. Wildhaber and colleagues<sup>70</sup> presented a group of 17 patients with recurrent HAEC either with or without retained aganglionosis, and showed a 75% response rate with the posterior myotomy/myectomy procedure with 23% having mild soiling. The authors point out that one advantage of the transanal posterior myotomy/myectomy procedure is that it is significantly less invasive than a redo pull-through operation. In the event that posterior myectomy is not successful in relieving enterocolitis, this does not preclude redo pull-through operation from being performed. One concern that has been raised regarding this procedure is the risk of incontinence in adulthood. Heikkinen et al<sup>71</sup> performed long-term follow-up (7-17 year) on 14 Finnish patients who underwent posterior myotomy/myectomy procedures as children and found that 4 had occasional or daily mild soiling and suffered soiling-related social problems.

### Internal sphincterotomy

Use of lateral internal sphincterotomy as a treatment for recurrent HAEC because of internal sphincter achalasia or "obstructive symptoms" has been reported with mixed results. Swenson et al<sup>7</sup> reported its use on 27 patients and abandoned the technique citing no significant benefit. Polley and colleagues<sup>72</sup> reported its application in 3 patients with "successful outcome" but did not include length of follow-up, and Blair et al<sup>73</sup> treated 4 patients and reported complete resolution of enterocolitis episodes. Marty et al<sup>74</sup> performed 8 internal sphincterotomies but did not report outcome of their patients. The known risk of fecal incontinence, with lateral internal sphincterotomy combined with its questionable benefit in these patients, suggests that application of this procedure for the treatment of refractory enterocolitis must be considered with the utmost caution.

### Recalcitrant HAEC

For patients with HAEC refractory to both medical treatment and appropriate surgical intervention, the last resort is diversion with either ileostomy or colostomy. Fortunately this is necessary in only a small subset of HAEC patients, often with

concomitant developmental delay, such as trisomy 21 or Bardet-Biedl syndrome. Although complete diversion is successful in treating HAEC in most of these refractory patients, it has been reported that a few patients continue to have HAEC even after diversion, although this is rare.<sup>9</sup> Interestingly, anecdotal observation of experienced pediatric surgeons have found that for some of these patients, this is a prolonged “temporary” diversion until around 5 years of age, when they seem to “outgrow” the HAEC. Some of these children can have their stomas successfully closed without recurrence of enterocolitis. Further research on this group of patients is needed to potentially identify factors that may predict positive or negative outcomes.

### HAEC and inflammatory bowel disease (IBD)

Levin et al<sup>15</sup> recently reported a series of 8 patients with HD who subsequently developed IBD 4-21 years after initial treatment. Six of these patients were given a diagnosis of HAEC that did not improve until it was recognized that they had chronic unregulated bowel inflammation more consistent with IBD. Once appropriate treatment for IBD was started, the patients responded. Although the clinical symptoms shared between HAEC and IBD, including pain, fever, diarrhea, and increased stool frequency, were present in some, if not all the patients, many also had features typical of IBD. These included anemia, elevated Westergren erythrocyte sedimentation rate (ESR), severe perirectal abscess, rectovaginal fistula post-repair, recurrent peristomal fistulae, and small bowel-fistula. Endoscopic findings revealed late inflammatory strictures and the presence of granulomata on intestinal biopsies. Although this group of patients is rare, any HD patient with chronic or recurrent HAEC symptoms who also develops these features of IBD should be worked up using upper and lower gastrointestinal endoscopy with biopsies, including appropriate inflammatory and serological markers for IBD.

### Summary

Applications of preventative strategies in high-risk patients combined with early aggressive treatment of HAEC are the goals of current therapy. Although progress has been made, the management of chronic and recurrent HAEC remains challenging for clinicians and patients alike. Only with a better understanding of the biological mechanisms causing HAEC can we develop novel rational prevention and treatment strategies for HAEC in the future.

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