Gut Microbiome profile on hirschsprung diseases with hirschsprung associated enterocolitis and non-hirschsprung associated enterocolitis: A systematic review

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ABSTRACT

Introduction: Hirschsprung's disease (HSCR), commonly known as aganglionic megacolon, is a rare congenital intestinal illness. Hirschsprung-associated enterocolitis (HAEC), an HSCR complication, is the major cause of morbidity and mortality in patients. Many research has highlighted specific microbiomes that promote HAEC, although there is still controversy on microbiome management. The aim of this study is to profile the gut microbiome of paediatric patients on HSCR with or without HAEC.

Materials and Methods: We conducted an analytical descriptive systematic review of relevant case reports from inception research articles between January 2014 to October 2024 using 3 databases following PRISMA guidelines. We extracted data of gut microbiomes in humans with HSCR with or without HAEC. Data about microbiome's effects on gut physiology were also extracted.

Results: This study identified 244 citations; 17 articles were included and analyzed. Proteobacteria were the most common bacteria in HSCR patients developing HAEC and Bacteroidetes were the most common bacteria found in HSCR patients without HAEC.

Conclusion: Proteobacteria were associated in HSCR patient developing HAEC. Therefore, gut microbiome dysbiosis may also be the key point to prevent HAEC.

KEYWORDS:
Gut microbiome, Hirschsprung diseases, Aganglionic megacolon, Hirschsprung Associated Enterocolitis

INTRODUCTION

Hirschsprung's disease (HSCR), commonly known as aganglionic megacolon, is a rare congenital intestinal illness caused by the early termination of craniocaudal migration of enteric neuroblasts during development, resulting in distal intestine aganglionosis and bowel obstruction.[1-2,4,8] This condition can extend into the proximal colon but rarely affects the small intestine.[2] Consequently, various lengths of the distal colon are unable to relax, resulting in functional colonic blockage over time.[2-3,6] It affects around 1 in every 5,000 births.[2] Most individuals with heritable variation are detected through rectal biopsy in the newborn period due to substantial constipation; nevertheless, a subset of infants shows symptoms until early childhood or even adolescence.[2,5]

The most serious complication is HSCR associated enterocolitis (HAEC), which occurs in up to between 17.3% and 35% of cases and can have severe long-term implications, including death, with a mortality rate of 1 to 10%.[2,5,7]

Hirschsprung's associated enterocolitis (HAEC), defined as a clinical syndrome characterized by diarrhea, stomach discomfort, fever, and, eventually, septic shock.[4,6]

The specific pathophysiology of HAEC is mostly unknown, even though various explanations have been hypothesized, including intestinal barrier failure, decreased gastrointestinal mucosal immunity, and dysbiosis of the enteric microbiota may contribute to HAEC.[3,5]

Most critically, HAEC remains the major cause of death among infants and children with HSCR HAEC is distinguished by inflammation of the intestinal crypts, crypt dilatation with mucus retention, abscess formation, mucosal ulceration, and transmural necrosis of the colon near the affected section.[4] Bacterial translocations across the intestinal wall in conjunction with particular changes of the intestinal microbiota have been hypothesized as a contributing mechanism in the development of HAEC.[4]

Recent studies suggest that an aberrant intestinal milieu, particularly gut microbiota, plays a role in the etiology of HSCR.[2]

The microbiome is the complete set of bacteria, genes, and genomes in a given environment.[5] The human body contains approximately 10 times more bacteria than somatic and germ cells.[5] Most live in human gastrointestinal system, which is thought to contain 10 to 100 trillion microbial cells and over 1000 species.[5] The gut microbiota is a diverse collection of bacteria. Most live in the distal ileum and colon, which have the ideal habitat for microbial nutrients (e.g., vital amino acids, vitamins) and indigestible substances (e.g., plant polysaccharides).[5]

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The gut microbiome begins to colonize after birth and changes dramatically.[2] Indeed, abnormal microbiome composition and dynamics have been found in HSCR patients, particularly those with HAEC.[1,2] Intestinal microbiome changes composition and relative microbial abundance during growth from infancy to adulthood.[1-2] Early childhood is characterized by differential temporal development of gut microbiota.[1,2] Certain microorganisms (Proteobacteria and Enterobacteriaceae amongst all) show major abundance after birth and decrease later, towards adulthood.[1]

Although certain microbes, bacteria, or viruses resemble pathogens, the majority of intestinal microorganisms provide numerous benefits, including as strengthening the gut barrier, creating nutrition, boosting pathogen interception, and modifying host immunity.[5] A healthy gut environment is distinguished by a diversified and plentiful microbiota that is dominated by Bacteroidetes, Firmicutes, and Actinobacteria.[5] Other typical characteristics include an intact mucosal barrier and high short chain fatty acid (SCFA) synthesis.[5] These balancing processes can be disrupted by altered microbial composition and function, known as dysbiosis, which is generally characterized by changes in the microbial population and its function, as well as disturbance of mucus and epithelial barriers.[5] Dysbiosis is linked to a variety of GI illnesses, including HSCR.[5,8]

Based on these considerations, our study aims is to profile the gut microbiome of pediatric patients on HSCR with or without HAEC.

MATERIALS AND METHODS

Following the guidelines set by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA), we developed the procedures for the current systematic review.

Literature Search

For this review, keywords and Medical Subject Heading phrases were utilized to search PubMed/Medical Literature Analysis and Retrieval System Online (MEDLINE) (2014-October 2024), Science Direct (2014-October 2024), and Springer (2014-October 2024) focusing on four key concepts: studies investigating microbiota in Hirschsprung Diseases (HSRC), HSRC with Hirschsprung Associated Enterocolitis (HAEC), HSRC without HAEC, and the microbiota profile leading to HAEC in HSRC. References found in the identified papers were reviewed to generate additional studies. After retrieving all full texts, 17 articles were included in this review. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) technique was used for search screening and article selection (Figure 1).

The inclusion criteria were English-language items only, journals focused on the gut microbiome of Hirschsprung Diseases with or without HAEC, and publications from the last 10 years with available full texts.

Exclusion criteria included Systematic Review journals, research data before 2014, and studies that did not discuss gut microbiota. Data collection yielded 203 papers after screening titles and abstracts out of 250 initial studies found, with 17 papers qualifying for analysis after full-text reading (Figure 1).

RESULTS

Out of 244 literatures, we include and analyze 17 articles, 16 of them were studies in humans and 1 of them was genome study. The sample used mostly came from fecal and soft tissue, but there were some studies using intestinal content and genome database for the sample.

In Figure 2 and Table I, we could see that most of the study found out that Bacteroidetes was the dominant gut microbiome in HSCR patients and Proteobacteria was the dominant gut microbiome in HAEC patients.

DISCUSSION

Hirschsprung-associated enterocolitis is severe and lethal complication that can happen in HSCR patient, this condition mostly characterized by fever, abdominal distention, diarrhea, and sepsis; this complication is leading cause of morbidity of HSCR patients and can occur pre- and postoperatively.[9]

There are several risk factors known that can develop HAEC; pre-operatively factor such as family history of HSCR, long segment HSCR, trisomy 21, presence of associated congenital anomalies, and delay in diagnosis of HSCR can lead to HAEC; postoperative risk factors such as the presence of the residual aganglionic segment after definitive surgery that can happen if an area of bowel or the transition zone between normal and aganglionic bowel is not entirely resected, bowel torsion proximal to the anastomosis site, formation of an anastomotic stricture, cuff stenosis on the pulled-through, bowel dysmotility or functional obstruction after pulled-through procedure.[9]

Dysbiosis is the novel insight of HAEC risk factor, dysbiosis is condition that happens when there is unbalance of gut microbiome.10 Our study found that microbiome in HSCR patients were dominated by Bacteroidetes, on the other hand HAEC patient dominated by Proteobacteria.

Bacteroidetes

Bacteroidetes frequently inhabit soil ecosystems and are associated with diverse eukaryotic hosts like plants, animals, and humans. Alterations in gut and plant microbiome community structures often align with dysbiosis and changes in host performance. The main bacterial phyla in eukaryotic microbiomes are Firmicutes, Bacteroidetes, Proteobacteria, and Actinobacteria.[11]

Bacteroides species are usually benign commensals in the gut but can turn into opportunistic pathogens when they move to other parts of the body. For instance, Bacteroides fragilis, a gut symbiont, is often found as an opportunistic pathogen and is the most common isolation from intra-abdominal abscesses. In the gut, Bacteroides species perform various roles, such as defending against pathogens and supplying nutrients to other gut microbes.[12]

Table I: Studies related to Gut Microbiome and the Pathomechanism

No	Title	Author	Years	Sample	Subject	Specimen	Gut Microbiome	Additional Treatment
1	16S rRNA Sequencing Reveals Alterations of Gut Bacteria in Hirschsprung-Associated Enterocolitis	HaoShi, YongShe, WuMao, YiXiang, LuXu, SanjunYin QiZhao	2024	30	Human	Intestinal content	Bifidobacterium, Lactobacillus, and Veillonella	The S group, the dominant phylum was Firmicutes, whereas Bifidobacterium, Lactobacillus, and Veillonella were notablyenriched in the H group, whereas Enterococcus showed a striking enrichment in the S group. Bifidobacterium is a commonly used probiotic, and recent studies have demonstrated its potential to attenuate major depressive disorder by regulating gut microbiome and tryptophan metabolism Lactobacillus, another probiotic, has been found to enhance immune checkpoint blockade therapy, highlighting its potential benefits in respiratory diseases
2	Association between gut microbiota and Hirschsprung disease: a bidirectional two-sample Mendelian randomization study	Wei Liu, Hanlei Yan, Wanying Jia, Jingjing Huang, Zihao Fu, Wenyao Xu, Hui Yu, Weili Yang, Weikang Pan, Baijun Zheng, Yong Liu, Xinlin Chen, Ya Gao, Donghao Tian	2024	18.340	Human	Genome-wide genotype	Eggerthella, Peptococcus, Ruminococcus, Clostridiaceae, Mollicutes RF9, Ruminococcaceae, and Paraprevotella	The abnormal intestinal microenvironment contributed crucially to the HSCR pathogenesis, especially gut GM, but without details flora colonizing the intestine
3	Prospective study reveals a microbiome signature that predicts the occurrence of post-operative enterocolitis in Hirschsprung disease (HSCR) patients A Metagenomics	Weibing Tang, Yang Su, Chen Yuan, Yuqing Zhang, Lingling Zhou, Lei Peng, Pin Wang, Guanglin Chen, Yang Li, Hongxing Li, Zhengke Zhi, Hang Chang, Bo Hang, Jian-Hua Mao, Antoine M Snijders, Yankai Xia.	2020	75	Human	Soft tissue	Gram-negative bacteria, especially Enterobacteriaceae family	Gram-negative bacteria, a major cause of enteric infection, can activate mucosal inflammation by binding LPS, a component of the outer membrane, to enteric toll-like receptor HSCR patients who were exclusively breastfed tended to have a lower abundance of Gram-negative bacteria, particularly Enterobacteriaceae HSCR patients without exclusive breast feeding had an enteric microbiome enriched for LPS biosynthesis proteins
4	Study on Hirschsprung's Disease Associated Enterocolitis: Biodiversity and Gut Microbial Homeostasis Depend on Resection Length and Patient's Clinical History	Alessio Pini Prato, Casey, Bartow-McKenney, Kelly Hudspeth, Manuela Mosconi, Valentina Rossi, Stefano Avanzini, Maria G. Faticato, Isabella Ceccherini, Francesca Lantieri, Girolamo Mattioli, Denise Larson, William Pavan, Carlotta De Filippo, Monica Di Paola, Domenico Mavilio, Duccio Cavalieri.	2019	31	Human	Fecal	Bacteroidetes, Alistipes, Enterococcus, Proteobacteria Non-HAEC : dominated by Bacteroidetes HAEC : dominated by Proteobacteria TCSA Total Colonic Aganglionosis showed lower biodiversity and increased Proteobacteria/Bacteroidetes relative abundance ratio.	Total Colonic aganglionosis had absence of Bacteroidetes affects the production of short chain fatty acids (SCFAs) which are fundamental for intestinal homeostasis. dysmotility and absence of bacteroidetes affect overgrowth of potentially harmful microbial species like Proteobacteria that can lead to HAEC colon resections can change the composition of intestinal microbiota and to dramatically reduce microbial diversity. The subsequent reduction of system robustness could expose TCSA patients to environmental microbes that might not be part of the normal microbiota. bacterial overgrowth, a potentially harmful microbial species, can outcompete commensals very rapidly and lead to HAEC as a result of systemic reaction to this dysbiosis

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5	Intestinal Microbiota in Hirschsprung Disease	Malla I. Neuvonen, Katri Korpela, Kristiina Kyrklund, Risto J. Rintala, Mikko P. Pakarinen.	2018	175	Human	Fecal	Abundances of Proteobacteria, Escherichia and Lactobacillus were significantly increased, Abundances of Clostridia, Oscillospira and Holdemania and Prevotella significantly decreased in patients with a history of recurrent HAEC	Patients with HD and HAEC had a significantly altered intestinal microbiome compared to healthy individuals, characterized by a lack of richness and pathologic expansions of taxa, particularly Enterobacteria and Bacilli.
6	Characterization of Bacterial and Fungal Microbiome in Children with Hirschsprung Disease with and without a History of Enterocolitis: A Multicenter Study	Philip K. Frykman, Agneta Nordenskjöld, Akemi Kawaguchi, Thomas T. Hui, Anna L. Granström, Zhi Cheng, Jie Tang, David M. Underhill, Iliyan Iliev, Vince A. Funari, Tomas Wester, HAEC Collaborative Research Group (HCRG).	2015	9	Human	Fecal	Lower proportion of Firmicutes and Verrucomicrobia, and a relatively increased proportion of Bacteroidetes and Proteobacteria in the HAEC group	These findings suggest a dysequilibrium in the gut microbial ecosystem of HAEC patients, such that there may be dominance of bacteria and fungi predisposing patients to development of HAEC. the microbiota differences between HSCR and HAEC groups may be caused by treatment; may be caused by HAEC; and may, or may not, actually contribute to HAEC.
7	Characterization of Intestinal Microbiomes of Hirschsprung's Disease Patients with or without Enterocolitis Using Illumina-MiSeq High-Throughput Sequencing	Yuqing Li, Valeriy Poroyko, Zhilong Yan, Liya Pan, Yi Feng, Peihua Zhao, Zhoulonglong Xie, Li Hong.	2016	13	Human	Fecal	HSCR patients (characterized by the prevalence of Bacteroidetes) and HAEC patients (characterized by the prevalence of Proteobacteria)	microbiota has been implicated in a variety of inflammatory gut disorders bacterial overgrowth or the presence of specific bacterial or viral pathogens

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							HSCR patients was characterized by high levels of Bacteroidetes (45%), Firmicutes (24%), and Proteobacteria (16%). HAEC patients was Proteobacteria (60%), followed by Firmicutes (30%) the HAEC-R patients was similar to that of the HAEC patients in that it was characterized by the abundance of Proteobacteria (70%) and Firmicutes (18%)	
8	Hirschsprung's Associated Enterocolitis (HAEC) Personalized Treatment with Probiotics Based on Gene Sequencing Analysis of the Fecal Microbiome	Georg Singer , Karl Kashofer, Christoph Castellani , and Holger Till	2018	1	Human	Fecal	Bacteroidetes, Proteobacteria, Firmicutes	disruption of the intestinal mucosal barrier ("leaky gut"), an increase of inflammatory parameters, an abnormal immune response of the intestinal tract, and infection due to specific pathogens dysbiosis, inflammatory bowel disease
9	Pathways and microbiome modifications related to surgery and enterocolitis in Hirschsprung disease	Roberto Biassoni · Eddi Di Marco · Margherita Squillario · Elisabetta Ugolotti · Manuela Mosconi · Maria Grazia Faticato · Girolamo Mattioli · Stefano Avanzini · Alessio Pini Prato	2022	31	Human	Fecal	Proteobacteria, Bacteroidetes, Firmicutes, and Actinobacteria	HAEC phase we found bacteria displaying Type I pili known to bind tightly to the gut wall, while after the acute HAEC phase, the taxa were characterized by virulence factors belonging to the polyamines dysbiosis or maturation of microbiome in infancy. several genes encoding for Type 1 pilus assembly proteins, biofilm formation, and antibiotic resistance virulence factors might be associated with severe colonic disease and are typical of entero-hemorrhagic E. coli (EHEC) pathogens. Of note, the inferred functional analysis of patients that have been sampled during or close to a HAEC episode showed bacteria strains characterized by type I pili found on enterotoxigenic E. coli and other bacteria which bind to intestinal epithelial cells, that are known to play an essential role in the virulence of bacteria pathogens leading to microbial invasion and colonization of the gut wall Bacteroidetes had a generic protective role in gut inflammation

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10	A pilot study characterizing longitudinal changes in fecal microbiota of patients with Hirschsprung-associated enterocolitis	Kristopher D Parker , Jessica L Mueller, Maggie Westfal , Allan M Goldstein , Naomi L Ward	2022	5	Human	Fecal	Proteobacteria, Bacteriodes, Firmicutes, B. fragilis	B. fragilis was primarily associated with active HAEC and disappearance in remission samples. Oral antibiotics have also been associated with depletion of beneficial lactobacilli and bifidobacterial
11	Exclusive breastfeeding reduces risk of enterocolitis by modulating the enteric microbiome in patients with Hirschsprung's disease	Weibing Tang,;Yang Su, MSc;Chen Yuan,;Yuqing Zhang,;Lingling Zhou, ;Lei Peng,;Pin Wang, ;Guanglin Chen;Yang Li,;Hongxing Li,;Zhengke Zhi,;Hang Chang, Bo Hang, ;Jian-Hua Mao, Antoine M. Snijders,and Yankai Xia	2019	253	Human	Soft tissue	HSCR patients observed increased Proteobacteria and Bacteroidetes as well as decreased Firmicutes, Increased Proteobacteria and decreased Bacteroidetes in HAEC cases Recurrent HAEC had increased Proteobacteria and Bacteroidete	Exclusive breastfeeding is an effective approach to reduce HAEC occurrence and can reduce the risk by 40%. Moreover, exclusive breastfeeding may decrease the biosynthesis and release of LPS and reduce postoperative HAEC occurrence. Breast milk ingestion may facilitate the enrichment of microbes during acquisition of the enteric microbiome (14). Exclusive breastfeeding contributes to an enteric microbiome characterized by higher a diversity, lower abundance of Gram-negative bacteria (particularly Enterobacteriaceae), and lower LPS concentrations, which subsequently reduced postoperative HAEC occurrence.
12	Fecal Microbial Profiling of Young Hirschsprung Disease Children After Pull-Through Operation	Kanokrat Thaiwatcharamas, Watcharin Loilome, Sinobol Chusilp1, Patchareeporn Tanming, Poramate Klanrit, Jutarop Phetcharaburanin	2022	10	Human	Fecal	The HD group had reduction of Bacteroidetes, Actinobacteria, Fusobacteria and TM7, while Firmicutes and Proteobacteria were increased compared to the healthy group. Firmicutes was the most prevalent in both the HD with and without HAEC groups The HAEC group had a reduction of Bacteroidetes and increased Proteobacteria compared to the HD without HAEC patients Our study found that Bacilli significantly increased in the HD	Most microbes reside in the distal ileum and colon that contain the majority of microbial nutrients including essential amino acids and vitamins, together with indigestible components such as plant polysaccharides that can be microbially fermented into SCFAs

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							group, while Erysipelotrichi and Actinobacteria significantly decreased. Although Bacilli are usually abundant in infants and are among the most common groups of probiotic bacteria, dysbiosis with a higher abundance of Bacilli was reported to be linked to diseases including HD	
13	Effectiveness of Irrigation Frequency Per Rectal on Intestinal Microbiota Colonies in Hirschsprung Associate Enterocolitis Patients	Shalita Dastamuar, Cesario Budi Prayitno1, Phey Liana, Theodorus M	2022	21	Human	Rectal swab	the most common bacteria found were Escherichia coli (52%) and then Klebsiela pneumonia (30%).	E. coli is the predominant facultative anaerobic flora of the human gastrointestinal tract. Most strains of E. coli are harmless in the lumen of the large intestine. However, more pathogenic strains have been identified and are commonly associated with urinary tract infections, enteric infections, and systemic infections, including bloodstream infections, neonatal meningitis, and pneumonia.
14	Evidence for Differentiation of Colon Tissue Microbiota in Patients with and without Postoperative Hirschsprung's Associated Enterocolitis: A Pilot Study	Ricardo A. Arbizu ,1 David Collins ,2 Robert C. Wilson,3 and Alexander V. Alekseyenko	2021	8	Human	Soft tissue	Bacteroidetes, Firmicutes and Cyanobacteria in HAEC patients Fusobacteria, Actinobacteria and Proteobacteria in HSCR patients	inflammatory, intestinal dysbiosis Total fecal SCFA composition of children with a history of HAEC
15	Altered fecal short chain fatty acid composition in children with a history of Hirschsprung-associated enterocolitis	Farokh R. Demehri, Philip K. Frykman, Zhi Cheng, Chunhai Ruan, TomasWester, Agneta Nordenskjöld, Akemi Kawaguchi, Thomas T. Hui, Anna L. Granström, Vince Funari, Daniel H. Teitelbaum	2016	18	Human	Fecal	Anaerobic microbiota (didn't mention the bacteria)	was 4-fold lower than that of HD patients without a history of HAEC. Anaerobic microbiota which produces fecal SCFAs children with HAEC history were found to have markedly reduced fecal SCFAs, and an altered SCFA profile. These findings suggest a complex interplay between altered local environment and changes in intestinal microbiota, which may influence the pathogenesis of HAEC

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16	Characterization of the intestinal microbiome of Hirschsprung's disease with and without enterocolitis	Zhilong Yan, Valeriy Poroyko, Song Gu, Zheng Zhang, Liya Pan, Jing Wang, Nan Bao, Li Hong	2014	4	Human	Intestinal content	Bacteroidetes occupied the largest portion (46%) of the genomic sequences in HD patients, followed by Proteobacteria (21%); In contrast, Proteobacteria occupied the largest portion (55%) in HAEC patients, followed by Firmicutes (18%).	The bacteria pathomechanism didn't mentioned
17	Reduced expression of the NLRP6 inflammasome in the colon of patients with Hirschsprung's disease	Christian Tomuschat, Caroline Rouget Virbel, Anne Marie O'Donnell, Prem Puri	2019	10	Human	Soft tissue	Bacteroidetes are dominant in HSCR Proteobacteria dominant in HAEC	Our results show significant differences exist in the relative levels of NLRP6 in the colon of patients with HSCR compared to healthy control colon. The pathomechanism of Proteobacteria (abundant in those patients suffering from recurrent HAEC), is penetration of the inner mucus layer by production of virulence factors with mucinase activity; however, if the inner mucus layer in patients with HSCR is defective, the clearance of those pathogens is diminished, rendering patients with HSCR to be prone to colonization with proteobacteria which may lead to HAEC.

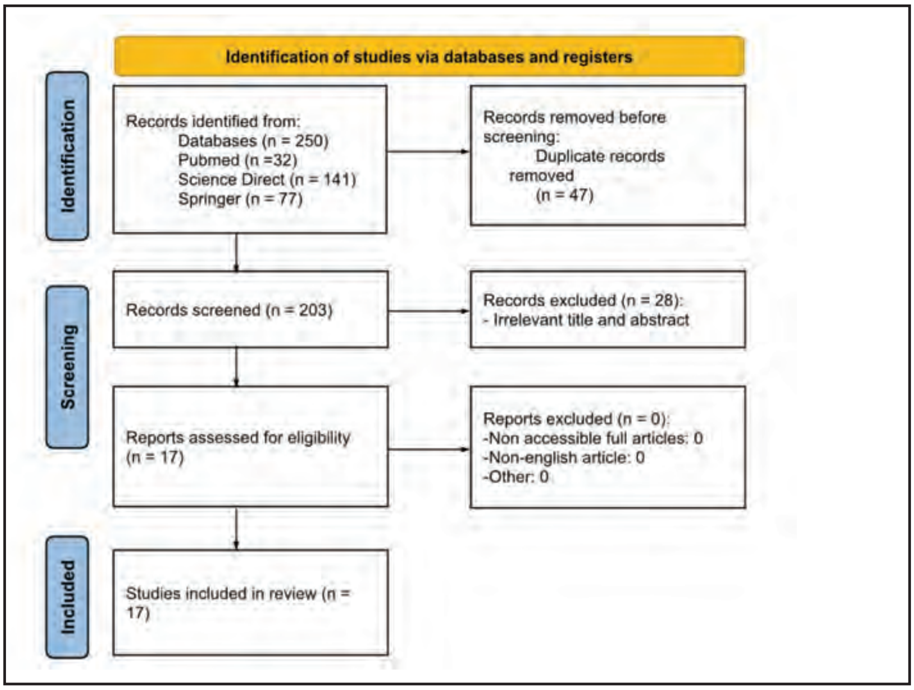

Fig. 1: Distribution of microbiome in HAEC and non-HAEC

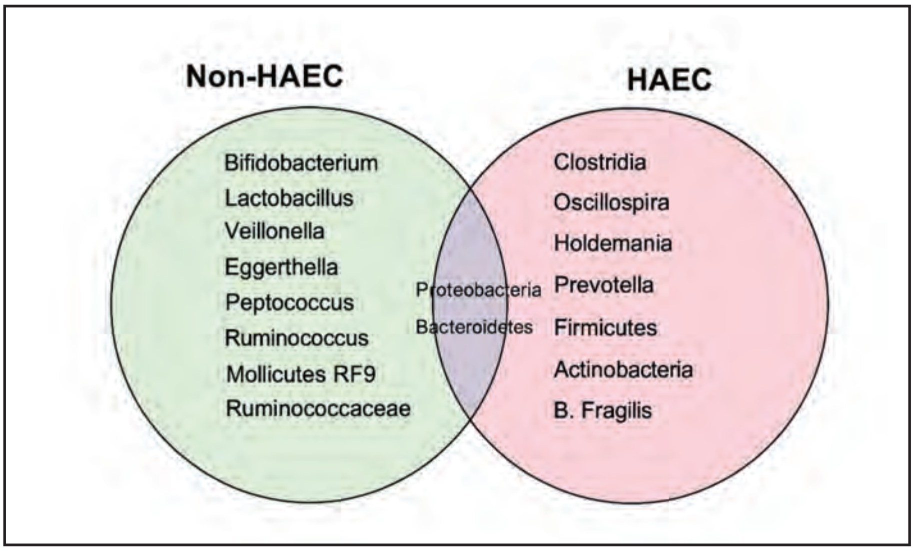

Fig. 2: Distribution of microbiome in HAEC and non-HAEC

Classifying Gram-negative Bacteroidetes has been challenging, but recent whole-genome sequencing data has improved their phylogenetic delineation. With over 32,000 genomes sequenced and assembled, the Bacteroidetes (Bacteroidota) phylum is now divided into six main classes: Bacteroidia, Cytophagia, Flavobacteriia, Chitinophagia, Sphingobacteriia, and Saprospira.[13]

A study by Prato et al. on gut microbiomes found that nearly 70% of RSA patients had gut communities composed of over 33% Bacteroidetes, while all TCSA communities had less than 2% Bacteroidetes, showing a significant difference. Additionally, the TCSA microbiota exhibited a greater presence of Proteobacteria compared to the RSA microbiota. At the genus level, Bacteroides made up more than 25% of the gut microbiota in most RSA patients, whereas all TCSA patients had less than 1% Bacteroides. Furthermore, Prato et al.'s study found no clear correlations between HEAC status, genetic background, phenotype, and gut microbiota both before and after surgery.[13]

Collectively, these findings suggest that Bacteroidetes may play a protective role in active HAEC and may return to baseline levels in HSCR patients after an HAEC episode.[14]

Proteobacteria

Proteobacteria — a diverse phylum that includes many facultative Gram-negative pathogens such as Escherichia and members of the Enterobacteriaceae — are consistently overrepresented in the guts of patients who experience recurrent HAEC.13 The pathomechanism of Proteobacteria, which are prevalent in patients with recurrent HAEC, involves breaching the inner mucus layer by releasing virulence factors that have mucinase activity (mucin-degrading enzymes, adhesins, endotoxin/LPS and secretion systems). However, if patients with HSCR have a compromised inner mucus layer, their ability to clear these pathogens is reduced, making them more susceptible to Proteobacteria colonization, which can potentially lead to HAEC.[15]

In children with HSCR the inner mucus layer and other barrier defenses are commonly altered — studies report reduced mucus integrity, disturbed short-chain fatty acid profiles that weaken mucosal defense and altered local immunity (decreased protective secretory IgA or dysregulated antimicrobial peptide expression).[20] When mucus production or organization is compromised, the normal mechanical and biochemical clearance of invading or overgrowing Proteobacteria is impaired; reduced motility from the aganglionic bowel segments further slows luminal clearance and favours overgrowth.[14]

These factors can create a permissive niche in which mucin-degrading Proteobacteria can expand, contact the epithelium more readily, and trigger an exaggerated mucosal inflammatory response — the clinical syndrome recognized as HAEC. This pathobiological model helps explain why some HSCR patients are repeatedly susceptible to enterocolitis even after surgery: persistent dysbiosis, a weakened mucus barrier, and impaired local immune/motility defenses act together to reduce pathogen clearance and permit Proteobacteria-driven inflammation.[13,20]

Decreasing the risk

Some studies mention that breast feeding can reduce the risk of development of HAEC by 40%, that proved by the decreasing biosynthesis and release of LPS and reduce postoperative HAEC occurrence moreover some studies also mentioned that HSCR patients with exclusive breastfeeding had diversity of gut microbiome.[17,18] Probiotic administrations especially that contain Bifodobacterium can reduce the risk of HAEC in HSCR patients, Bifidobacterium can suppress inflammation process using the SCFA that it produced; that was proved by some studies that found that SCFA in HAEC patients 4 times lower than in HSCR patients, moreover Bifodobacterium also higher in healthy individuals than in HSCR patients with history of HAEC.[1,16]

LIMITATIONS AND RECOMMENDATION

The numbers of patients and samples were limited. Additional research is needed to understand more fully the role and effect of microbiota and complex interactions that cause HAEC. There is a lack of clinical trials available in the field, and thus, the management strategies remain quite limited.With increasing knowledge of the role of gut microbiota dysbiosis in HAEC can provide novel specific interventions to improve dysbiosis and protect against the development of enterocolitis in the future.

CONCLUSIONS

We conclude that Proteobacteria were associated in dysbiosis HSCR patient developing HAEC. and Bacteroidetes were found in non-HAEC. With this information, Bacteriodetes microbiota can be used to control HAEC and Procteobacteria populations. In the future, microbiome nutritional therapy can be created so that microbiota can become dominant and avoid HAEC.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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