Enterocolitis Complicating Hirschsprung's Disease

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10.1 Introduction

Enterocolitis is a clinical condition with symptoms including diarrhea, abdominal distension, pyrexia, colicky abdominal pain, lethargy and the passage of blood-stained stools [1]. Enterocolitis is a significant complication of Hirschsprung's disease (HD) both in the pre- and postoperative period [2]. Hirschsprung's-associated enterocolitis (HAEC) can occur at any time from the neonatal period onwards into adulthood and can be independent of the medical management and surgical procedure performed. Recurrent enterocolitis can occur even in the presence of a diverting colostomy which is termed "diversion enterocolitis" [3–5].

The incidence of enterocolitis ranges from 20% to 58% (Table 10.1) [6–13]. The incidence in the preoperative period is 16% and in the postoperative period is 18% [1]. Fortunately, the mortality rate has declined over the last 30 years from 30% to 1% [11, 13–15]. Results from Japan demonstrate a decline in mortality from 1978 to 1998 from 6.5% to 0.7% [13]. This decrease in mortality is related to earlier diagnosis of HD and enterocolitis, rectal decompression, appropriate vigorous resuscitation and antibiotic therapy.

Although the concept of HAEC was alluded to in the literature in 1950 by Burnard [16], Fisher and Swenson [17] in 1956 and Dorman [18] in 1957, it was not until 1962 that Bill and Chapman [19] presented the first definitive description of the condition.

10.2 Pathogenesis

Despite multiple investigations and studies, a complete understanding of the etiology of HAEC is still unavailable. Numerous theories have been put forward to explain its occurrence including a physical dilatation of the proximal bowel, variations in the mucin components and production, rotavirus, *Clostridium difficile*, increased prostaglandin E1 activity, mucosal immunity defects, a Schwartzman-type reaction, disordered motility associated with protein sensitization and sucrase-isomaltase deficiency. Other histological and immunological studies indicate that some patients are prone to recurrent HAEC

Table 10.1 Incidence of HAEC

Reference	Incidence (%)	Mortality (%)
6	38	0
7	35	3
8	34	0
1	32	4
9	30	10
10	27	4
3	25	3
12	23	1
13	17	0.7

due to persistent inflammation within the bowel, or an immune deficiency either local or systemic with defective white cell function [20–22].

10.3 Theories of Pathogenesis

10.3.1 Mechanical Obstruction

Bill and Chapman [19] argued in 1962 that partial mechanical obstruction was involved in the pathogenesis of HAEC causing mechanical dilatation of the proximal bowel leading to fecal loading and stasis resulting in further dilatation and thus mucosal ischemia and bacterial invasion which was cured by colostomy [19]. This suggests that enterocolitis only occurs in dilated ganglionic proximal bowel. However, this theory does not explain the enterocolitis that occurs in distal colon with a defunctioning proximal stoma, the occurrence of enterocolitis in postoperative patients or histological evidence of enterocolitis in aganglionic bowel [12, 13]. In discussing the theory of Bill and Chapman it is important to note that the length of the aganglionic segment has been identified as a possible risk factor for HAEC. Studies including our own have shown that longer segments of aganglionosis have a higher risk of HAEC [8, 9, 23]. It is postulated that the increased length of aganglionic bowel implies a greater proximal obstruction with greater intraluminal pressure, increased bacterial stasis and proximal dilation. However, other studies on this condition have shown no difference as regards length of the aganglionic bowel [11, 19, 24].

10.3.2 Sucrase Deficiency

In 1973 Ament and Bill [25] presented the case of a 6-year-old boy with chronic enterocolitis following surgery for HD. Clinical investigations revealed the presence of a sucrase-isomaltase deficiency, and the child recovered on a low sucrose diet. This led to the postulation that nonobstructed HAEC is caused by an inborn error of metabolism. Its is important to note that this has not been replicated and that Ament and Bill acknowledged that the boy was an Eskimo, and that 10% of Greenland Eskimos are sucrose-intolerant [25].

10.3.3 Shwartzman Reaction

Berry and Frazer [26] in 1968 suggested that HAEC is initiated by a sensitivity reaction similar to a Shwartzman reaction caused by intraluminal organisms invading the submucosa [26]. They injected endotoxin directly into the exteriorized rabbit bowel proximal to an obstruction and produced enterocolitis in six of nine animals.

10.3.4 Prostaglandins

A single case was reported by Lloyd-Still and Demers [27] of HAEC with fulminant unresponsive diarrhea which revealed high PgE1 levels [27]. In response to cholestyramine a 12-fold decrease in prostaglandin E (PgE) levels in the colostomy fluid was detected. It was postulated that increased PgE activity, enterotoxin, and bile acid malabsorption may be involved in HAEC [27].

10.3.5 Defective White Cell Function

In 1988 Wilson-Storey et al. [22] postulated that defective white cell function may be a predisposing factor for HAEC [22]. White cell counts were analyzed in nine patients with HD of whom five developed HAEC and ten age-matched controls. Their data showed a statistically significant difference between the neutrophil count (2.0, 3.6, 8.6×10^9/l) in those with HAEC, HD and controls, respectively. This relative neutropenia worsened in three patients during and after an episode of HAEC. Wilson-Storey et al. also postulated that white cells in HAEC patients are "sluggish" in response to the inflammation.

10.3.6 Immature Mucosa

Blood group-associated antigen Le^b is normally present in fetal colon and absent in a normal ganglionated bowel [28]. Fujimoto and Miyano demonstrated strong expression of Le^b which was uniformly present along the entire length of the crypts of the aganglionic bowel [20]. This expression in aganglionic bowel could indicate a proliferation of the immature crypt cells, or that the colonic mucosa has not matured and hence the mucosa persists in a fetal stage. Thus it is postulated that there is an underlying abnormality of the epithelium lining found in HAEC which may be causative rather than related to the effect.

10.3.7 Mucin

Other theories focus further on the role of increased and altered intestinal mucin/mucus. Clinically the voluminous amount of mucus produced during HAEC is quite obvious and dramatic. Needless to say this has led to speculation that the mucus is a pathogenetic factor in this condition. The preepithelial mucus or mucin consists of glycoproteins and secretory immunoglobulins (IgA) and acts as the first line of defense by binding and inactivating organisms. In the normal bowel most of the mucin is silated or sulfated, and thus there is relatively little neutral mucin present. The neutral mucin is present in the upper half of the crypts and the acid mucin in the

lower [20]. The colonic mucin is kept in a stable ratio by the rapid removal of epithelial cells in the crypts and the routine desulfation of the mucin by the bacteria [29].

In 1981 Akkary et al. performed rectal biopsies in ten patients with HD after formation of a colostomy and in six controls with normally ganglionated bowel, and reported abnormal mucin composition in the patients with HD [30]. They found a "marked increase" in the volume of sulfated mucin and that most of the goblet cells contained less mucin especially in patients with severe diarrhea [30]. They postulated that increased bacterial stimulation leads to both decreased mucosal cell renewal and increased sulfatization of the mucin causing abnormalities of the mucin ratio. This alteration of the ratio leads to increased adherence of enteropathogenic organisms to enterocytes. Changes in the mucin may lead to altered susceptibility to bacterial degradation [20]. Increased amounts of neutral mucin and a decrease in the acidic sulfated mucins were also detected in the resected enterocolitic bowel using PAS-AB staining [20, 31, 32].

Teitelbaum et al. proposed in 1989 that the presence of HD implies an alteration in the mucins of the large bowel with associated mucin retention and crypt dilatation [32]. Teitelbaum et al. proposed a histological grading system ranging from normal to gross abnormality using both histological features and the feature of mucin retention which is unique to HD and cystic fibrosis (Table 10.2) [32]. They demonstrated that 88% of patients with HAEC had grade III or higher while 83% of those without HAEC had grade II or lower. Despite the high incidence of HAEC in infants with trisomy 21, their histology findings were frequently inconsistent with their clinical features. This supports the theory that their decreased immunity allows increased susceptibility to HAEC with a less severe immune response. If patients with trisomy 21 were excluded from the study, 100% of patients with HAEC had grade III or higher. Teitelbaum et al. have used this grading system to predict the development of enterocolitis in patients with HD of grade III or higher. However, they admit that the uneven distribution of HAEC histological changes in resected specimens makes clinical correlation difficult. These histological changes demonstrate how the mucosa has become susceptible to enterocyte-adherent organisms which release toxins. The toxins cause both local (crypt abscesses, ulceration and perforation) and systemic (sepsis and coagulopathy) inflammatory responses.

Aslam et al. demonstrated that total mucin turnover is significantly reduced in patients with HD compared with to age-matched normal controls. Although ganglionated colon demonstrated similar mucin turnover alterations the changes were more significant in the aganglionic bowel [33]. This signifies an abnormal mucus defensive barrier in the colon of patients with HD, even in the histologically normal bowel. The same team also studied the colonic mucins of the proximal ganglionated bowel in nine patients with HD at the time of pull-through [34]. Radioactive precursors ^{35}S-sulfate and ^{3}H-glucosamine were added to the mucins of the intact remaining mucosa and the patients were followed for a mean of 30 months. They found that four patients without enterocolitis had a turnover rate six times higher than those with HAEC [34]. This reduced turnover of mucins will give rise to a defective mucus-defensive barrier allowing enterocyte adhesion and toxin release [34]. In 1999 Aslam et al. demonstrated that the mucin glycoproteins in children with HD, although quantitatively deficient, show no qualitative histological or immunological differences from those of normal controls [35]. The mucin gene expression and the quality of mucins was also similar to those of normal controls [35]. Yet those patients who developed HAEC had mucin turnover rates that were seven times lower than those without HAEC [35]. Gork et al. showed that mucin inhibits bacterial translocation in vitro across both fetal and adult cultured intact enterocyte monolayers [36]. Also in this study, they demonstrated that the inhibitory effect on translocation is lower in the fetal cells than in the adult cells.

Table 10.2 Histological grading system for HD

Grade	Histopathology
0	No abnormalities
I	Crypt dilatation and mucin retention
II	Cryptitis or two crypt abscesses
III	Multiple crypt abscesses
IV	Fibrinopurulent debris and mucosal ulceration
V	Transluminal necrosis or perforation

MUC-2 has recently been shown to be the predominant mucin gene expressed in human bowel [37]. Mattar et al. have shown that MUC-2 protein expression is significantly lower in patients with HD than in controls (19.8±15 vs 121±47) and not detectable during active enterocolitis [38]. The decline in MUC-2 expression in patients with no inflammatory response implies an intrinsic problem which could allow bacterial adherence and translocation. The authors suggest the use of probiotics prophylactically, such as *Lactobacillus casei* strain *GG*, in order to increase the epithelial expression of MUC-2 and possibly decrease bacterial translocation [38].

Overall the evidence has not proven whether mucin alteration is due to the underlying aganglionic condition or a result of the enterocolitis. However, the balance of data supports the concept that the mucin variations are an expression of an altered mucosal barrier and the underlying aganglionic process itself [38].

10.3.8 Intestinal Wall Defenses

Secretory IgA immunoglobulin provides a major immunological barrier in the gastrointestinal tract. IgA is the predominant immunoglobulin at all levels in the intestinal tract both in the lumen and within the wall. Albanese et al. have shown that secreted IgA binds to bacteria and prevents bacterial translocation across an intact segment of viable intestinal tissue [39].

Piebald mice have a congenital megacolon with absent distal ganglion cells, and hence are an excellent model of HD [40–42]. A number of studies have been performed in our center with a breeding colony of piebald mice to investigate the model and establish mucosal secretory function in HAEC [43, 44]. Two distinct patterns of mortality occur with the majority of mice (64%) characterized by becoming unwell acutely with evidence of acute enterocolitis at 3 to 4 weeks and then dying quickly or dying between 9 and 11 weeks due to ileus with massive abdominal distension and megacolon [43]. Interestingly two different immunological responses were evident. Those with a more acute history had acute splenitis and a severe diffuse lymphocytic response in the intestinal submucosa and lamina propria with a significantly raised level of IgA in contrast to controls and the late death group. The late death group had increased plasma cell distribution within the deep layer of the lamina propria only. This increased level of plasma cell infiltration in the ganglionic segment of the colon in the early death group implies that the local antigenic stimulation is the principle pathological event [43].

Wilson-Storey et al. postulated that there is a marked deficiency in the transfer of IgA across the intestinal mucosal membrane in patients with HAEC. They based this on the absence of secretory IgA in the buccal mucosa in patients with HAEC [17]. Five out of six patients with HD had no detectable secretory IgA in their saliva. These patients also had an increased amount of IgA in their buccal mucosal tissue. Imamura et al. demonstrated similar results in colonic resection specimens including elevated levels of IgM and J chain plasma cells in the bowel of those with enterocolitis [45]. Multiple factors including elevation of CD68-positive monocytes/macrophages and CD45RO-positive and CD57-positive natural killer (NK) cells were present in those with HAEC. Marked increases in IgA plasma cells in the lamina propria were found, yet there were a distinct reductions in the luminal IgA in four of the five patients with HAEC. Normal luminal and epithelial IgA was present in the ganglionated bowel.

Since 1976 the question has been asked as to whether the decrease of luminal IgA reflects a primary deficiency in transfer of IgA out of the cells onto the luminal surface or whether it is due to inflammatory change [46]. Turnock et al. attempted to answer the question as to whether or not there is a premorbid deficiency of the intestinal immune response in patients who develop HAEC [47]. They examined rectal suction biopsies of 20 patients with HD of whom eight developed HAEC. They found no evidence of a significant deficiency or difference in population in the IgA, IgM or IgG plasma cells in the lamina propria in patients with HD, HAEC or normal controls [47]. Overall there is evidence that IgA function and formation are normal in the cells but that there is a deficiency in the transfer of the immunoglobulin into the lumen to assist the mucin in its role in the front line of immunological response; however, this hypothesis has not been proven conclusively.

Mucosal neuroendocrine cells (NE) mediate intestinal function through synthesis and storage of neuroendocrine neuropeptides and biogenic amines which act as chemical messengers [48, 49]. Soeda et al. demonstrated in 1992 that NE cells are increased in the aganglionic segment of bowel in HD as opposed to the ganglionated bowel and normal controls [50]. In 1993 they noted a marked reduction in NE cells in ganglionated bowel in HAEC compared to those without. These diminished NE cells may represent an impaired immune response or a deficiency which may facilitate the initialization of inflammation [51]. This impaired immune response theory is echoed in trisomy 21. The combination of HD and trisomy 21 is associated with a higher incidence of enterocolitis with 50% of patients with trisomy 21 and HD developing HAEC in contrast to 29% among the normal population [1]. Infants with trisomy 21 have an intrinsic immune deficiency due to both decreased cytotoxic T-lymphocytes and derangement in humoral function which may explain their increased risk of HAEC [52–54].

Histological evidence of enterocolitis consists of a number of features including crypt abscesses, leukocyte aggregates, ulceration and Paneth cell metaplasia [31]. Paneth cells are normally present in the small bowel and secrete lysozymes which digest the bacterial wall membranes. Their presence in HAEC colon suggests an attempt at reinforcement of the mucosal immunity [31]. ICAM-1 is a cell surface intercellular adhesion glycoprotein which is involved in leukocyte recruitment when inflammation occurs. Kobayashi et al. have demonstrated that ICAM-1 shows increased expression in the endothelium of both the ganglionated and aganglionic bowel in patients with HAEC [55]. This emphasizes the importance of endothelial cell activation in HAEC pathogenesis. Elhalaby et al. postulated that the occurrence of a single episode of HAEC can alter intrinsic intestinal immunity by causing a chronic change to the mucosa to an increased the risk of further episodes [8]. This would help to explain the lower but real recurrence rate of HAEC following a "diversion" colostomy or a successful pull-through [8, 9].

10.3.9 Abnormal Motility and Macrophages

Suzuki et al. in 2004 used endothelin receptor null rats as a model for long-segment HD as they have a megaileum proximal to a constricted aganglionic region [56]. They

showed that the number of macrophages is increased in the tunica muscularis suggesting that macrophages play an important role in the inflammation of tunica muscularis in rats [56]. They postulated that the increased numbers and activation of macrophages may result in damage to networks of interstitial cells of Cajal leading to disordered intestinal rhythmicity in regions of the gut in which myenteric ganglia are intact. This disordered movement may encourage stasis, bacterial growth and, with the abnormal mucins, increased translocation.

10.4 Microbiology

Bacteria and viruses have been linked to enterocolitis by a number of studies. *Clostridium difficile* was first reported in 1982 by Thomas et al. when high titers of the toxin were detected in four of six patients with HAEC [57]. In 1986 Thomas et al. detected the cytopathic toxin in 7 of 13 (54%) and *C. difficile* was isolated in 77% of children with HAEC [58]. In the control groups *C. difficile* was isolated in 18% of those with HD and in 30% of children without. Thomas et al. postulated that the toxin was pathogenetic due to the incidence of toxin in the feces, the magnitude of the toxin levels and the isolation rates for *C. difficile* which were significantly higher in HAEC patients than in those without HAEC or even HD [58]. The possibility that HAEC could prevent the development of a "benign" colonic bacterial flora and aggressively treating *C. difficile* could improve this made this a very exciting theory. However, this has not been proven on subsequent investigations: 50% of all patients with HD have *C. difficile* and there is no variation in incidence between before and after surgery [59]. Wilson-Storey et al. in 1990, demonstrated a broad spectrum of organisms present in the stools with no significant difference in the Clostridium carriage rate between those with HAEC and those without HAEC or normal controls [60]. Stool samples in our center reveal a wide range of colonic flora present during episodes of HAEC. However, after an episode of enterocolitis, 70% of patients with HAEC have *C. difficile* present as opposed to 42% of those without HAEC [61]. It is postulated that after the initiation of the enterocolitis episode alteration in mucosal immunity allows *C. difficile* to flourish. Although it may not be causative, it can significantly complicate the colitis. Pseudomembranous colitis with stools positive for *C. difficile* is rare and has been reported in four patients with a 50% mortality despite vancomycin therapy [62].

Bacterial adherence has been viewed as an important factor for the last 15 years being demonstrated histologically in up to 40% of pull-through specimens in patients with prior HAEC. When in the mouse model intestinal mucus was removed there was an increased adherence of *Escherichia coli* colonic mucosal layers [63]. *Escherichia coli*, *C. difficile* and *Cryptosporidium* were the adherent organisms found, suggesting that the adherent nature of the organism is an important factor. Suzuki et al. observed abnormal intestinal flora with a marked increase in gram-negative aerobes (Enterobacteriaceae) and anaerobes (Bacteroidaceae) in the distended region of the small intestine of their endothelin receptor-null rats [56].

Imamura et al. hypothesized that the diversity of the altered local response in HAEC is due to a multifactorial microbiology etiology [45]. They examined the entire resected colon from 12 patients with HD. CD57-positive NK cells which act as antiviral agents were found to be significantly increased in the ganglionic segment of the HAEC patients while no difference was found in those without enterocolitis or the normal controls. This has led to the postulation that the increase in these antiviral cells implies a viral etiology [45].

Wilson-Storey agrees that HAEC has a multifactorial infective etiology [61]. Rotavirus was identified in seven of nine patients with enterocolitis [60]. Of note, there were no symptoms of vomiting in these patients which is pathognomonic for rotavirus gastroenteritis. Also there was no evidence of contact before, during or after admission to hospital [60]. However, these results have not been replicated.

10.5 Pathology

Historically in 1886 Harold Hirschsprung described "deep ulcerations that penetrate to the serosa … an abscess under the mucosa … mottled spaces that can be seen in the submucosa containing pus" in his first report of the condition [64]. Thus he became the first to describe a number of key pathological features of HAEC. Histological evidence of enterocolitis consists of a number of features including crypt abscesses, leukocyte aggregates, ulceration and Paneth cell metaplasia [31]. Paneth cells are normally present in the small bowel and secrete lysozymes which digest the bacterial wall membranes. Their presence in the colon of those with HAEC suggests an attempt at reinforcement of the mucosal immunity [31].

10.6 Risk Factors for Enterocolitis

A number of factors have been proposed as important in the etiology of HAEC. These factors include delay in the initial diagnosis of HD, gender, a family history of HD, and the presence of trisomy 21. Delays in the diagnosis of HD leads to a higher incidence of enterocolitis as the presenting condition [65]. Our own series [9] in 1994 revealed that the incidence of enterocolitis in neonates increased from 11% in the first week of life to 24% after. In Ann Arbor a decrease in the incidence of preoperative enterocolitis has been explained by a protocol of early diagnosis of HD and washouts. The incidence of preoperative enterocolitis has also significantly fallen in Japan. In a nationwide study of 3852 patients over 30 years the

incidence fell from 29% in 1978–1982 to 17% in 1998–2002 [13]. Historically early decompression enterostomy was recommended but now commencement of an early washout program and prompt surgery are viewed as key features in prevention of HAEC [66]. The length of the aganglionic segment has been identified as a risk factor. Studies have shown that HAEC is significantly more common in patients with aganglionic segments longer than the sigmoid [8, 23]. Our own experience reflects this result [9]. A neonate with total colonic aganglionosis can present with perforation of the ganglionic bowel. However, some studies on this condition have found no difference as regards length of the aganglionic bowel [11, 19, 24].

Some studies have shown a higher incidence since the introduction of the pull-through procedure ranging from 2% to 27% [67]. The high HAEC incidence of 21% has been reported after Swenson's pull-through operation by Swenson himself in a 40-year follow-up [12]. However, Wildhaber et al. [68] demonstrated no correlation between the incidence of HAEC and the type of pull-through performed. Higher HAEC incidences of up to 55% have been noted in Ann Arbor, but the center acknowledges a very low threshold for diagnosis and treatment [69, 70]. Our study, similar to that of Polley et al. [71], found no difference in the incidence of HAEC following different types of pull-through [9]. No increase in HAEC has been found in the postoperative period after a primary pull-through without stoma formation [6]. Down's syndrome is associated with an incidence of 3–16% of HD of all causes [72, 73]. The combination of HD and trisomy 21 is associated with a higher incidence of postoperative morbidity, prolonged hospitalization and poor long-term bowel function. Infants with trisomy 21 have an intrinsic immune deficiency due to both decreased cytotoxic T-lymphocytes and derangement in humoral function which may explain their increased risk of HAEC [74–76]. Of patients with trisomy 21, 50% develop HAEC as opposed to 29% in the normal population [1]. In our experience 47% of patients with trisomy 21 and HD develop one or more episodes of HAEC [72, 73]. HAEC occurs in 54% of patients with trisomy 21 [24].

Some postulate that the occurrence of a single episode of HAEC can alter intrinsic intestinal immunity leading to an increased risk of further episodes [8]. Carneiro et al. [1] reported that HAEC occurs predominantly in females (50% vs 29%); however, although this has been noted by others, it has not been found to be statistically significant [8, 77].

The presence of associated anomalies is also associated with an increased incidence of HAEC. Klein et al. [78] initially reported associated anomalies in 35% of patients with HAEC in 1984. Carneiro et al. and Elhalaby et al. reported HAEC in 53% and 47% of those with anomalies, respectively [1, 8]. A lower incidence of 15% was noted in South Korea [3].

In 1977 we reported a case of intestinal neuronal dysplasia (IND) in association with HD [79]. In 1995 10 of 31 patients following a definitive pull-through procedure were demonstrated to have IND in the proximal margin of the resected bowel [80]. All ten patients with IND had persistent bowel problems after the definitive operation for HD, including enterocolitis (n=5), soiling, and constipation. Only 4 of the other 21 patients had persistent bowel symptoms. This suggests that IND is commonly associated with HD, and emphasizes the importance of histochemical examination of the resected segment to predict postoperative bowel function in patients with HD.

Our experience demonstrates that although HAEC does occur with a defunctioning colostomy, its incidence is substantially lower [9]. Hackam et al. [77] evaluated 62 cases of HAEC in 33 patients at a mean of 8 months from definitive surgery. They found no significant difference in gender, age at pull-through and weight at surgery, the type of operation, or the number of stages. The presence of an anastomotic leak and bowel obstruction requiring release of adhesions were significant risks for HAEC with a relative risk of 2.8 and 3.0, respectively [77].

10.7 Clinical Presentation and Diagnosis

As stated at the start of this chapter enterocolitis is a clinical condition with diarrhea, abdominal distension, pyrexia, colicky abdominal pain, lethargy and the passage of blood stained stools [1]. A grading system for the clinical features of HAEC is presented in Table 10.3. In the neonate the classical presentation consists of a history of constipation from birth associated with occasional loose foul-smelling stools and progressive abdominal distension. Among neonates with HD, 16–33% present with diarrhea [2, 8, 9, 15]. The presence of diarrhea is pathognomonic of enterocolitis which occurs in 93% of patients with HAEC [1, 2, 8, 9, 12, 23]. Vomiting rarely occurs in HAEC. A markedly distended hyperresonant

Table 10.3 Clinical grading system for HAEC

Grade	Clinical symptoms		
	Explosive diarrhea	Abdominal distension	Systemic manifestations
I	Mild	Mild to moderate	None significant
II	Moderate	Moderate to severe	Mild
III	Severe	Marked	Shock or impending shock

abdomen occurs in 32–83%, vomiting in 9–76%, pyrexia in 12–54%, and less commonly rectal bleeding in 5–9% of patients with HAEC [8]. Rectal examination either by digit or soft catheter which is both diagnostic and therapeutic results in a characteristically explosive foul smelly stool and gaseous decompression which once witnessed is never forgotten. Patients after a pull-through operation or those with a defunctioning stoma will present in the same fashion.

The significant morbidity associated with HAEC occurs with the toxic megacolon which is characterized by bilious vomiting, fever, dehydration, marked abdominal distension, and signs of shock [81]. Fortunately, bowel perforation is a rare complication occurring in only 2–3% of patients [1, 8].

Although in the majority of patients the diagnosis can be made easily on clinical evaluation, plain abdominal radiographs are the most useful investigation. Simple anterior-posterior and lateral decubitus abdominal radiographs can show thickening of the bowel wall, mucosal irregularity, dilated bowel loops, pneumoperitoneum and evidence of toxic megacolon (grossly dilated colonic loop) (Fig. 10.1). A large 40-year study of 880 patients following Swenson's procedure revealed a 3% incidence of spontaneous perforation [12].

A barium enema in a patient with HAEC can demonstrate mucosal nodularity, ulceration and edema, speculation, narrowing of the anorectal junction and colonic dilatation (Fig. 10.2). However, most of the radiological findings can persist after the cessation of the active enterocolitis and have no specificity. Elhalaby et al. [8] assessed 150 plain radiographs acquired during and between episodes of HAEC. Colon dilatation was the most radiologically sensitive sign (90%), but it had a sensitivity of only 24%. "Intestinal cut-off" sign which appears when the gaseous intestinal dilatation is abruptly cut off at the pelvic brim was both sensitive (74%) and specific (86%) for HAEC.

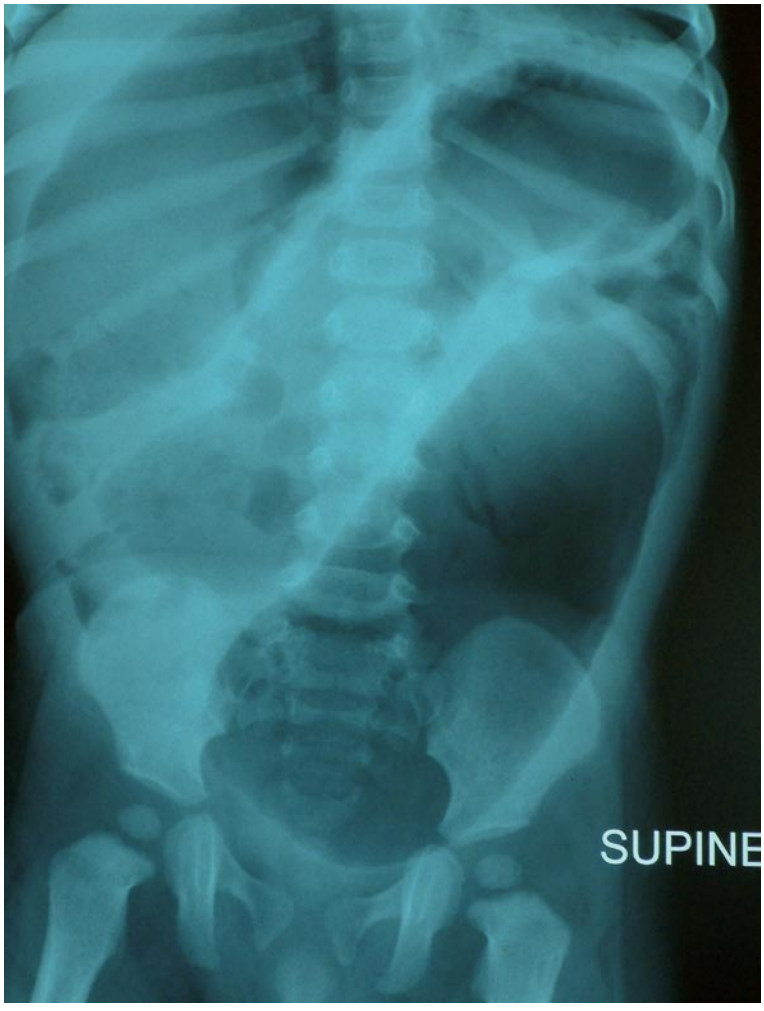

Fig. 10.1 Plain abdominal radiograph demonstrating thickened bowel wall, gross distension and the "pelvic cut-off" sign

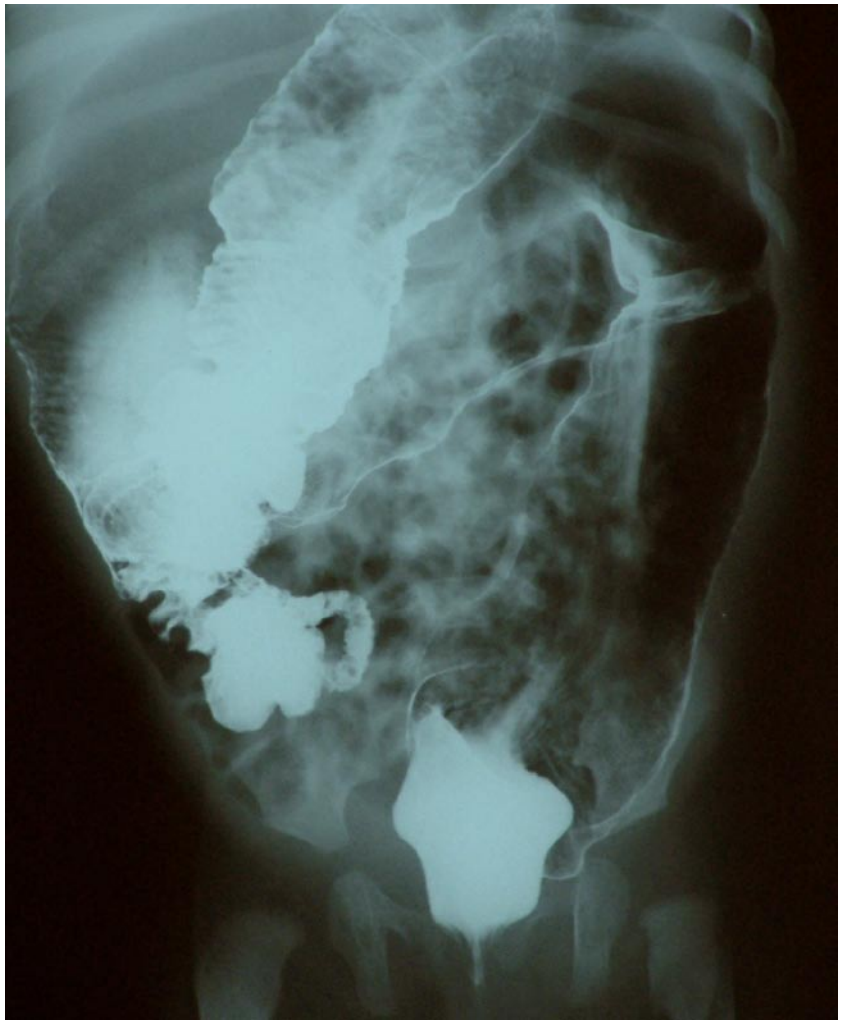

Fig. 10.2 Barium enema demonstrating colonic distension, speculation, edema and mucosal nodularity

10.8 Treatment

The key step in the initial management of a patient with HAEC is urgent resuscitation and correction of electrolytes. Shim and Swenson [82] recommended the use of a flatus or rectal tube to enable colonic decompression. Rectal washouts should be performed as soon as possible using a large-bore soft catheter with multiple side holes. The tube is well lubricated and advanced into the colon. In preoperative HAEC the tube should be passed into the transient zone if technically possible. Chest tubes with extra side holes have been used with some success in our institution to treat patients with HAEC who do not decompress via smaller catheters. Repeated tube decompression and gentle rectal washouts with 30–50 ml of normal saline make a significant clinical impact on these patients.

Vancomycin can be given either orally or via enema if *C. difficile* is found on stool culture. It has been reported by Carneiro et al. [1] to be successful in 14 of 15 "stool-positive" patients with episodic enterocolitis. Oral metronidazole has also been used with some success. Clinical deterioration in the neonate particularly those with long-segment disease in which washouts have a high failure rate may require an emergency decompression colostomy.

Concerns over the mortality rate due to fulminant enterocolitis in the postoperative period led Marty et al. [10] to suggest routine postoperative rectal washout to decrease both the incidence and the severity of episodes of enterocolitis following definitive surgery. They recommend a policy of rectal irrigation performed by the parents commencing 2 weeks following surgery twice daily for 3 months followed by once daily for 3 months. This

policy reduced their incidence of HAEC from 36% (34 of 95 patients) to 10% (4 of 40 patients).

In episodes of recurrent enterocolitis which can develop in up to 56% of patients, anal dilatation has been recommended [8]. However, prior to commencing a treatment regimen a repeat contrast enema should be performed to rule out a mechanical obstruction. In our center rectal biopsies are also taken to ensure the presence of ganglionated bowel. Patients with a normal rectal biopsy may require a sphincterotomy [8, 12]. Wildhaber et al. [69] found that 59% of patients had recurrent enterocolitis of whom 75% were symptom-free following a posterior myotomy/myectomy. Similar results have been reported by Menezes and Puri [83]. Redo pull-through operations when appropriate appear to be as effective as primary procedures in terms of continence and stooling frequency, and can decrease episodes of HAEC [84]. Rintala and Lindahl [85] treated eight patients with recurrent HAEC with sodium cromoglycate, a mast cell stabilizer that is used successfully in patients with inflammatory bowel disease. Significant clinical improvements were noted in six of the eight patients, four of whom had trisomy 21. No side effects of sodium cromoglycate were noted. Sodium cromoglycate may be a useful adjunct in the therapy of recurrent HAEC, especially in the difficult management of trisomy 21 combined with HD.

10.9 Prognosis

The medical management of those with HAEC is 2.5 times more costly than of those with just HD. Mortality rates in enterocolitis have fortunately fallen from 30% to 1% [13, 32]. Results from Japan demonstrate a decline in mortality from 6.5% in 1978 to 0.7% in 1998 [32]. This decrease in mortality is related to earlier diagnosis of HD and HAEC, rectal decompression, appropriate vigorous resuscitation and antibiotic therapy [1, 65, 86].

However, despite the improvement in mortality rates in HAEC, the morbidity has a profound impact with prolonged hospitalization with a mean of 13 days ranging from 6 to 29 days [1]. Teitelbaum et al. found that neonates with HAEC have a mortality rate of 5% and a morbidity rate of 30%, and their hospitalization is twice as long as neonates without HAEC [32].

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