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Enterocolitis complicating Hirschsprung's disease

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Enterocolitis remains a relatively common complication of Hirschsprung's disease with significant morbidity and mortality. The etiology of Hirschsprung's enterocolitis (HEC) is multifactorial and remains poorly understood. Preventative measures and better treatment modalities will evolve out of a better understanding of the underlying pathophysiology. Prompt recognition of HEC allows early intervention and a potential reduction in disease severity and mortality. This review of HEC describes the epidemiology, clinical and pathological features and current best practice in management. Some of the areas of research into etiology and treatment are discussed.

Hirschsprung's enterocolitis (HEC) is the most serious and potentially life-threatening complication of Hirschsprung's disease (HD). Swenson and Fisher recognized the association in 1956 but it was first described in detail by Bill and Chapman in 1962.[1]

Caneiro and coworkers defined HEC as a clinical syndrome of diarrhea, abdominal distension, fever, colicky abdominal pain, lethargy, and the passage of bloodstained feces.[2]

Despite advances in the treatment of HD, enterocolitis remains a relatively common complication with significant morbidity and mortality.[1] The mortality has however dropped significantly in the last 10 to 15 years[2] due mainly to improvements in critical care. As the etiology and pathophysiology are poorly understood prevention remains a difficult problem. This review of HEC describes the epidemiology, clinical and pathological features and current best practice in management. Some of the areas of research into etiology and treatment are discussed.

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Case report

HS, a patient with trisomy 21, an associated cardiac anomaly (atrial septal defect) and a left hydroureter, presented on day 15 of life with abdominal distension and bilious vomiting. A diagnosis of Hirschsprung's Disease was made on rectal suction biopsy and a primary Duhamel pullthrough was performed at 21 days of age. Following the pullthrough procedure HS suffered ongoing feeding difficulties, intermittent abdominal distension and periodic foul-smelling stool managed with intermittent oral metronidazole and microlax enemata. Twenty-one months following her surgery for HD she was admitted under the care of the pediatricians with diarrhea, abdominal distension, lethargy, pyrexia and dehydration. Stool and blood cultures were negative and a course of metronidazole was commenced. HS was discharged on day 11 but represented 5 days later with ongoing symptoms of increasing severity and HEC was diagnosed. Intravenous (IV) antibiotic and fluid therapy was commenced but 12 hours after readmission HS suffered an EMD arrest (electromechanical dissociation) secondary to hypovolemia, was resuscitated and admitted to the pediatric intensive care unit (PICU). She subsequently developed respiratory, renal and liver failure with a coagulopathy. Stool samples were positive for *Clostridium difficile* toxin

Table 1 Incidence of Hirschsprung's enterocolitis (listed chronologically, expressed as % age of all HD)

Reported Series	Incidence of HEC % (*n*)	HEC Present at Diagnosis of HD % (*n*)	Pre-operative EC % (*n*)	Postoperative Enterocolitis	
				Post-stoma % (*n*)	Post-pullthrough % (*n*)
Bill 1962[1]	50 (24)	not stated	44 (21)	0	35 (13)
Swenson 1975[5]	not stated	24 (120)	24 (120)	0	34.2 (164)
Kleinhaus 1979[3]	not stated	15 (168)	not stated	0	9.8 (98)
Teitelbaum 1988[13]	24 (19)	16.3 (13)	16.3 (13)	2.6 (2)	5.3 (4)
Cameiro 1992[2]	32 (24)	13 (10)	13 (10)	9 (7)	9 (7)
Rescorla 1992[4]	18 (47)	5.7 (15)	5.7 (15)		12.3 (32)
Blane 1993[11]	not stated	not stated	not stated	not stated	33 (57)
Surana 1994[7]	30 (41)	12.5 (17)	18.5 (25)	2.5 (3)	18.3 (20)
Elhalaby 1995[20]	33.9 (57)	12.5 (21)	12.5 (21)		26 (44)
Moore 1996[15]	21.6 (71)	16.6 (55)	16.6 (55)	0	11 (36)
Sarioglu 1997[18]	22 (113)	not stated	26 (79)	0	14 (34)
Murthi 2003[27]	not stated	11 (7)	11 (7)	0	22 (14)

and treatment with IV metronidazole and cefotaxime, and vancomycin via the naso-gastric tube was commenced. HS remained dependent on peritoneal dialysis and inotropes for 27 days, and required ventilatory support for 42 days. Due to excellent critical care facilities she made a gradual recovery from her multiorgan failure and was discharged to the ward on day 48. She continued to require parenteral nutrition for a further 4 weeks and was then discharged home. HS has had two further admissions with milder episodes of HEC 25 and 29 months after her definitive surgery. There are ongoing problems with her stooling pattern but she has otherwise remained well since then.

This case illustrates some of the salient features of HEC discussed in this review and highlights the importance of good critical care support and early recognition of HEC.

Epidemiology

Incidence

The incidence of HEC varies markedly between published series (17% to 50%) which may be due to the use of different diagnostic criteria. The mean incidence is 25% (see Table 1).

An early series found that 87% of enterocolitis occurred preenterostomy and accounted for all of the deaths in their series.[1] The greatest risk of developing HEC is before diagnosis of HD. EC is the presenting feature of HD in 5 to 24% of infants[3-5] and it tends to be most severe in this group.[6]

HD is thought to be rare in prematurity but has been reported in 4 premature neonates (5% of their patients) who presented with necrotizing enterocolitis (NEC).[2] In this group the risk of perforation was found to be very high.

HEC has been described in patients with a defunctioning stoma but this is rare.[7]

The incidence of postpullthrough EC varies from 5 to 35% in reported series.[1,8-10] It can occur in the immediate postoperative period or later, even more than a year after definitive surgery.[1] In one series the mean and median times of presentation were both greater than 18 months after surgery.[11] Swenson reports, however, that the greatest risk of EC is within the first year after definitive surgery; 92% of their patients had the last episode of EC requiring hospital admission within 2 years of their pullthrough procedure.[5]

Recurrent enterocolitis varies in incidence from 5.2% to 41%.[1,2,7] The frequency of bouts of HEC tend to decrease with time.[12] Chronic symptoms are particularly common in children with trisomy 21.

The incidence of HEC has declined over the last 40 years due to improved and more prompt diagnosis of HD but it has remained a major cause of morbidity and mortality.

Risk factors for HEC

Delay in diagnosis of HD beyond 1 week of age has been shown by several authors to increase the risk of HEC. Neonates presenting with enterocolitis do so at an average age of 16 days.[13]

Klein and coworkers reported no cases of enterocolitis in those infants who underwent decompressive formation of stoma in the first 2 weeks of life.[14] Surana and coworkers found that 11% of those diagnosed with HD in the first week of life presented with EC, compared with 24% with EC as the presenting feature of HD after the first week of life.[7] Kleinhaus and coworkers concluded from their series that a definitive diagnosis must be established within the first month of life in those children with suspected HD if the incidence of HEC is to be kept to a minimum.[3]

Trisomy 21 is a well known risk factor for the development of HEC and Carneiro reports an incidence of 50% in children with Down syndrome compared with 29% in all other children.[2] This increased incidence has been confirmed in many other series.[7,13,15]

Table 2 Mortality related to Hirschsprung's enterocolitis (HEC) listed chronologically

Reported Series	Mortality (% age of all HEC) (*n*)	Pre-operative (% age of all pre-op HEC) (*n*)	Postoperative (% age of all post-op HEC) (*n*)	
			Post-Stoma	Post-Pullthrough
Bill 1962[1]	33 (8)	39 (8)	0	0
Swenson 1975[5]	not stated	not stated	0	9.7 (16)
Kleinhaus 1979[3]	39 (103)	30 (47)	0	9.2 (9)
Teitelbaum 1988[13]	5 (1)	5 (1)	0	0
Rescorla 1992[4]	8.5 (4)	27 (4)	0	0
Cameiro 1992[2]	4.1 (1)	0	14.2 (1)	0
Surana 1994[7]	9.7 (4)	0	100 (3)	5 (1)
Elhalaby 1995[20]	0	0	0	0
Sarioglu 1997[18]	1.2 (6)	7.6 (6)	0	0
Murthi 2003[27]	0	0	0	0

Some series report an increased incidence of HEC with a long segment of aganglionosis.[4,9,16,17] Surana and coworkers found a 28% incidence of HEC in those with rectosigmoid involvement compared with 38% in those with long-segment or total colonic aganglionosis.[7] These findings have not, however, been confirmed in other studies.[1-3,13,18]

Genetic factors may predispose to the early onset of EC.[3,19] A family history of HD is known to predispose to HEC and in a study by Carneiro and coworkers 57% of patients with positive family histories compared with 29% of those without developed HEC.[2] This may be due the fact that those patients with a positive family history tend to have longer segment disease. These two risk factors for HEC have not been assessed independently in any of the reported series.

An increased incidence of HEC has been noted in those patients with major associated anomalies (including cardiac, gastrointestinal, genitourinary, central nervous system). Carneiro and coworkers reported a twofold increase in the incidence in those with associated anomalies compared with those without other anomalies.[2] This was confirmed by Elhalaby and coworkers who found an incidence of 47% compared with 29% in their series.[20] These findings, however, may be due to the large number of children with associated anomalies that have trisomy 21 in both series and were not studied as a separate group.

Carneiro and coworkers report a lower incidence after Duhamel procedure[2] and Kleinhaus, Ikeda and more recently Moore report a significantly higher incidence of postpullthrough EC after Swenson's procedure.[3,9,16] The procedure has since been modified to a more distal anastomosis and the majority of recent series found the incidence of postpullthrough EC to be unrelated to type and timing of definitive surgery.[2,7,10,21]

Anorectal stenosis or stenosis at the anastomotic site following primary pullthrough procedure predisposes to the onset of EC.[3,13] In a series reported by Hackman and coworkers the only significant risk factors for the development of postpullthrough HEC were postoperative complications related to the anastomosis, such as anastomotic leak or stricture.[10]

Previous episodes of HEC have been reported to be a risk factor[1,3,5,22] and some authors have speculated that early onset EC in HD permanently alters the defense mechanisms of the intestine and therefore predisposes the patient to recurrent episodes. Other studies, however, do not report such an association.[2,13,21]

Morbidity and mortality

The mortality of HD is very low but most series report that the majority of deaths that do occur are related to EC. Swenson and Davidson reported a mortality of 33% after onset of enterocolitis compared with 4% in HD patients without EC.[23] In their analysis of the causes of death in HD, Frank and Nixon found that 56% of all deaths could be attributed to HEC. EC was the single most common cause of mortality in the preoperative, postcolostomy and postpullthrough groups.[24]

The reported mortality varies greatly (0 to 39%) (see Table 2). HEC present at diagnosis of HD and postoperative EC were associated with a high risk of death in earlier studies.[3,25,26] The mortality of HEC has fallen over time[22,10,27] presumably due to improved critical care.

Murthi reported that EC at presentation of HD was the only statistically significant risk factor for poor outcome after Soave-Boley endorectal pullthrough procedure.[27] It remains unclear, however, whether a subgroup of patients with HD have factors such as abnormal gut mucosa predisposing them to poorer long-term functional outcome as well as EC or whether the HEC at presentation compromises their outcome from pullthrough surgery.

In our own experience mortality has been markedly reduced over recent years due to vast improvements in supportive care in the pediatric intensive care unit (PICU). However, EC still remains the major source of morbidity in HD[2,6,7] and may lead to lengthy and complicated hospital admissions. Early recognition is needed to prevent serious morbidity and death.

Clinical presentation and diagnosis

The clinical features of EC complicating HD were first characterized by Bill and Chapman.[1]

Since then a number of authors have reported the following features in order of decreasing frequency: diarrhea (foul smelling, explosive and watery) 80 to 100%, abdominal distension 30 to 83%, vomiting 10 to 77%, explosive expulsion of flatus and liquid feces on rectal examination 30 to 69%, abdominal pain 20 to 30%, pyrexia 11 to 50%, lethargy 30%, blood in stools 2.5 to 10%, bowel perforation 2 to 5% and shock.[2,7,18,28]

HEC can be difficult to differentiate from infectious childhood gastroenteritis and postoperative complications such as adhesive small bowel obstruction or intraabdominal abscess formation. The disease varies from mild diarrhea of short duration with no systemic effects to severe fulminant enterocolitis with gross abdominal distension and severe systemic involvement leading to septic shock. Hypovolemic shock can develop extremely rapidly and unless vigorous resuscitation is commenced may lead to death within 24 hours.[1]

Elhalaby and coworkers developed a clinical grading system ranging from mild disease (grade I with no systemic manifestations) to severe disease (grade III with shock or impending shock) but this is not widely in use.[20]

Diagnosis is based on a history of HD or features suspicious thereof followed by abdominal distension and diarrhea. The abdomen is distended and tympanic on percussion and there is often a forceful discharge of flatus and foul smelling liquid feces on removal of the finger following rectal examination.

Abdominal radiographs may reveal a distended loop of colon often associated with small bowel dilation and/or multiple air fluid levels (see Figure 1). There may be thickening of the bowel wall and mucosal irregularity and if perforation occurs a pneumoperitoneum is seen. In some cases pneumatosis intestinalis may be seen, making it difficult to differentiate between NEC and EC complicating HD. Blane and coworkers describe an intestinal "cutoff sign" in the rectosigmoid region with abrupt termination of gaseous distension and an absence of air distally, which was seen in 74% of their patients with acute EC.[11] Contrast enema shows an irregular mucosal lining, with ulceration and cobble-stoning (see Figure 2A and B); it is, however, not recommended as an investigation during the acute phase of HEC due to the high risk of perforation.

Rectal biopsy may be performed as part of the investigation for HEC but is not recommended during the fulminant phase as there is a high risk of perforation. The biopsy may show the classical pattern of HEC but also serves to confirm that ganglion cells are present after pullthrough procedure and some authors have reported intestinal neuronal dysplasia in association with HD, which may contribute to the development of HEC.[29] NEC in term infants should raise suspicion and a rectal suction biopsy should be performed. HD should also be considered in some premature infants with NEC, as this may be a presenting feature.

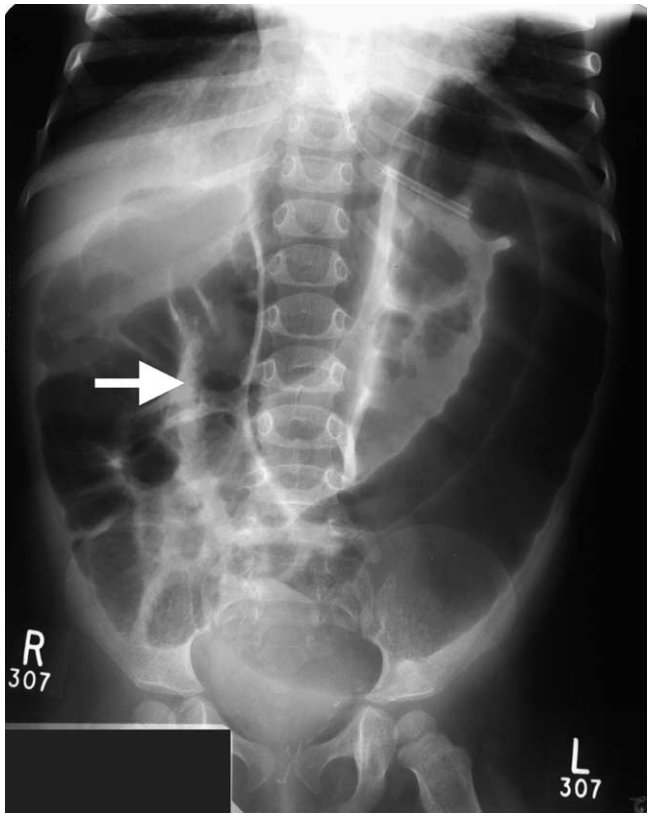

Figure 1 Abdominal radiograph of a 3-year-old girl with HEC showing gaseous distension of the large bowel. Toxic megacolon is seen with evidence of mucosal thickening (arrow).

Chronic HEC is characterized by persistent diarrhea or loose stools, soiling, intermittent abdominal distension, nausea, vomiting, and poor feeding leading to failure to thrive. Recurrent bouts of enterocolitis after pullthrough surgery should be investigated by contrast enema, endoscopy and rectal biopsy to exclude a mechanical cause such as obstruction in the neo-rectum or a residual segment of aganglionic bowel.

Pathology

The gross pathology of HEC was described initially by Harald Hirschsprung: there is full-thickness ulceration penetrating to the serosa, abscess formation in the submucosa and mottled submucosal spaces containing pus.[30]

Microscopically HEC is characterized by infiltration of intestinal crypts with neutrophils (cryptitis) and formation of crypt abscesses. Mucus retention with crypt dilation is often seen (see Figure 3A).[31] There is a progressive increase in crypt abscesses followed by progressive ulceration of the mucosa eventually leading to transmural necrosis (see Figure 3B) and perforation. The late stages are indistinguishable from ulcerative colitis. Crypt

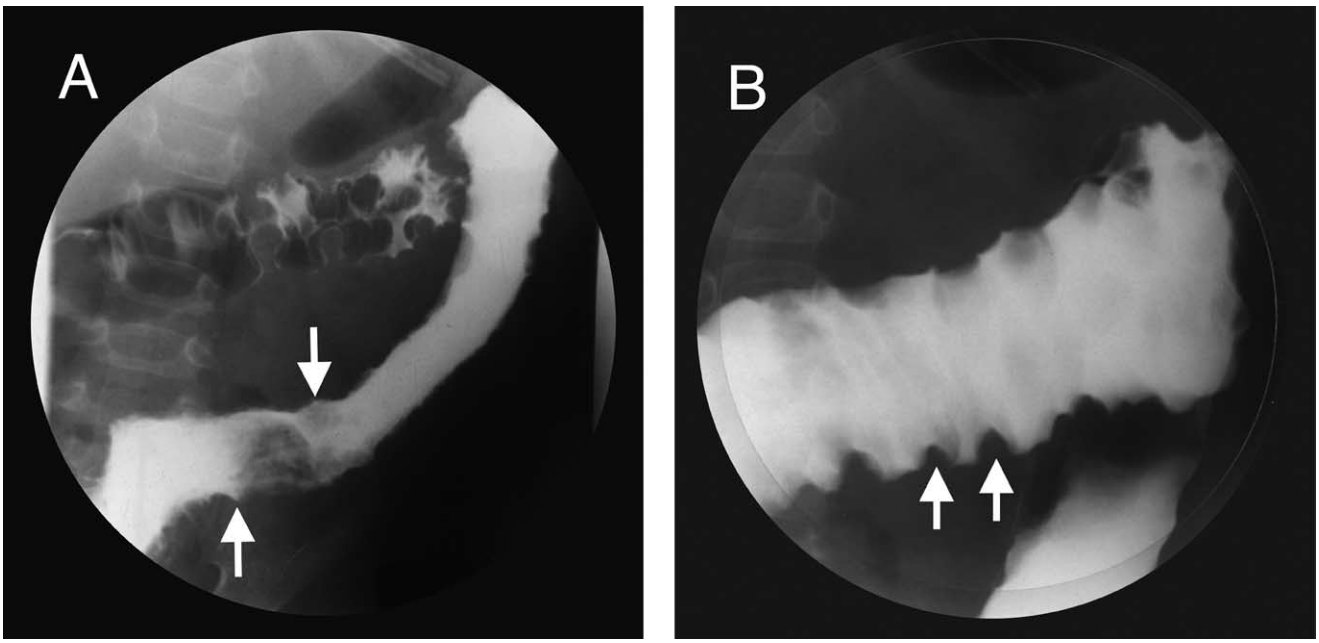

Figure 2 Contrast enema of a 2-year-old girl with HEC. (A) Mucosal thickening with ulceration of the sigmoid and descending colon (arrows). (B) Marked mucosal edema of the distal transverse colon illustrated by thumb-printing (arrows).

abscesses are seen in both ganglionic and aganglionic bowel.[31]

Teitelbaum and coworkers suggest a pathological grading system (currently not widely in use) ranging from Grade 0 = normal mucosa to V = severe necrosis with perforation. Eighty-eight percent of their patients with clinical enterocolitis were graded III (Multiple crypt abscesses) or greater.[6] In their series 86% of patients without clinical evidence of enterocolitis at the time of rectal biopsy who were assigned grade II or higher on histological staging went on to develop clinical enterocolitis.

Ischemic enterocolitis is a rare finding in HD[32] and those cases reported occurred in moribund neonates who were in septic shock. It is possible that inadequate perfusion and bowel distension led to the ischemic changes seen in the intestine.

Brearly and coworkers report pseudomembranous colitis (PMC) in association with HD. Histology was typical of PMC in 35% of patients with clinical colitis from whom biopsy material was available. This affected both aganglionic and ganglionic bowel. PMC was clinically indistinguishable from the inflammatory colitis more typically associated with HD but carried a greater mortality (43% compared with 23%).[33] PMC in these cases of HD was unrelated to recent antibiotic therapy.

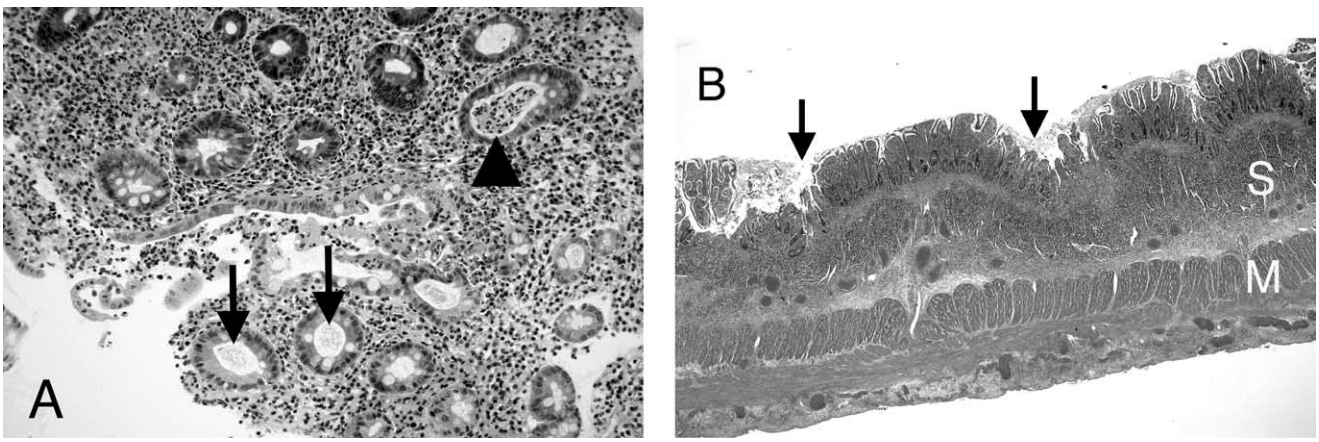

Figure 3 (A) Colonic mucosal biopsy from a patient with enterocolitis showing dilated glands with retained mucin (arrows) and a crypt abscess (arrowhead). (B) Histology from a resection specimen of a 3-month-old patient with fulminant HEC. The colonic wall shows focal mucosal necrosis (arrows) and severe ischemic changes in the submucosa (S) and muscle (M).

Potential etiology

Obstructive

Mechanical dilation and fecal stasis secondary to obstruction was the earliest proposed etiology of HEC. Partial mechanical obstruction with chronic distension was thought to result in ischemia by Bill and Chapman.[1] Glotzer and coworkers induced ulcerative colitis in a dog model by partially obstructing the colon. Mucus retention and crypt abscesses were not observed however.[34]

Harrison and coworkers postulate that postpullthrough EC may be attributable in part to internal sphincter spasm.[8] On the other hand Rintala and coworkers reported that none of their patients in a recent series investigating chronic or recurrent postpullthrough EC had strictures or stenosis of the bowel outlet and their anal pressures on manometry did not differ from those patients with HD who did not suffer with EC.[35]

Moreover obstruction as a sole cause for HEC does not explain the occurrence of EC in those infants and children with a defunctioning stoma or postpullthrough EC in those without sphincter spasm.

Infective

There is no consistent evidence for specific organisms causing EC in HD but a number of authors have reported an association with both bacterial and viral infective agents.

Thomas and coworkers reported that cytopathic *Clostridium difficile* toxin was present with significantly greater frequency and in consistently higher concentration in the stools of children with HEC compared with controls.[36] Those patients with the most severe manifestations of HEC were all found to have toxin-positive stools. In another series all patients found to have fecal *C. difficile* toxin (63% of HEC) responded to vancomycin given orally or via their stoma.[2]

Hardy and coworkers showed that children with HEC carry *C. difficile* for a prolonged period of time compared with controls.[37] Other studies however report that very few of their patients were positive for *C. difficile*.[7,31,35] Furthermore it has been shown that up to 90% of healthy neonates have *C. difficile* in their stools and many secrete the toxin,[38] suggesting that the pathogen alone does not cause HEC. Thomas and coworkers proposed that in healthy infants colonized with *C. difficile* the organism is shed from the gut flora as the pattern of bacterial colonization changes with age but those children with HD have difficulty in shedding the organism. It has been suggested that a secreto-motor abnormality may lead to overgrowth of *C. difficile*.[36] While colonization of the gastrointestinal tract with *C. difficile* may be well tolerated in healthy infants it poses a significant threat to those with HD.[33,36]

Wilson Storey and coworkers found rotavirus in the stools of 77% of their patients with HEC. Immunologic defense against rotavirus is dependant on IgA in the gut wall. Rotavirus is thought to play some part in the pathogenesis of HEC that may be related to an underlying deficiency in host defense.[39]

Golderman and coworkers showed that enterocyte adherence allows organisms to invade epithelial barriers.[40] In a study of HEC 39% of patients demonstrated enterocyte adherence on histology, the organisms identified were *Escherichia coli, C. difficile* and Cryptosporidium.[31] The susceptibility to infection seems more important in the etiology of HEC than a specific pathogen.

Defective mucosal barrier

The mucus gel layer covering the luminal surface of the gastrointestinal tract acts as a lubricant, protects against mechanical trauma and forms the first line of defense against potential pathogens, foreign compounds and toxins.[41,42] Mucus glycoproteins, the main components of the gel, provide visco-elastic properties and act as adhesion sites for bacterial and viral pathogens preventing binding to epithelial cells. Mucin prevents bacteria from colonizing the mucosal cells[41] and has been shown to inhibit the replication of rotaviruses.[43,44] A deficient or altered mucosal barrier may lead to an increased susceptibility to infection in HD.[45]

Histological studies have been conducted to assess characteristics of mucus and mucus glycoproteins which describe a loss of sulfated mucins in HEC. There is a well known association of loss of sulfation and inflammatory conditions of the bowel.[42] Alterations in the sulfate and sialic acid content of mucus glycoproteins render the mucus barrier more susceptible to degradation by both normal gut flora and bacterial pathogens.[46] Deficient secretion of acidic sulfomucins allows increased adherence of enteropathic organisms, such as *C. difficile* or *E. coli* resulting in increased susceptibility to bacterial invasion of the intestinal wall. Bacterial toxins may then initiate the enterocolitic process.[31,47,48]

Abnormalities of the mucus protective barrier have been shown in the proximal ganglionic bowel after definitive surgery, this may explain the occurrence of postpullthrough enterocolitis and of recurrent episodes of EC associated with HD.[31]

An extensive study by Aslam into the mucus barrier in HD and HEC showed that there are changes in the mucin secretion of ganglionic and aganglionic bowel.[45] There is an increase in the ratio of intracellular to secreted mucins and there is a reduction in mucin turnover, detected by metabolic labeling with ([35S]-sulfate and [3H]-glucosamine) in cells from aganglionic and ganglionic bowel compared with age-matched controls.[45,49] The expression pattern of mucin genes was found to be normal in HD indicating that at genetic level mucin synthesis is intact. However, mucin turnover is decreased therefore the quality and quantity of the mucus barrier is compromised.[50,51] Physical protection and immune function, and with it the first line of defense, are impaired leaving the patient susceptible to bacterial

colonization and invasion.[42,45] In a prospective study of the outcome of patients with known mucin turnover rates the authors showed that a low mucin turnover in the ganglionic bowel retained at definitive surgery correlates with a greater risk of developing enterocolitis: the lower the turnover, the more prone a patient is to enterocolitis.[50] The authors suggest that it may be possible to use mucin turnover rates in culture from the proximal bowel at the time of pullthrough surgery as a predictive laboratory test for postoperative enterocolitis.[50] The ganglionic bowel retained after surgery is affected for an unknown distance proximal to the transition zone and further studies are in progress to examine the proximal extent of abnormal mucosal protection.

MUC-2 has been shown to be the predominant mucin expressed in the human colon.[52] In a recent study by Mattar and coworkers MUC-2 protein expression was assessed in stool samples and was found to be significantly decreased in patients with HD compared with controls.[53] The study reported nondetectable levels in those patients with HEC. The deficit in MUC-2 production may allow bacterial pathogens to invade the mucosal epithelium.

Patients often outgrow their susceptibility to recurrent enterocolitis. This may be explained by the fact that even in normal children the mucus defensive barrier is weakest at 3 months to 3 years and with increasing age a more robust barrier is formed with an increased turnover of mucins.[49] The older child is better able to withstand mucosal invasion by bacteria and the barrier offers greater protection against toxins and foreign compounds. Further studies are being conducted to assess whether the mucin turnover in patients with HD improves with increasing age.

Mucus secretion is partly under the control of the autonomic nervous system.[54] Soeda and coworkers demonstrated a reduction in neuroendocrine (NE) cells in patients with HEC compared with controls.[55] The weak mucus defensive barrier in HD may be due to an abnormality of the autonomic nervous system and a reduction in NE cell populations in the ganglionic bowel. This would explain the poor mucus secretion as well as the motility disturbances often seen in association with HD even after definitive surgery.

A recent study by Lui and coworkers suggested that as well as a defective mucus gel layer there may be further loss of mucosal integrity due to defective epithelial cell proliferation and differentiation. The group demonstrated a downregulation of caudal type homeobox gene-1 and -2 (CDX-1 and CDX-2) expression in patients with HEC. CDX genes are involved in maintaining the integrity of the gastrointestinal mucosa by control of epithelial cell proliferation and differentiation.[56]

Immunological

The complex immunologic defense mechanisms of the intestine comprise both humoral and cellular pathways. Secretory IgA is present within the mucus and there are numerous T-lymphocytes in the epithelium and the lamina propria as well as in Peyer's Patches and mesenteric lymph nodes.

Impaired cellular and humoral immunity has been described in patients with HD.[57] There is a significant reduction in the absolute neutrophil count and defective neutrophil chemotaxis and neutrophil degranulation, measured by chemiluminescent activity. The neutrophils are therefore unable to respond to a microbiological challenge in the normal way. The same study also showed a decrease in serum complement levels and in serum IgA. Fujimoto described an early onset EC in the piebald lethal mouse model of HD with an increase in the number of IgA containing plasma cells infiltrating lamina propria but demonstrating a decrease in intraluminal IgA suggesting that there is a defect in the release of immunoglobulins.[48] Wilson-Storey and coworkers reported a marked deficiency in the transfer of IgA across the gastrointestinal mucosa and propose that this leads to a deficiency in immunoglobulin mucosal defense in children who develop HEC compared with HD controls.[57,58] A further study confirmed an increase in IgA, IgM and J chains in plasma cells but low levels of luminal secretory compounds in aganglionic colon of patients with HEC.[59]

Patients with trisomy 21 and HD are known to be at increased risk of developing EC. Studies have shown an intrinsic immunological deficiency in trisomy 21 with decreased cytotoxic T-lymphocyte function and deranged humoral immunity.[60]

None of the studies on immunologic defenses in the intestine of patients with HD have been conducted in a serial fashion. It is therefore impossible to say whether the changes noted are cause or effect of HEC.

Prevention

Bill and Chapman in their early series of HEC stated that the best treatment for enterocolitis is its prevention and advocated the formation of colostomy in all infants as soon as the diagnosis of HD has been made.[1]

Regular rectal irrigation may prevent EC: twice daily rectal irrigation for 3 months then once daily for a further 3 months after definitive pullthrough surgery has been shown to reduce the incidence and mortality of EC.[26] This may be due to a combination of bowel decompression and washing out of potentially pathogenic bacteria as well as preventing colonic distension and fecal stasis. Hackman and coworkers found that postoperative complications related to the anastomosis or causing intestinal obstruction were the only significant risk factors for postpullthrough EC and therefore emphasized the importance of minimal trauma to the bowel during definitive surgery. They suggest that laparoscopic pullthrough procedures may be associated with a decreased incidence of postoperative EC.[10]

Having demonstrated that their histologic grading classification was reliably predictive of the development of

clinical enterocolitis in their series, Teitelbaum and coworkers suggest that it might be prudent to commence prophylactic antibiotics in those patients who demonstrate a histological grade III or higher on rectal biopsy.[31]

Management

Prompt diagnosis, rectal washouts and stoma formation are critical factors in the prevention of severe morbidity associated with HEC.

In the management of acute HEC aggressive fluid resuscitation to correct the fluid and electrolyte imbalance is of utmost importance. In severe enterocolitis the involvement of the critical care team should be sought early as multiorgan failure may develop.

Decompression of the bowel must be achieved as soon as possible by placement of a nasogastric tube and rectal irrigation. A large bore rectal catheter is passed, gas and stool are aspirated followed by repeated irrigations of 20 to 50 ml (dependent on the size of the infant) of warmed saline using a total volume of 100 to 150 ml. Volumes of 500 to 1000 ml may be needed in the older child. Washouts should be repeated two to three times per day until decompression has been achieved as assessed by regular clinical examination. Rectal washouts, however should not be performed during fulminant disease because of the risk of perforation. Phosphate enemata and enemata without decompression tube must be avoided as they may worsen the enterocolitis and phosphate toxicity may occur.

If the bowel cannot be successfully decompressed with washouts the patient will require a laparotomy and formation of stoma just proximal to the transition zone. Frozen section histology by an experienced pediatric pathologist is essential to ensure that the stoma is sited in ganglionic bowel. In the most severe cases of HEC the colon may become purulent and gangrenous and a total colectomy is indicated.

Bowel rest must be instigated and in prolonged disease parenteral nutrition should be initiated.

Antibiotic therapy is commenced with broad-spectrum intravenous antibiotics in severe disease. *C. difficile* cover must be ensured,[33,36] a common regime being intravenous metronidazole and/or vancomycin administered via the nasogastric route or the stoma if present.

It has been suggested that *Saccharomyces boulardii* may be a useful adjunct to therapy in the presence of positive *C. difficile* toxins. It has been shown that this nonpathogenic yeast inhibits the effects of *C. difficile* toxins A and B in the human colon.[61]

Corfield and coworkers have shown that there is a symbiotic relationship between the normal gut flora and mucin synthesis, posttranslational modification and also degradation.[42,46] A study by Mattar and coworkers showed that addition of *Lactobacillus* GG casei to a Caco-2 cell line could induce MUC-2 mRNA expression in a dose dependent manner.[62] Gork and coworkers showed that application of mucins in a neonatal epithelial cell line had an inhibitory effect on bacterial translocation.[63] Some centers use probiotics in the treatment of HEC to manipulate mucin expression and synthesis and decrease the risk of bacterial translocation.

Cholestyramine may be a useful adjunct as it binds *C. difficile* toxin and Prostaglandin E (PGE). PGE causes increased secretion of water and electrolytes from the jejunum. Binding of PGE by cholestyramine may help to reduce this loss and reduce the incidence of hypovolemic shock.[64]

There are no generally accepted guidelines for the management of chronic or recurrent enterocolitis. Dietary manipulation with low residue and lactose-free diet has been suggested to diminish the substrates for bacterial overgrowth.[35] Severe disaccharidase deficiency and sugar intolerance have been noted after definitive pullthrough surgery.[65]

Enteral antibiotics are advocated at the time of exacerbations and most authors use metronidazole.[35]

Sodium cromoglycate has been suggested as a treatment for recurrent EC. This nonabsorbable mast cell stabilizing agent has been documented to be effective in the management of inflammatory bowel disease and food allergies. The usefulness in HEC has been investigated by Rintala and coworkers[35] Sixty percent of their patients with chronic EC responded favorably with a decrease in the frequency of bowel motions and a more solid consistency of stool leading to diminished soiling. Exacerbations of EC requiring hospital admission and antibiotics were abolished in the median follow-up period of 14 months. All 3 patients with recurrent enterocolitis responded favorably. The same group gave budesonide, a potent antiinflammatory agent to a patient who did not respond to sodium cromoglycate, with significant improvement in their symptoms.[35]

Swenson and coworkers initially proposed sphincterotomy to help patients with postpullthrough EC, since their rectal sphincters are often found to be very tight on examination. They report, however, that no significant benefit was obtained.[5] But Polley and coworkers and Marty and coworkers performed internal sphincterotomies with good results on patients with recurrent post pullthrough enterocolitis. Both authors advocate a significant period of time on conservative management as most children with post pullthrough EC will improve with time.[66,67]

Future management strategies may be guided by studies on abnormalities of the mucus barrier. It may be possible in the future to define the extent of abnormal mucosal protection and resect a longer segment of bowel at the definitive surgery to include ganglionic bowel with an impaired mucus barrier.

Other future strategies may involve replacement of the defective mucus with a synthetic mucus substitute or to encourage secretion of mucus using secretogogues.

Conclusion

The etiology of HEC is multifactorial and remains poorly understood. The mainstay of management remains intensive supportive care and the reduction in mortality witnessed over the last 5 to 10 years is primarily due to improvements in critical care. Preventative measures and better treatment modalities will evolve out of a better understanding of the underlying pathophysiology. Prompt recognition of HEC allows early intervention and a potential reduction in disease severity and mortality. To this end, a higher level of awareness of HEC is required in parents and the medical profession.

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