Hirschsprung Associated Enterocolitis
Valentina Rossi, Stefano Avanzini, Manuela Mosconi, Girolamo Mattioli, Piero Buffa, Vincenzo Jasonni and Alessio Pini Prato*
Department of Paediatric Surgery, Giannina Gaslini Institute, Genoa, Italy

Abstract
Hirschsprung-associated enterocolitis is an infrequent inborn abnormality of the enteric nervous system. Characteristics are the absence of ganglia in both submucosal and myenteric plexuses of the hindgut with a variable proximal extension. This review acknowledge all patients and families regarding the possibility of HAEC occurrence either pre- and postoperatively and to make them prepare deal with this terrible complications with early washout and prompt hospital referral.

Keywords: HSCR; Enterocolitis; Neuroimmune; Neuroendocrine; Botulinum

Background
In 1886 Sir Harald Hirschsprung, a Danish paediatrician, described for the first time two young patients who died of septic shock and turned out to have huge colonic dilatation at post-mortem assessment. This was the first clinical description of congenital megacolon or recto-sigmoid aganglionicosis that was subsequently named Hirschsprung’s disease (HSCR). HSCR is a rare congenital abnormality of the enteric nervous system characterized by the absence of ganglia in both submucosal and myenteric plexuses of the hindgut with a variable proximal extension. HSCR occurs in roughly 1 into 5000 live births with a certain regional and continental variability (higher incidence in Asian and lower incidence in African populations). Over 80% of patients have aganglionicosis confined to the recto-sigmoid colon, the remaining 15-20% of patients have aganglionicosis extended beyond. Of note, total intestinal aganglionicosis is extremely rare and is almost incompatible with life.

HSCR has always been one of the most interesting topic for paediatric surgeons due to its intriguing features and challenging treatment. Although this congenital anomaly is curable and significant advance in the treatment was obtained during the last decades, a minority of patients can still develop serious complications and eventually died. The main cause is certainly to be found in Hirschsprung-associated enterocolitis (HAEC), which can basically occur from birth to adulthood, regardless of the length of aganglionicosis and is characterized by abdominal distension, explosive diarrhoea, fever, lethargy, and even septic shock.

The original description of HAEC in detail is credited to Bill and Chapman in 1962, who reported a high mortality rate, particularly in infants who developed enterocolitis before the operation. Though great advancements in HSCR treatment have been made in the past 60 years thanks to distinguished surgeons including Orvar Swenson, Franco Soave, Bernard Duhamel, and others, HAEC remains a great question mark in the landscape of this pathology. In fact, Hirschsprung pathophysiology is largely unknown and predisposing factors as well as specific prevention strategies has not been determined yet. Various hypotheses regarding the aetiology have been postulated. Based on experimental and clinical studies, several contributory factors have been identified that may help to explain its development.

Incidence/Epidemiology/Risk Factors
HAEC can occur either preoperatively or after radical surgery. Owing to improved and prompt diagnosis, the incidence of pre-operative HAEC (ranging between 6% and 26% of cases) has decreased over the past decades (1, 2). Also mortality rate has markedly decreased, thanks to the advancements in its recognition and prompt management. HAEC occurs postoperatively in between 5% and 42% of patients [1,2]. The wide variation in incidence rates is probably the result of heterogeneous definitions and diagnostic criteria of HAEC. In our series of 313 patients treated between 1993 and 2010, the incidence of HAEC turned out to be 34% preoperatively and 15% postoperatively, being overall mortality rate 7.5%.

Table 1 shows the overall incidence of HAEC in a series of published papers, listed chronologically. Mortality rate decreased to nearly 10% to 0% though the average mortality rate in the last 20 years is around 3% [3].

Pathogenesis
The pathophysiology of HAEC remains poorly understood. HAEC represents a clinical entity determined by a combination of various dysfunctions and/or disruptions of intestinal homeostasis [4-10].

The assessment of the histological abnormalities observed in the gut of patients suffering from HACE has provided understanding regarding the pathogenesis of the disease. From a histological point of view, HACE is characterized by the presence of cryptitis, with a huge inflammation and neutrophilic infiltration of the crypts. In a mild stage of HACE, the crypt retains mucus as occurs in cystic fibrosis. In more advanced stage of HACE, there is a microscopical progression of the disease, with cryptic abscesses, collection of intraluminal fibrinopulent debris, mucosal ulceration and subsequent progression to transmural necrosis.
and intestinal perforation. These findings have been described in both ganglionic and aganglionic bowel, suggesting a mechanism that goes beyond the simple absence of ganglia.

One of the theories of pathogenesis of HAEC is partial obstruction, due to the aganglionicism itself or surgical issues that determine a persistent state of faecal and bacterial stasis. This lack of bowel emptying leads to bacterial overgrowth, bowel dilatation, bowel wall stretching, impaired blood flow to the mucosa and subsequent increased permeability with bacterial translocation.

The abnormal development of the enteric nervous system (ENS) plays a pivotal role in the pathogenesis of HAEC. In fact, the ENS is of utmost importance in gut homeostasis, as it regulates motility, mucosal immune defence, intestinal barrier function, and commensal micro flora with a complex neuroimmune modulation effect. In particular, the myenteric plexus seems to deal with the regulation of the intestinal motility, whereas the sub mucosal plexus seems to be mostly involved in regulating the complex neuroimmune system. When ENS is compromised, the integrity of epithelial barrier is at risk; the neuroimmune dysfunction may thus lead to the propagation of the inflammatory vicious circle of HAEC.

Abnormalities in the amount or composition in mucin, produced by goblet cells may contribute to this dysfunction. Mucus makes a thin primary layer against bacterial invasion, preventing from damage to epithelial cells. Moreover, Paneth cells contribute to the mucus production thanks to the secretion of defensins, antimicrobial proteins that reinforce the viscoelastic and defensive properties of the intestinal layer. It is well demonstrated that deficient mucin secretion (regulated by sub mucosal neuroendocrine cells) may predispose to the adherence of enteropathogenetic organism, promote the infection and consequently contribute to the development of HAEC. Abnormalities of the mucus layer have been shown in the proximal ganglionic bowel after a surgical definitive pull-through, which may contribute to the post-operative recurrence of HAEC.

Also the mucosal immune system is involved in preventing bacterial translocation in the gut. In fact HSCR patients have a deficiency in the transfer of secretory immunoglobulin IgA across the intestinal mucosa. This results in a deficient microclimate and has been proposed by some authors as one of possible causes for HAEC. In patients with HAEC, mucosal IgA production is intact but intraluminal transfer is deficient, compared with control subjects, limiting the role of IgA in mucosal defence.

We recently adopted a qualitative metagenomic approach named ARDRA (Amplified Ribosomal Digestion Restriction Analysis) to describe and assess bacterial community’s dynamics in patients with HSCR during different HAEC episodes. We could demonstrate the existence of an altered and predisposing micro flora in patients with recurrent HAEC as well as the existence of similar protective microenvironments. Yet, we could not determine the bacteria leading to specific HAEC episodes due to the non-specific approach of our study. The factors described above may create a dysfunctional environment in the “acceptable” gut microbiome, with a decreased colonization of bifidobacteria and lactobacilli, probiotic organisms that maintain a microbial equilibrium. Disruption of these mutually beneficial relationships could result in HAEC. However, the mechanism is still uncertain.

Clostridium difficile and Rotavirus have been frequently detected in patients with HAEC, even if no specific organism has been found to consistently cause HAEC. In particular, a cytopathic toxin of Clostridium difficile has been found in the stools of a consistently high percentage of patients with HAEC. Although this toxin has been detected in patients with severe clinical manifestations of HAEC, the majority of healthy neonates and infants younger than 1 year of age carry Clostridium difficile in their stools. This aspect suggests that the toxin itself is not enough to trigger an HAEC episode. The knowledge of micro flora before, during and after HAEC episode may help in establishing preventive and therapeutic strategies.

The genetic of HSCR is complex and it is possible that a genetic predisposition to HAEC may exist. The increased risk of HAEC in patients affected by Down syndrome has been suggested by some and could be the result of an immunodeficiency, still not well clarified. We could recently demonstrate that patients with RET mutations (RET being the major disease-gene in HSCR) have a significantly higher expression of RET itself on circulating immune cells and that RET has a crucial role in the immune system development and activation. This could explain the measure of susceptibility towards HAEC observed in many HSCR patients.

Other trivial theories have been suggested and summarized in a paper by Murphy and Puri. They included sucrase isomaltase deficiency (typical of Eskimos who carry this deficiency in 10% of cases), Schwartzman reactions and altered prostaglandin levels that have not been confirmed so far.

Many investigators have identified certain predisposing factors associated with the development of HAEC:

- **Age at presentation:** early symptoms onset seems to correlate with HAEC severity and susceptibility.
- **Associated anomalies and syndromes:** Down syndrome, central nervous system anomalies and congenital cardiac malformations has been considered strong risk factors by many Authors [11].
- **Post-operative issues:** all complications or surgical issues leading to bowel obstruction or impaired bowel emptying increase the likelihood of HAEC development.
- **Personal history (previous HAEC episodes):** patients who previously developed HAEC are at higher risk of recurrence in a sort of predisposition/susceptibility.
- **Extent of aganglionosis:** patients with ultra-long HSCR (i.e. Total Colonic Aganglionosis) have a higher likelihood of developing HAEC both preoperatively and postoperatively with an overall incidence approaching 50% [2].

Other debated issues:

- **Type of pull-through:** at present, there is no evidence of significant correlation between the type of pull-through and HAEC incidence [11].
- **Gender:** some Authors suggested that females are at greater risk to develop HAEC but others failed to demonstrate this correlation.

**Clinical Features/Diagnosis**

Enteroocolitis is a clinical diagnosis. Elhalaby et al. in 1995 described the clinical aspects of HAEC, proposed straightforward diagnostic criteria, and characterized the most frequent symptoms [2]. Abdominal distension, explosive diarrhoea, fever, vomiting, rectal bleeding, lethargy and shock are, in order of frequency, the “classic” clinical features. In
addition, some patients may present with less specific symptoms, such as loose stool or perianal excoriation.

Pastor and co-workers, in 2008, developed a more standardized definition of HAEC. They used a Delphi method, a technique for achieving consensus among a panel of experts [1]. The Authors developed a scoring system and established HAEC definition basing on 18 clinical-radiologic criteria including symptoms, blood tests, X-rays and personal history.

Both Elhalaby and Pastor criteria are useful tools for HAEC definition and diagnosis [1,2,12].

The most reliable clinical grading system developed for HAEC is that from Elhalaby that stratified HAEC severity into three major categories:

- **Grade I**: mild explosive diarrhoea, mild to moderate abdominal distension, no significant systemic manifestations;
- **Grade II**: moderately explosive diarrhoea, moderate to severe abdominal distension associated with mild to moderate systemic manifestations (e.g. fever, and tachycardia);
- **Grade III**: explosive diarrhoea, marked abdominal distension, shock or impending shock.

The initial symptoms of HAEC may be indistinguishable from acquired infective gastroenteritis. Nonetheless, as HAEC can progress rapidly and even result in death, most paediatric surgeons will treat all patients regardless of univocal HAEC diagnosis, in order to avoid delayed treatment or misdiagnosis.

Diagnostic imaging for HAEC consists mostly in a plain abdominal radiographs, which can show the typical intestinal “cut-off sign” in the recto sigmoid colon with absent distal air, dilated loops of bowel, air fluid levels, and even free abdominal air in case of perforation. The X-ray has a good sensitivity (90%) but low specificity (24%). In some cases ultrasonography can be used to identify peritoneal ascites or internal septations that are suggestive of peritonitis or intestinal inflammation. Other suggested diagnostic tools include endoscopy and urgent biopsy. Nonetheless those procedures have drawbacks. In fact, colonoscopy may show the typical plaque-like lesions of pseudomembranous enterocolitis secondary to *Clostridium Difficile* but should be approached with caution because the risk of perforation. Similarly, the role of rectal suction biopsy is controversial and not recommended in an acute phase of HAEC due to the high risk of perforation.

**Treatment**

The treatment of children with HAEC is:

1. **Resuscitation in case of impending shock**;
2. **Decompression of the gastrointestinal tract**;
3. **Antibiotics**, directed mostly against Gram negative and anaerobic species.

A key aspect in the management of an acute HAEC episode is a good fluid resuscitation, close hemodynamic monitoring and in some severe case, ventilatory support and admission to intensive care unit. In case of prolonged disease, a parenteral nutrition support may be indicated.

Rectal washouts, flatus tubes and bowel decompression should be performed as soon as possible, with 2-4 times daily irrigations with saline until the effluent are clear. Usually it is possible to continue twice daily until symptoms settle. At the beginning of HAEC treatment the patients should be kept fasting. Feeding should be allowed once symptoms improve.

Some authors reported a decrease incidence of postoperative episodes in children receiving rectal washouts daily after a pull-through [13]. We recently suggested limiting postoperative washout or daily decompression to high-risk patients (neonates with congenital heart disease, see below).

Depending on the severity of the disease, in particular when *Clostridium Difficile* is detected in the stools, HAEC can be effectively treated with oral or intravenous metronidazole (10 mg/kg three times a day for patients older than 1 year of age, 7.5 mg/kg for younger patients). Severe HAEC episodes sometimes require other antibiotics (i.e. vancomycin) driven by specific culture evidences.

In case of chronic or recurrent HAEC, cycles of decontaminations with oral metronidazole (regardless of culture evidences) have been suggested and can be used in 10 days intermittent courses, with simultaneous administration of high concentrated probiotics. Severe refractory HAEC could represent a serious problem in paediatric patients. Inability to adequately decompress the bowel or severe and uncontrolled septic shock may be an indication for urgent bowel diversion with a levelling colostomy fashioned proximally to the transitional zone (intraoperative histochemistry). Nonetheless, a stoma may not resolve HAEC in all cases.

In case of pseudomembranous colitis (Figure 1), caused by *Clostridium Difficile*, total colectomy should be considered to reduce mortality, provided reliable diagnosis is made. Lamontagne et al. [14] suggested to perform colectomy before patients increase their lactate levels ≥ 5 mmol/L otherwise prognosis is dismal with or without surgery.

With specific regard to conservative medical management of HAEC, there is no evidence that support the use of antibiotic prophylaxis. Furthermore, its wide use could increase the risk of selecting multi-resistant organism.

Sodium cromoglycate is a stabilizer of mast cells and decrease the release of histamine from the inflammatory cells. This substance is largely used in the management of allergic conditions of the respiratory tract and it has been proposed by Rintala et al. as a good effective treatment for patients affected by chronic or recurrent HAEC, even if there is no other follow-up study that confirmed the routine use of this agent [15].

**Figure 1**: Pseudomembranous HAEC (intraoperative picture of a patient who ultimately died of septic shock regardless of subtotal colectomy performed as soon as pseudomembranous HAEC was confirmed by the pathologist).
Children with recurrent HAEC after surgery, the surgeon has to consider possible complications such as retained aganglionic rectum or residual dysganglionosis in the pulled-through bowel. A barium enema and a rectal suction biopsy will help to rule out these issues along with other less frequent complications (twisted pull-through, cuff stenosis, perirectal fibrosis). Most frequently postoperative HAEC are facilitated by internal anal sphincter residual achalasia (defined as the lack of relaxation of the internal anal sphincter that is steadily present in all children with HSCR regardless of a correct surgical procedure). Surgical interventions will therefore include botulinum toxic injection, sphincterotomy and posterior myotomy/myectomy of internal anal sphincter.

Intrasphincteric botulin toxin therapy determines reversible relaxation of the internal anal sphincter without permanently impairing continence. Botox injection acts for roughly 6 to 9 months and can be used for multiple injections, if required. However, it is difficult to predict preoperatively, who will favourably respond to the treatment [16].

All in all, most patients with recurrent HAEC or postoperative issues (once complications have been ruled out), if managed with adequate decompression modalities seem to improve spontaneously and will ultimately settle within 4 years after surgery (personal communication).

Another surgical approach for treatment of HAEC includes the posterior myotomy/myectomy. The procedure should be performed posteriorly, above the dentate line to reduce risk of damage of internal sphincter. A possible redo surgery can still be performed with a good expected functional outcome, in case myectomy is not successful [17].

Prevention

Ideally, the best treatment for HAEC is the prevention.

The main foresight is rectal washout, especially pre-operatively in the newborn [13,14].

Immediate diuresis should be strongly considered for patients presenting with sepsis or severe HAEC, especially in newborn when this is the initial presentation.

Radical surgery (pull-through) should be performed as soon as possible. In fact, most of severe cases of HAEC do occur preoperatively being surgery mostly event free. Preoperative and postoperative probiotics use recently failed to demonstrate a beneficial or protective role over HAEC likelihood and severity [18].

We could recently demonstrate that severe and/or fatal HAEC are more likely to occur in patients with syndromes or congenital heart diseases. On the ground of these considerations patients with congenital heart disease should undergo prophylactic stoma fashioning in order to minimize the risk of HAEC and consequently possible fatal complications. Nonetheless, although enterostomy could consider protective towards the development of HAEC, it cannot prevent cardiocirculatory problems or issues related to pre-existing syndromes and HAEC could potentially occurs also after stoma formation [3].

Fortunately, mortality rate has been drastically reduced over the years, but HAEC remains a problem. Currently HSCR mortality has now felt down to roughly 3% but HAEC still remains the major cause of death.

All patients and families should be acknowledged regarding the possibility of HAEC occurrence either pre- and postoperatively and should be prepared to deal with this terrible complications with early washout and prompt hospital referral.

Molecular genetics, animal models studies and metagenomic are the field of research that will hopefully disclose the aetiology of HAEC and help in developing more accurate prevention diagnosis and treatment approaches.

References