Risk factors and treatment outcome of Hirschsprung's associated enterocolitis in a LMIC setting

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Abbreviations

ICU- Intensive care unit

IND- Intestinal neuronal dysplasia

HD- Hirschsprung's disease

HAEC- Hirschsprung's associated enterocolitis

LMIC- Low and middle income country

OR- odds ratio

PT- Pull through

SPSS- Statistical Package for the Social Sciences

TASH- Tikur Anbessa Specialized Hospital

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Abstract

Background: Hirschsprung's associated enterocolitis (HAEC) is an important complication in pediatric patients with Hirschsprung's disease (HD). This study aimed to examine risk factors for the occurrence of HAEC, assess recurrence and evaluate treatment outcome for affected patients.

Methods: A retrospective study was conducted, including 42 patients diagnosed with HAEC from 2019 to 2024. Data were collected from medical records, focusing on demographics, clinical presentation, treatment modalities, and recurrence rates.

Results: Among the 42 patients, 30 were male, with a median age of 17.5 months. A total of 83 episodes of HAEC were recorded, with 36% occurring pre-pull-through and 64% post-pull-through. Key symptoms included vomiting (76%), foul-smelling diarrhea (76%), and fever (64%). Twenty-six percent of patients experienced recurrent HAEC, with univariate analysis revealing that pre-pull-through HAEC significantly increased the risk of recurrence. Multinomial regression analysis indicated that patients with pre-pull-through HAEC were eight times more likely to develop recurrent enterocolitis (CI 1.3-48.3, P=0.02).

Conclusions: HAEC remains a challenging condition with a notable incidence of recurrence. The findings emphasize the importance of early diagnosis and management strategies, including preventive measures such as oral Metronidazole and rectal stimulation. Future multi-center studies are required to corroborate these results and improve the clinical outcomes of patients with HAEC.

Key Words: Hirschsprung's associated enterocolitis, recurrence, outcome

Inroduction

Background

“Hirschsprung’s disease (HD) is a developmental disorder of the enteric nervous system characterized by the absence of ganglion cells in the myenteric and submucosal plexuses of the distal intestine”. [1] It is one of the most common causes of distal intestinal obstruction, with biopsy being the gold standard for diagnosis. The primary management for this congenital anomaly involves surgical resection of the aganglionated segment and restoration of intestinal continuity through various pull-through procedures, which can be performed in single or multiple stages while preserving sphincter integrity.

Hirschsprung’s associated enterocolitis (HAEC) is an important complication characterized by intestinal inflammation, presenting with abdominal distension, diarrhea, fever, and sepsis. [2] Despite a decline in its incidence over recent years, HAEC remains a major cause of morbidity and mortality in HD patients. It is associated with longer hospital stay and increased healthcare costs. [3,4,5] HAEC can occur pre-operatively, after colostomy, or following the definitive pull-through procedure. Despite the advancement in medical technology, the etiology and pathogenesis of HAEC remain unclear. Understanding these factors is crucial for identifying at-risk patient subsets and developing effective treatment and prevention strategies.

The variability of presenting signs and symptoms complicates the establishment of standard diagnostic guidelines, contributing to the wide range of reported incidence. Patients may present with mild symptoms that do not require admission or with severe hemodynamic instability, necessitating care in a pediatric intensive care unit. Common clinical features include abdominal distension, fever, and foul-smelling diarrhea. Pastor et al. proposed an 18-item criterion based on history, physical examination, radiologic findings, and laboratory parameters for diagnosing HAEC, suggesting that a score of at least ten is necessary for diagnosis. [2] However, the practical application of these criteria has primarily been limited to outcome comparisons in research studies. [2,6]

Ultimately, making a diagnosis of HAEC relies heavily on clinical parameters [7], and treatment typically includes resuscitation, gastrointestinal decompression, and antibiotic therapy.

Statement of the problem

The incidence of Hirschsprung's associated enterocolitis (HAEC) varies across different studies, but it is recognized as one of the leading causes of mortality in patients with Hirschsprung's disease (HD). While the exact magnitude of this disease has not been specifically studied in our country, HD ranks as the second most common gastrointestinal congenital anomaly among pediatric surgical admissions. [8]

Significance of the study

Risk factors for Hirschsprung's associated enterocolitis (HAEC) vary across different studies, making it essential to identify specific factors to develop effective management plans and prevention strategies for affected patients. To our knowledge, there is currently no literature addressing this issue in our country, and only a limited number of studies exist across the continent. This study aims to fill this knowledge gap and lay the groundwork for future pragmatic research in this critical area.

Objectives

General objective

The primary objective of this study is to identify the risk factors associated with the development of Hirschsprung's associated enterocolitis and to evaluate the treatment outcomes for affected patients.

Specific objectives

a. To describe the magnitude of Hirschsprung's associated enterocolitis (HAEC).

b. To identify the common symptoms and signs at presentation.

c. To outline the diagnostic laboratory and radiologic findings associated with HAEC.

d. To identify the risk factors for developing HAEC.

e. To assess the degree of recurrence, investigate the work-up for affected patients, and evaluate the preventive strategies employed.

f. To determine the severity of HAEC in affected patients.

g. To evaluate the treatment outcomes for patients with HAEC.

Methodology

Study Setting

The study was conducted at the Pediatric Surgery Unit, Department of Surgery, Tikur Anbessa Teaching Hospital in Addis Ababa, Ethiopia. This hospital is a major referral center for pediatric surgical care, serving patients from across the country. All patients under 13 years of age who require surgical intervention are treated in this unit.

Study Design

A retrospective cross-sectional study design was employed to identify risk factors and treatment outcomes for patients with Hirschsprung's associated enterocolitis (HAEC).

Source Population

The source population consisted of all patients diagnosed with Hirschsprung's disease (HD) during the study period.

Study Population

The study population included all patients who presented to the emergency department with HAEC and received treatment.

Inclusion Criteria

All patients treated in the emergency department for HAEC from 2019 to 2024 were included in the study.

Exclusion Criteria

Patients whose charts were lost or had incomplete data were excluded from the study.

Variables

Dependent Variables

a. Development of Hirschsprung's associated enterocolitis (HAEC)
b. Treatment outcomes for HAEC
c. Recurrent HAEC

Independent Variables

a. Time of diagnosis of Hirschsprung's disease (HD)
b. Gender
c. Presence of Down syndrome
d. Associated anomalies

e. Length of aganglionosis
f. Type of pull-through procedure
g. Pre-operative enterocolitis
h. Histology of the proximal resected segment
i. Obstructive symptoms post-operatively

Sampling Technique

Non-probabilistic sampling technique was utilized.

Data collection methods

Pediatric surgery morning reports were utilized to identify patients with Hirschsprung's associated enterocolitis (HAEC) during the study period. Patients' medical record numbers were retrieved to access their information. Secondary data was collected using a structured questionnaire designed to capture relevant clinical and demographic information.

Operational definition

Hischsprung's disease- Patients with a histologic diagnosis of HD

Hirschsprung associated enterocolitis- The presence of abdominal distension and foul smelling diarrhea with or without systemic illness with biopsy confirmation of HD.

Anastomotic stricture- narrowing at the site of anastomosis detected with digital rectal examination

Recurrent Hirschsprung associated enterocolitis- two or more episodes of enterocolitis

Long segment aganglionosis- transition zone proximal to mid-transverse colon

Mild HAEC- the presence of abdominal distension and foul smelling diarrhea with biopsy confirmation of HD

Moderate HAEC- features HAEC with fever, lethargy, tachycardia, leukocystosis or leucopenia

Severe HAEC- features of HAEC with altered mentation, decreased peripheral perfusion, deranged organ perfusion, peritonitis or pneumoperitoneum

Data analysis and interpretation

Categorical variables were summarized using frequencies, while continuous variables were summerized using median and range. The association between recurrence of Hirschsprung's associated enterocolitis (HAEC) and various risk factors were assessed using the Chi-square test for univariate analysis. Variables that demonstrated significant associations ($P < 0.05$) in the univariate analysis were subsequently analyzed using multinomial regression, controlling for other independent factors. Statistical significance was defined as a P value of less than 0.05.

Ethical considerations

Ethical clearance was obtained from the Institutional Review Board of the Faculty of Medicine at Addis Ababa University, along with cooperation letters addressed to the Medical Records Department of Tikur Anbessa Teaching Hospital (TASH). Health facility records were coded to ensure confidentiality and protect patient privacy.

Results

A total of 42 patients were treated for Hirschsprung's associated enterocolitis (HAEC) from 2019 to 2024. Among them, 30 were male and 12 female.

Eighteen patients were from the capital city, with ages at presentation ranging from 14 days to 5 years and a median age of 17.5 months (Figure 1). During this period, there were a total of 83 episodes of HAEC: 30 (36%) were pre-pull-through and 53 (64%) occurred post-pull-through. For half of our patients, the diagnosis of HD was made during the neonatal period. Four patients had Down syndrome, and 9% had associated anomalies, including congenital heart disease, retroviral infection, and Caroli's disease. One patient with Down syndrome had multiple associated conditions, including congenital heart disease, pulmonary hypoplasia, duodenal atresia, and Caroli's disease, for which a diamond duodenoduodenostomy, staged Soave pull-through, and liver transplantation were performed in that order.

Eighty-five percent of the patients who underwent definitive procedures had a Soave pull-through, while the rest of the patients underwent primary endorectal pull-through. Three patients had long segment HSD. Biopsy of the most proximal segment at the time of pull-through showed hypogangliosis in two patients and agangliosis in the remaining two, while the others showed gangliosis. Of the 42 patients, 27 experienced post-pull-through enterocolitis, 12 had pre-pull-through enterocolitis without a colostomy, and 3 had enterocolitis while on colostomy. Seven of the 27 patients with post-pull-through enterocolitis had one or more pre-pull-through episodes.

The duration of symptoms ranged from 1 to 15 days, a median of 4 days. The most common presenting symptoms were vomiting (76%), foul-smelling diarrhea (76%), and fever (64%). Additionally, 26% of the patients presented with severe malnutrition. On physical examination, 91% exhibited abdominal distension, 74% had explosive stool, and 12% presented with hemodynamic instability (Figure 2). Imaging revealed that 98% had dilated bowel loops, 38% had a colon cut-off sign, and 10% had multiple air-fluid levels. Sixty-two percent of our patients had mild HAEC, 24% had moderate, and 14% had severe HAEC. All patients received antibiotic therapy and rectal irrigation, with hospital stays ranging from 2 to 30 days, and a median of 5 days. Five patients required a leveling colostomy.

Two patients died from severe sepsis and multi-organ failure. The first was pre-pull-through, presented with two days of illness, was in shock, and had severe HAEC. The

second patient, post-staged Soave pull-through, had severe HAEC and experienced one episode of pre-pull-through and three episodes of post-pull-through enterocolitis. He was on oral Metronidazole prophylaxis and presented 15 days after symptom onset, severely malnourished and in shock. Neither patient had Down syndrome or other known associated anomalies. Both were admitted to the intensive care unit, started on intravenous antibiotics, and received rectal irrigation.

Twenty-six percent (11/42) of our patients experienced recurrent HAEC. Three patients had 4 recurrences, five had 3 recurrences, and three had 2 recurrences. Univariate analysis revealed that the presence of pre-pull-through HAEC was significantly associated with an increased risk of recurrence. Adjusting for Down syndrome, associated anomalies, the presence of stricture, and long segment HSD, multinomial regression analysis showed that patients with pre-pull-through HAEC were 8 times more likely to develop recurrent enterocolitis (CI 1.3-48.3, P=0.02). Gender, Down syndrome, associated anomalies, long segment Hirschsprung disease, and stricture presence were not associated with an increased risk of recurrence (Table 1).

Four of the eight patients with recurrent post-pull-through HAEC were investigated for the cause of their recurrence. Two patients underwent examination under anesthesia and dilation of a stricture, while the other two had a barium enema suggestive of Hirschsprung disease, confirmed by rectal biopsy. Both underwent repeat pull-through procedures.

Various preventive strategies were implemented to decrease the risk of recurrence. Forty percent of our patients were put on oral Metronidazole, while 12% received rectal irrigation and 12% rectal stimulation. Metronidazole ([OR] 0.14, CI 0.02-0.81, P=0.03) and rectal stimulation ([OR] 0.05, CI 0.004-0.69, P=0.02)) were found to reduce the risk of recurrence.

Figure 1

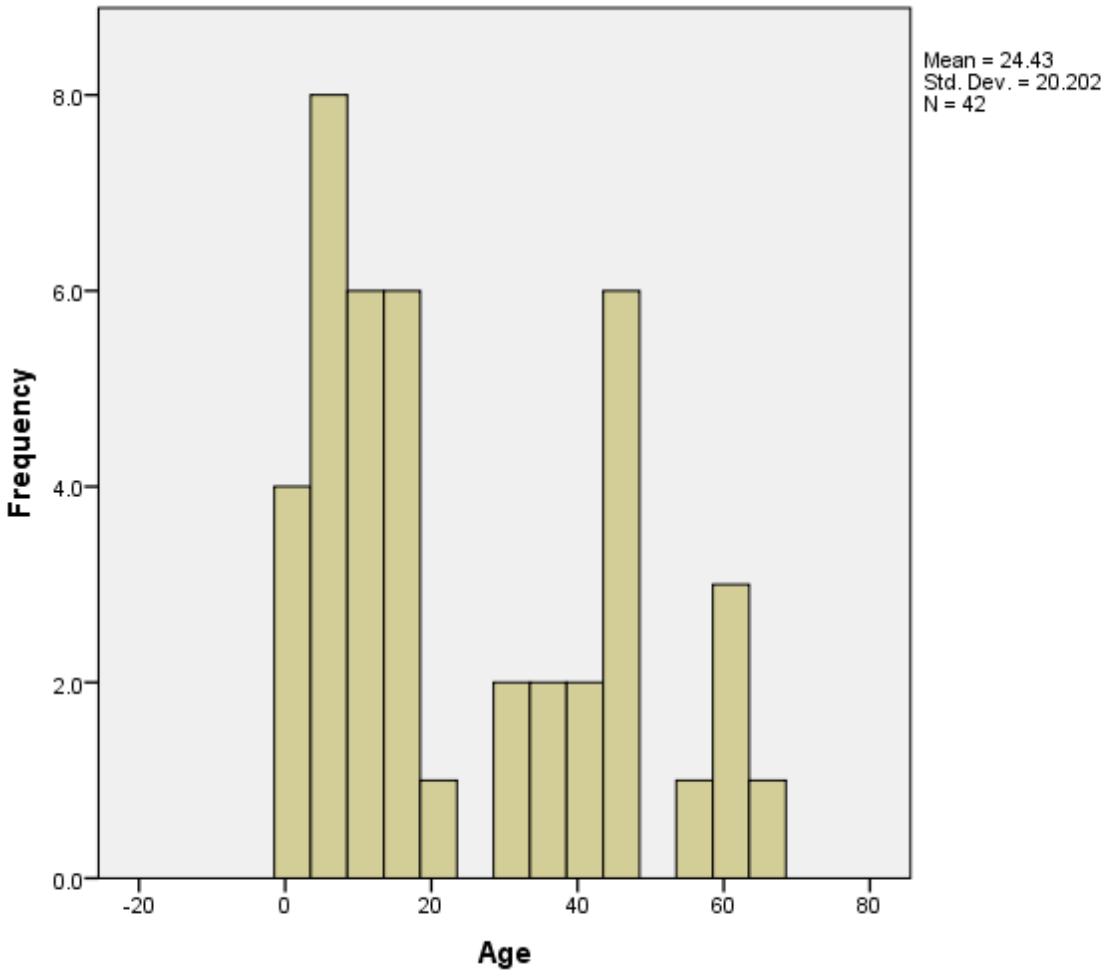

Mean = 24.43
Std. Dev. = 20.202
N = 42
Frequency
8.0
6.0
4.0
2.0
0.0
-20
0
20
40
60
80
Age

Figure 2

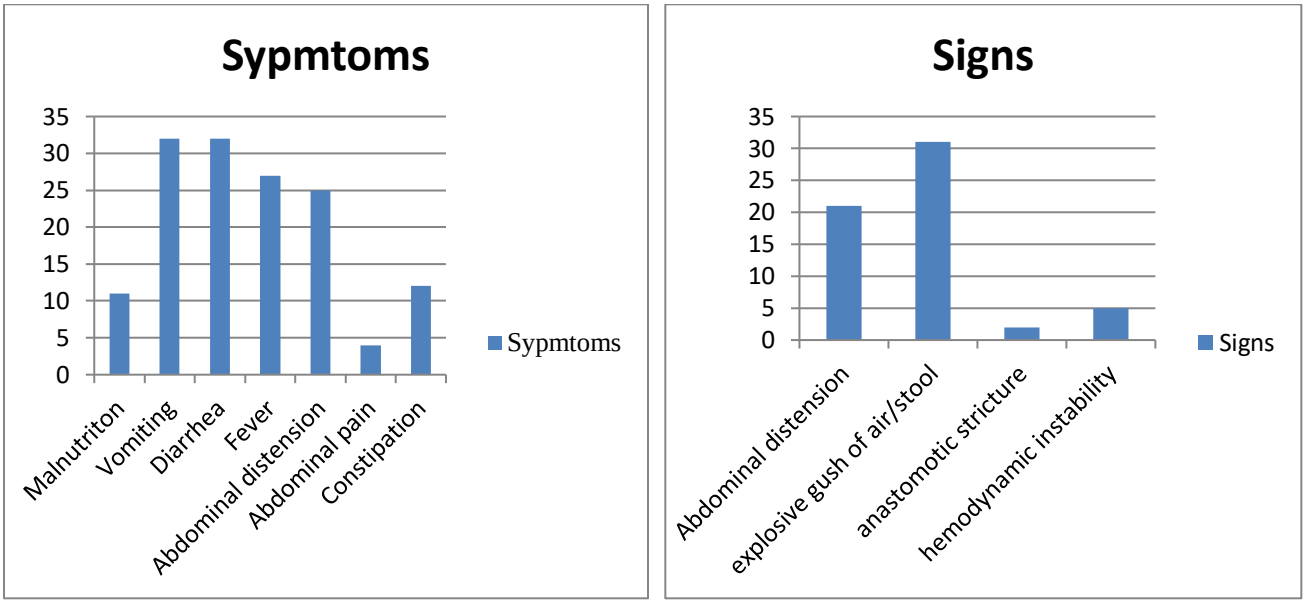


Table 1: Risk factors for recurrence

Risk Factor	Odds ratio	Confidence interval	P value
Pre HAEC	8	1.3-48.3	0.02
Down syndrome	1.2	0.04-31.1	0.93
Presence of stricture	0.4	0.1-11.1	0.57
Long segment HSD	5.7	0.4-73.16	0.18

Figure 3

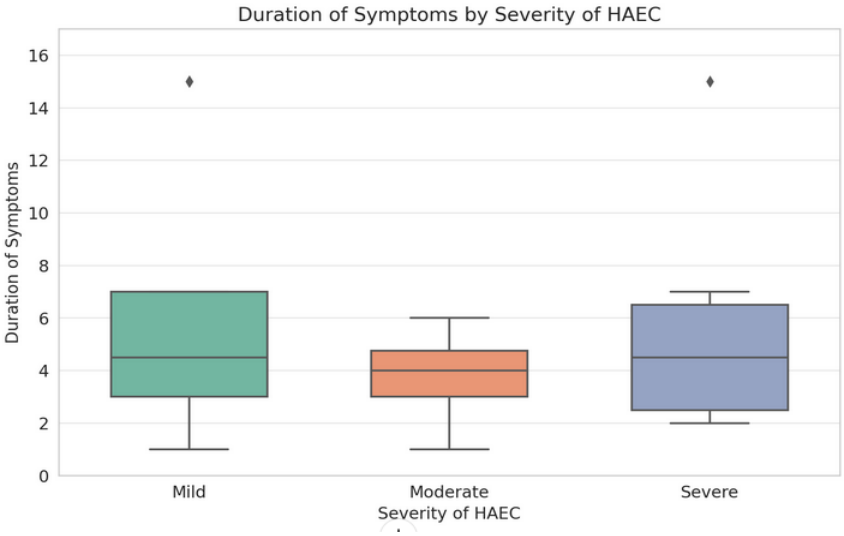
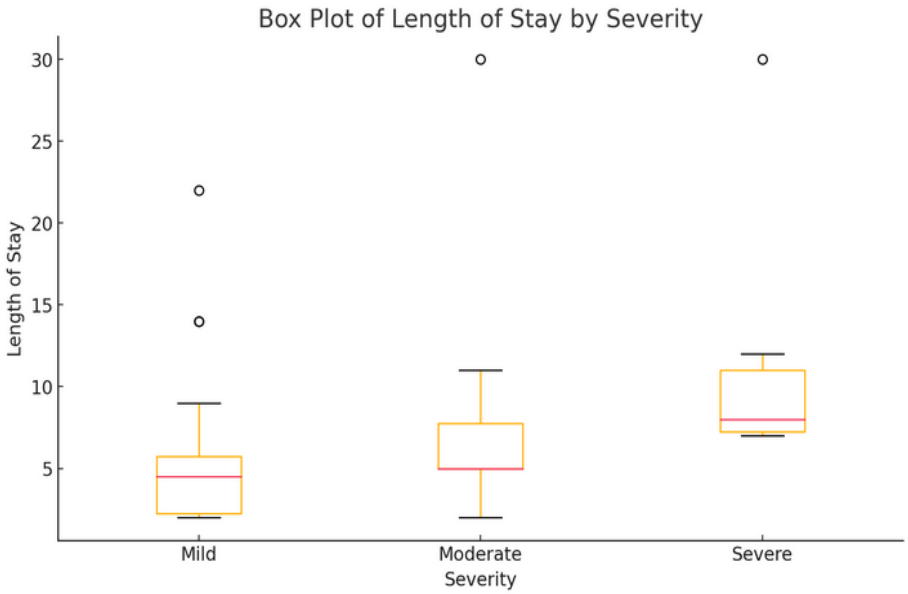


Figure 4



Discussion

Hirschsprung's disease (HD) is estimated to occur in 1 out of 5000 live births. [1] It accounted for nearly 14% of the total pediatric surgical admissions and procedures in Black Lion Hospital, Addis Ababa, Ethiopia. [8] This study aimed to examine risk factors for the occurrence of Hirschsprung's associated enterocolitis (HAEC), assess recurrence and evaluate treatment outcome for affected patients.

HAEC is a major source of morbidity and mortality in HD patients, although rates have declined in recent years. Various theories have been put forward as a cause for HAEC but the underlying mechanisms remain unclear.

Bill and Chapman suggested partial mechanical obstruction may contribute to HAEC by leading to stasis and bacterial overgrowth. [9] This theory is supported by a Canadian study that found mechanical factors, such as bowel obstruction and anastomotic stricture, increased the risk of post-pull through HAEC. [3] Anastomotic strictures were associated with a 2.8-fold increase in the incidence of HAEC, as reported in Hackam's study, which is consistent with findings from the Ohio study and others. [3,10,11] In our cohort, two patients presented with a stricture, indicating the importance of recognizing and addressing mechanical factors in the management of HAEC.

Down syndrome, characterized by inherent immune deficiencies, has been suggested as a risk factor for HAEC. Quinn et al. reported that 47% of their patients with Down syndrome experienced enterocolitis, a finding echoed in other studies. [3,4,12-15] These groups of patients also continue to have disturbances in their bowel function compared to those without Down syndrome. [16] However, this association is not universally accepted [17]; for instance, only10% (4/42) of our HAEC patients had Down syndrome, indicating variability in risk across different populations.

Carneiro et al. found that female gender was a risk factor for HAEC, with 50% of girls developing the condition compared to 29% in boys. However, this finding is not

consistently supported by other studies. [4,18-20] In our cohort, 71% of the patients were male.

Initial findings suggested that the type of surgery (Swenson and endorectal pull-through vs. Duhamel) influenced HAEC risk, but subsequent studies have failed to confirm this association. [4,20] In our center, we primarily perform Soave pull-through, limiting comparisons with other surgical techniques.

While some studies, including those from China, indicated and increased incidence of HAEC in cases of long segment aganglionosis, other research has found no significant association. [3,4,18,20,21] Our cohort included only three patients with long segment HD (transition proximal to the mid-transverse colon), making it difficult to draw strong conclusions.

The incidence of enterocolitis in patients with significant associated anomalies has been suggested to be higher than in those without anomalies. [4,22] In our study, four patients had associated anomalies, though the overall impact on HAEC development remains debated in the literature. [18]

The presence of intestinal neuronal dysplasia (IND) in HD patients has been linked to persistent bowel symptoms, including enterocolitis. [23,24] However, since our pathologists do not routinely report on IND, we cannot definitively state it as a risk factor in our cohort.

Our study supports existing literature indicating that pre-operative enterocolitis is an independent risk factor for post-operative HAEC. Twenty-six percent of patients who developed post-operative HAEC had one or more episodes of pre-operative enterocolitis. This aligns with studies that show an association between pre-operative enterocolitis and subsequent recurrence. [5,9,18,21,22]

The incidence of recurrent HAEC varies widely in the literature, ranging from 5.2% to 56%. [3,10,13,17,21,22,25,27] Our study found a 26% recurrence rate, consistent with these findings. “Histologically, enterocolitis is characterized by infiltration of

neutrophils into the crypts and retention of mucus leading to crypt dilatation and intestinal wall inflammation, which can contribute to the loss of epithelial barrier function. Consequently inflammation can worsen and persist, initiating a vicious cycle of perpetual inflammation." [10,21]

Patients with pre-operative HAEC have a heightened risk of recurrent enterocolitis. [21,26,27] In our study, those with pre-operative HAEC were found to be eight times more likely to experience recurrent enterocolitis (CI 1.3-48.3, P=0.02).
Few studies have assessed risk factors for recurrent HAEC. Pruitt et al. found that congenital neurologic anomalies, pre-operative HAEC, and a history of central nervous system infection significantly increased the risk of recurrence, while chromosomal abnormalities did not. [28] Similarly, our study found no association between Down syndrome and recurrence, nor did gender or the presence of associated anomalies confer an increased risk.

In infants presenting with recurrent enterocolitis post-pull-through, it is crucial to rule out mechanical causes of partial bowel obstruction. If contrast enema is unrevealing, further evaluation via examination under anesthesia and rectal biopsy may be necessary to exclude aganglionosis. If biopsy results are normal, posterior anal myotomy or myectomy should be considered. [7,12,15,18,27,29,30] In patients suspected of having internal anal sphincter achalasia or colonic dysmotility, anorectal manometry can be used to make a diagnosis [30] In cases of anastomotic strictures, dilation trials are recommended, with redo pull-through reserved for unsuccessful dilations.[7,17,30] However, our center faced challenges in investigating recurrent HAEC, as only four patients underwent further evaluations, likely due to financial constraints.

The most common presenting symptoms in our cohort were vomiting (76%), foul-smelling diarrhea (76%), and fever (64%). Additionally, 26% of the patients presented with severe malnutrition. On physical examination, 91% exhibited abdominal distension, 74% had explosive stool, and 12% showed signs of hemodynamic instability. These findings are consistent with previous studies that identified abdominal distension, fever, and foul-smelling, explosive diarrhea as the most common symptoms of HAEC. [12,15,19,31]

Elhalaby reported colonic dilation as the most sensitive radiologic finding (90%), albeit with low specificity (24%), while the colon cut-off sign demonstrated both sensitivity (74%) and specificity (86%). “Dilated bowel loops, ectopic air, and signs of bowel obstruction, though nonspecific, are highly indicative of HAEC and were significantly associated with the condition.” [22,31] In our series, dilated bowel loops were the most common radiologic finding (98%), and 38% of patients demonstrated the colon cut-off sign. However, normal radiologic findings do not eliminate the diagnosis of HAEC.

The principles of managing HAEC have remained largely unchanged, focusing on resuscitation, fluid and electrolyte stabilization, bowel decompression, and antibiotic therapy. If there is no improvement with the aforementioned measures, a leveling colostomy is recommended, particularly in neonates. [4,11,12,15,22,30] In our series, all patients were treated with antibiotics and rectal irrigation, and five required a leveling colostomy. While sodium cromoglycate has shown efficacy in treating recurrent HAEC [10], it is not available in our country. Mortality has ranged from 0-33%. [30]Our study reported a low mortality rate of 4.8%, which is favorable compared to other literature. [3,5,9,11,20,22,24,32]

Preventing HAEC is paramount. Various medical and surgical measures have been proposed, including parental education about HAEC and its early management.[33] Irrigation protocols, such as those initiated by Marty et al., have demonstrated a reduced incidence and severity of HAEC, [34] although long-term prophylactic use of antibiotics remains controversial due to concerns about resistance. [29,30] Anal dilation may have a protective effect against HAEC. However, since anal dilations are not routinely performed after pull-through procedures, the effectiveness of routine anal dilation as a preventive measure for HAEC remains uncertain. [11,30] In our series Metronidazole ([OR] 0.14, CI 0.02-0.81, P=0.03) and rectal stimulation/dilation ([OR] 0.05, CI 0.004-0.69, P=0.02) were found to reduce the risk of recurrence. Irrigation was not found to significantly influence the recurrence of HAEC in this series (P=0.59).

Limiations

A small sample size was the primary limitation of our study, and, like many retrospective studies, it faced inherent and unavoidable challenges, including the loss of important clinical information, such as instances where investigations were not recorded.

Conclusion

This study highlights the significant impact of Hirschsprung's associated enterocolitis (HAEC) on pediatric patients, revealing a high incidence of both pre- and post-pull-through episodes. Despite the limitations of a small sample size and the inherent challenges of retrospective data collection, our analysis identified key risk factors associated with recurrence, notably the presence of pre-pull-through HAEC. Implementing preventive strategies, such as the use of oral Metronidazole and rectal stimulation, may help mitigate recurrence rates. Future research with larger, multi-center cohorts is essential to validate these findings and further enhance our understanding of HAEC management, ultimately improving outcomes for affected patients.

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Annexes

Questionnaire

1. **Socio-Demography:**

   Age: _____ Sex: _____ Address: _____

   Card no: _____ Phone number: _____

2. Time at diagnosis of HSD _____
3. Presence of Down's syndrome Yes □ No □
4. Associated other anomaly Yes □ No □ Unknown □
5. If yes what: (please mention all): _____

   _____
6. At current presentation the child is: Pre Pull-through & colostomy □ Post-colostomy □ Post Pull-through □
7. Pre Pull-through enterocolitis Yes □ No □
8. If so how many times: _____
9. Number of recurrence: pre colostomy _____,on colostomy pre PT_____, post PT_____
10. Investigation for recurrence:_____
11. Pre-pull through malnutrition Yes □ No □ Not assessed □

    At current presentation:

12. Duration of symptoms: _____

    Vomiting Yes □ No □

    Diarrhea Yes □ No □

Fever	Yes □	No □
Abdominal distension	Yes □	No □
Abdominal pain	Yes □	No □
Constipation (Post-op)	Yes □	No □

13. Signs

Abdominal distension	Yes	□	No □
Fever	Yes	□	No □
Explosive gush of air and stool	Yes	□	No □
Narrowing at the sight of anastomosis	Yes	□	No □
Hemodynamic instability at presentation	Yes	□	No □

14. Laboratory and radiologic findings

Leukocytosis	Yes □	No □
Left shift	Yes □	No □
Elevated CRP	Yes □	No □
Dilated bowel loops	Yes □	No □
Colon cut-off sign	Yes □	No □

15. Others:_____

_____

16. Severity of HAEC Mild □ Moderate □ Severe □

17. Type of definitive surgical repair

Primary PT □ Soave □ Swenson □ Still on colostomy □ Not done □

18. Biopsy (Proximal end) Ganglionated □ Hypoganglionated □ Aganglionic □

19. Long segment aganglionosis Yes □ No □

20. Treatment outcome

Length of hospital stay_____

Needed leveling colostomy Yes □ No □

Died □ Survived □

21. Prevention strategies

Irrigation □ Rectal stimulation □ Metronidazole □ None □