Proceedings of the 2nd International Conference on Modern Medicine and Global Health
DOI: 10.54254/2753-8818/15/20240467

Microbiome and common viral infections in acute viral gastroenteritis patients

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Abstract. Acute gastroenteritis (AGE) is a disease that exhibits a high death rate among children, particularly in underdeveloped nations. It is noteworthy that the majority of affected persons are children below the age of five1. The primary etiological factors contributing to AGE are viral and bacterial infections. This study employs a literature review methodology to investigate the variations in microbiome composition between individuals diagnosed with AGE and those who are considered to be in good health. This article also presents an overview of prevalent viral infections that contribute to acute gastroenteritis (AGE) and provides strategies for its prevention. This paper presents a comprehensive analysis of various perspectives and empirical evidence pertaining to the intricate interplay between gut microbiota and viral pathogens, as well as potential strategies for mitigating viral infections.

Keywords: AGE Patients, LEfSe, Next-Generation Sequencing.

1. Introduction

Acute gastroenteritis (AGE) is a disease that exhibits a notably high death rate in children, particularly in underdeveloped nations. It is worth noting that the majority of affected persons are children who are under the age of five [1]. The primary etiological factors contributing to AGE are viral and bacterial infections. The norovirus is not only a prevalent etiological factor for acute gastroenteritis (AGE) in children, but it is also a prominent causative agent of gastroenteritis on a global scale across all age groups [2, 3]. A link has been observed between the microbiome and digestive disorders. Drawing upon previous studies investigating the effects of medicinal interventions on the composition of gut microbiota and its correlation with the well-being and ailments of neonates [4]. The relationship between gut microbiota and the development of inflammatory bowel disease has been documented to involve both hereditary and environmental factors. Additionally, it has been suggested that advanced glycation end products may be associated with atypical manifestations of the disease. Patients who have compromised microbiota following a Norovirus infection may experience an elevated susceptibility to long-term health issues [5, 6]. This paper employs a literature review methodology to investigate the disparities in microbiome composition between individuals diagnosed with AGE and those who are considered healthy. This article also presents an examination of prevalent viral infections that contribute to acute gastroenteritis (AGE) and proposes preventive measures. This paper presents a comprehensive analysis of various perspectives and empirical evidence pertaining to the intricate interplay between gut microbiota and viral pathogens, as well as potential strategies for mitigating viral infections.

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2. Review of relevant experiment

The present study, as described in the cited references [7, 8], seeks to evaluate the microbiota composition in pediatric patients afflicted with severe or complex illnesses and experiencing acute viral gastroenteritis. A study was conducted utilizing next-generation sequencing technology to identify a cohort of 20 children diagnosed with severe or complex acute gastroenteritis (AGE), as well as a control group of 20 healthy persons. The primary objective of this study was to assess and compare the composition of the fecal microbiome in these two groups. The metagenomics data was compared using a Wilcoxon rank-sum test and hierarchical clustering analysis of bacterial reads. The results of the statistical analysis indicated a substantial reduction in the Shannon diversity index (entropy score) of gut microbiota in severe acute gastroenteritis (AGE) patients when compared to both the normal control group ($P = 0.017$) and mild to moderate AGE patients ($P = 0.011$).The gut microbiota score of five patients diagnosed with acute gastroenteritis (AGE) caused by rotavirus was shown to be considerably lower compared to individuals infected with Norovirus ($P = 0.048$). In comparison to the control group, individuals diagnosed with complicated AGE exhibited a significantly greater prevalence of Campylobacter ($P = 0.0003$), Neisseria ($P = 0.0115$), Methylobacteriaceae ($P = 0.0004$), Sphingomonas ($P = 0.0221$), and Enterobacteriaceae (0.0451).

A further investigation was conducted to analyze the patterns in the causal agents of diarrhea and the associated gut microbiota in Ghana. This analysis utilized microbiome analysis techniques, namely 16S rRNA sequencing, on stool samples from individuals experiencing diarrhea [8]. The study involved a total of 80 patients presenting with symptoms of diarrhea and 34 healthy persons serving as controls, throughout the period spanning from 2017 to 2018. The examination of species richness indicates that individuals with diarrhea exhibited a lower level of species richness compared to the control group. The examination of beta diversity revealed statistically significant distinctions between the two groups. Various infections associated with diarrhea, including Escherichia Shigella, Klebsiella, and Campylobacter, have been identified in individuals presenting with symptoms of diarrhea. Furthermore, the presence of co-infection involving these pathogens alongside enteroviruses, such as norovirus and rotavirus, was identified in multiple instances.

3. Results analysis

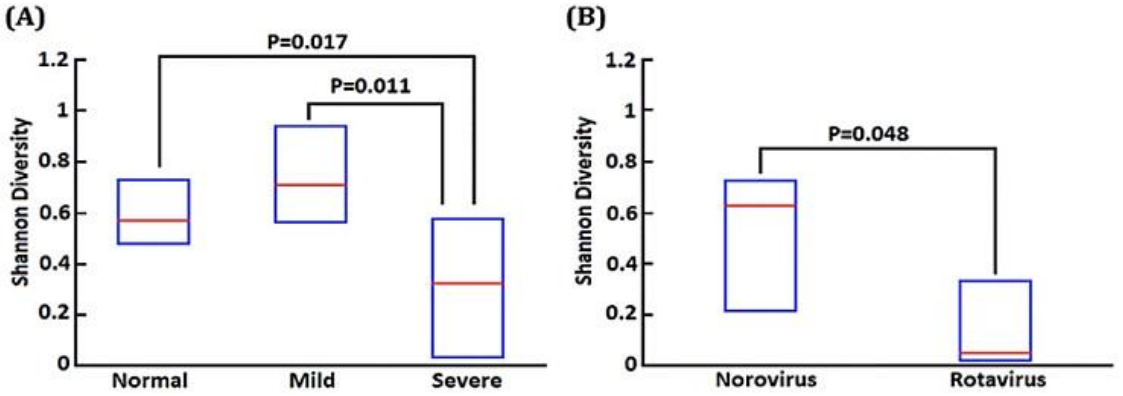

Figure 1. Diversity of microbiota among healthy controls and AGE patients with different severity. (A)Diversity of microbiota among patient with norovirus and rotavirus.(B) Statistical analysis showed that compared with the normal control group (P=0.017) and mild to moderate severe patients ($P = 0.011$) (A), the Shannon diversity (entropy score) of the gut microbiota in severe viral AGE significantly decreasedThe entropy score of the rotavirus infection was 0.05 (0.02–0.35), that was significantly lower than norovirus infection group (P = 0.048) (B) [7].

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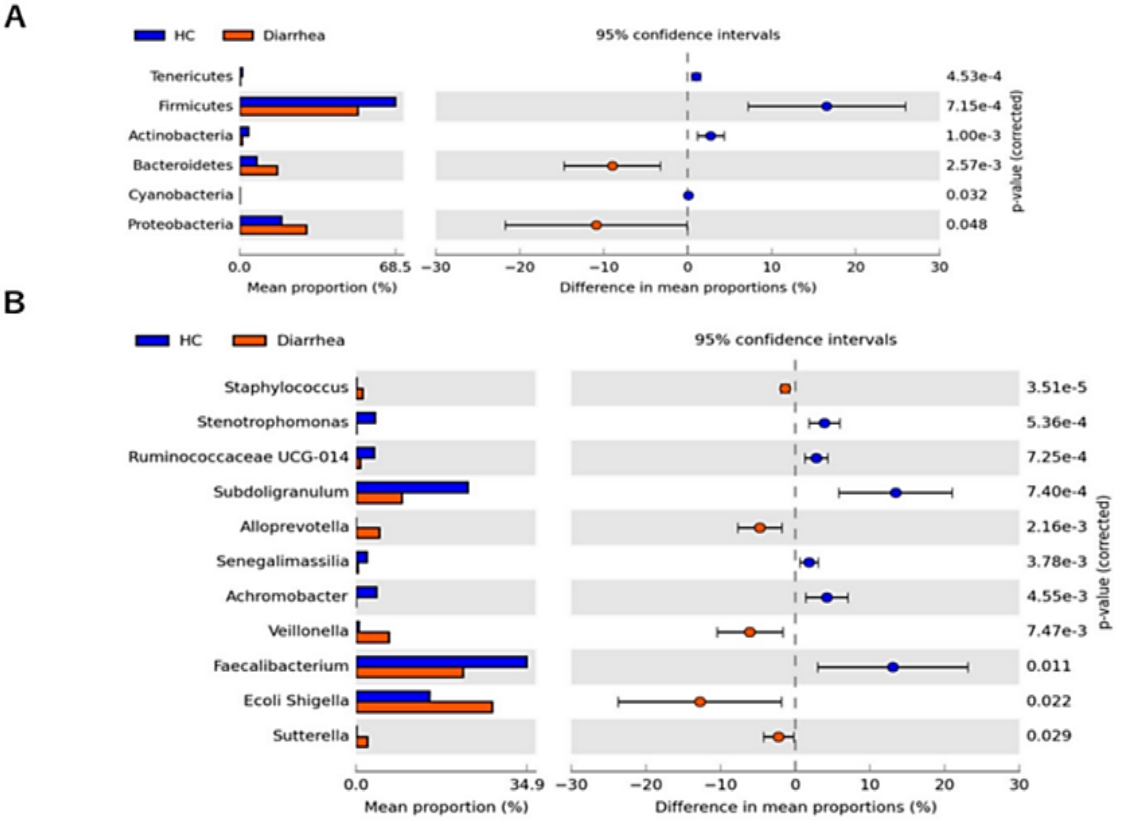

Figure 2. Fecal bacteria abundance at the phylum level by STAMP analysis. Comparison of gut microbiota between the healthy adult controls and adult patients with diarrhea by STAMP analysis at the phylum level (A) and genus level (B). HC healthy adult control, Diarrhea adult patient with diarrhea [8].

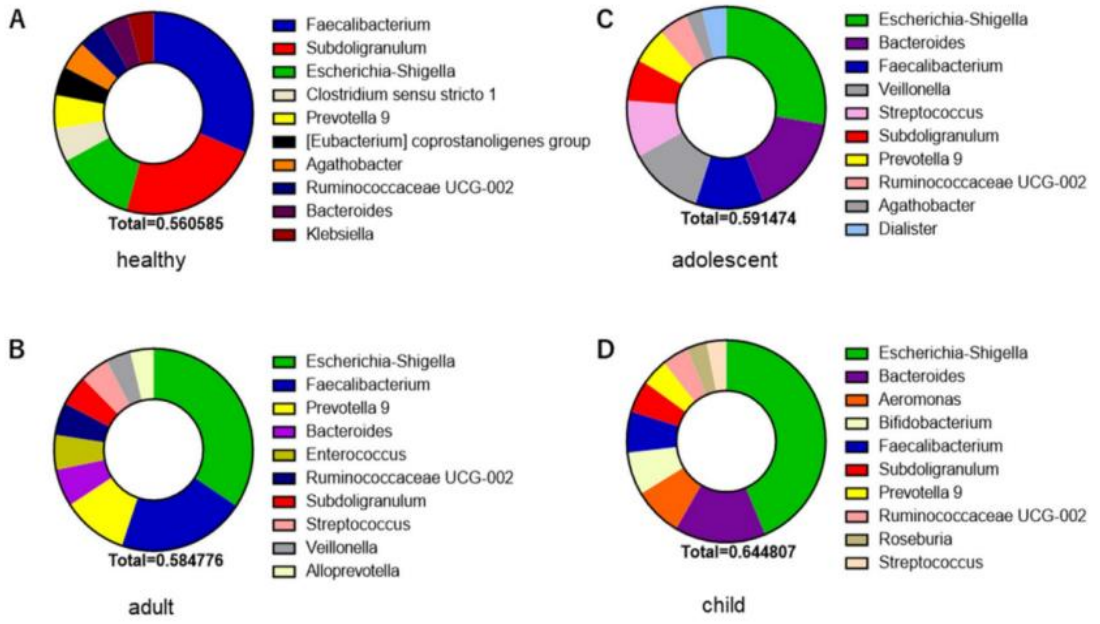

Figure 3. Taxonomic profiles (genus) of fecal bacteria in patients with diarrhea and healthy controls. Top 10 relative abundance of fecal taxa at the phylum level in healthy adult controls (A) and patients with diarrhea; adults (B), adolescents (C), and children (D) [8].

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The study examines the diversity of the bacteriome in patients diagnosed with severe gastroenteritis [7].The Shannon diversity index was computed for the fecal samples and afterwards expressed as an entropy score of 16. These findings demonstrate the makeup of the internal microbiota and its disruption, as seen by a decrease in the score when there is an overgrowth of a single bacterial species. The entropy scores of the gut microbiota in the normal control group and in patients with mild to moderate and severe acute gastroenteritis (AGE) were 0.56 (0.47-0.73), 0.7 (0.56-0.93), and 0.3 (0.05-0.6), respectively (Figure 1A). The Shannon diversity index, which serves as a measure of entropy, exhibited a statistically significant decrease in severe acute gastroenteritis (AGE) patients compared to both the normal control group ($P = 0.017$) and mild to moderate AGE patients ($P = 0.011$). The mean severity score of five patients infected with rotavirus was found to be 13.8 (range: 11-15), which was considerably higher compared to the mean severity score of 15 patients infected with norovirus (mean: 10.3; range: 8-11) ($P = 0.03$). The entropy score of patients diagnosed with Norovirus infection was determined to be 0.65 (0.2-0.75), indicating no statistically significant variance when compared to the control group consisting of those without the infection. The entropy score of patients diagnosed with rotavirus infection was found to be 0.05 (0.02-0.35), which was observed to be substantially lower compared to patients diagnosed with norovirus infection ($P = 0.048$) (Figure 1B).

Additionally, the presence of bacteriome was observed in patient [8]. The analysis of Figures 2A and 2B reveals that the top 10 phyla exhibiting the greatest relative abundance of fecal bacteria are present in both healthy adults and individuals suffering from diarrhea. The primary phyla observed in both healthy adults and adult patients with diarrhea are Firmicutes, Proteobacteria, and Bacteroidetes, although the relative abundance ratios may differ among individuals. The results of the STAMP analysis indicated significant variations in the abundance of Tenericides, Firmicutes, Actinobacteria, Bacteroides, Cyanobacterium, and Proteobacteria between healthy adults and adult patients with diarrhea, as depicted in Figure 2A. The user provided a numerical reference [9]. Figure 3 illustrates the additional ten genera that exhibit the greatest relative abundance of fecal bacteria within each category of patients suffering from diarrhea (adults, adolescents, and children) as well as healthy adults. The major genera in healthy individuals are Faecalibacterium (17.6%), Subdoligranuum (12.9%), and Eschericha Shigella (7.1%) (Figure 3A). The genus Escherichia Shigella is observed to be the most prevalent among individuals suffering from diarrhea across various age groups, with a prevalence of 20% in adults, 16.4% in adolescents, and 28% in children (Figure 3B-D).In contrast to those without any health issues, individuals experiencing diarrhea caused by norovirus or rotavirus have a higher abundance of bacteria at the genus level that are known to be associated with specific forms of diarrhea (Figure 3). This suggests that in certain instances of diarrhea, both viral and bacterial pathogens may be present.

Rotavirus infection is the third most prevalent viral infection [10]. Based on the findings from empirical evidence presented in Figure 1 [8], it is evident that individuals afflicted with severe viral acute gastroenteritis (AGE) have a diminished level of gut microbiota diversity. This observation suggests that the composition and functionality of the microbiota may have been perturbed or impaired by the proliferation of certain bacterial species. A recent study has demonstrated that Rotavirus infection leads to a reduction in microbiome diversity in comparison to norovirus infection, and is associated with greater severity [7]. During the initial stages of rotavirus-induced diarrhea, a substantial quantity of rotavirus particles is excreted in the feces. The primary mode of transmission of the virus is mostly through the fecal-oral pathway, predominantly occurring via close interpersonal contact among individuals. Furthermore, rotavirus infection has the potential to induce symptoms such as vomiting, pain, and fever, in addition to diarrhea. Vomiting is considered a clinical manifestation of rotavirus infection, as it serves the purpose of facilitating fluid loss and potentially impeding the efficacy of therapeutic measures, such as oral rehydration therapy [11].

Furthermore, the fourth factor to consider is the occurrence of norovirus infection. Norovirus is a frequently seen viral pathogen that is commonly associated with acute gastroenteritis (AGE). The findings from a recent study indicate that the principal symptoms of acute gastroenteritis (AGE) were found to be correlated with both the age of the individuals affected and the specific virus genotype involved. The symptoms were ranked in descending order of prevalence as follows: vomiting, nausea,

DOI: 10.54254/2753-8818/15/20240467

stomach pain, fever, and diarrhea. According to the data shown in Table 1, it can be observed that the prevalence of vomiting and fever among middle school students was notably lower (88.5% and 5.8% respectively) compared to kindergarten and primary school children. Conversely, the rates of nausea, abdominal discomfort, and diarrhea were significantly higher among middle school students in comparison to their younger counterparts [12]. According to the data presented in Table 2, it can be observed that the prevalence of nausea is greater among those infected with GII.17. While abdominal pain, fever, and diarrhea are often encountered symptoms, no significant variations in genotype-specific ratios were detected among the three genotypes.

Table 1. The distribution characteristics of parameters by organization [12].

Primary symptom	Kindergarten	Primary school	Middle school	P
cases with vomiting(n=914)	355(92.7%)	513(97.9%)	46(88.5%)	<0.001
cases with nausea(n=444)	152(39.7%)	263(50.2%)	29(55.8%)	0.003
cases with abdominal pain(n=279)	145(37.9%)	113(21.6%)	21(40.4%)	<0.001
cases with fever(n=160)	57(14.9%)	100(19.1%)	3(5.8%)	0.023
cases with diarrhoea(n=100)	22(5.7%)	61(11.6%)	17(32.7%)	<0.001

As depicted in Table 1, the classified data is reported in terms of frequency and percentage. The range of cases is expressed as the mean ± standard deviation. The median of each outbreak is represented by the median (upper and lower quartiles). When dealing with categorical data, it is recommended to employ either the chi-square test or the Fisher exact probability test to assess the disparities across groups when the sample size (n) is less than or equal to 300. The utilization of one-way analysis of variance (ANOVA) is employed in the examination of continuous data to ascertain the disparities that exist among various groups [12].

Table 2. Parameter distribution characteristics by genotype [12].

Primary symptom	GII.2	GII.4	GII.17	P
cases with vomiting(n=751)	202	389	160	<0.001
cases with nausea(n=376)	100	156	120	<0.001
cases with abdominal pain(n=210)	52	105	53	0.099
cases with fever(n=130)	34	66	30	0.655
cases with diarrhoea(n=79)	23	39	17	0.969

As illustrated in Table 2, Categorical data are typically represented using frequencies accompanied by corresponding percentages. On the other hand, when presenting data that involve a range of values, such as the time span between the first and last instances, it is common to express it as the mean value plus or minus the standard deviation. Similarly, for data related to the duration of outbreaks, such as months, it is customary to report the median value together with the upper and lower quartiles. To analyze categorical data, the chi-square test or Fisher's exact probability test was employed to assess differences between groups, particularly when the sample size (n) was equal to or less than 300.The one-way analysis of variance (ANOVA) was employed to assess variations among groups in the context of continuous data.

4. Discussion

The etiology of diarrhea pathogens in regions with high prevalence remains uncertain, with the primary contributing factor hypothesized to be a confluence of unsanitary water and food sources, as well as suboptimal hygiene conditions. The author believes that there is a higher prevalence of Campylobacter

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at the genus level among individuals with diarrhea compared to the healthy control group. Campylobacter has been identified as a causative agent associated with elevated mortality rates in low and middle-income nations. The presence of elevated levels of Erysipelotrichaceae has been seen in individuals experiencing diarrhea as a result of Norovirus infection. This observation maybe pertains to the occurrence of intestinal inflammation. Additionally, according to the results above, it is believed that patients suffering from rotavirus-induced diarrhea exhibited a significant reduction in the presence of Dialister and Ruminococcaceae. The decline in the relative abundance of Ruminococcaceae, as a consequence of rotavirus infection, could potentially exert detrimental effects on the intestinal milieu of individuals suffering from diarrhea. Based on the findings shown in Figure 3, it can be inferred that the occurrence of concurrent infections involving both viral and bacterial populations, which include harmful bacteria, is highly prevalent. Based on preliminary research findings, it can be inferred that the simultaneous presence of these pathogens may synergistically contribute to the development of more severe diseases, hence influencing the prevalence of severe gastroenteritis and diarrhea.

Additionally, children experiencing stomach pain had higher levels of Prevotellaceae, Staphylococcaceae, and Coriobacteriaceae. The prevalence of Streptococcidae was notably greater in non-comorbid patients in comparison to those with complex acute gastroenteritis. The number of Paraacteroides and Porphyromonadaceae was found to be higher in the healthy control group compared to severe acute gastroenteritis (AGE) patients.

According to a recent research report, vaccinations have been identified as a very efficacious approach in the prevention of acute gastroenteritis (AGE) [13, 14]. Following the implementation of rotavirus vaccines, numerous countries have reported a notable decrease in the prevalence and impact of rotavirus-related illnesses. The incidence of hospitalizations due to diarrhea in children under the age of 5 witnessed a significant reduction of 38% (with a range of 5-63%). Similarly, hospitalizations specifically attributed to rotavirus disease experienced a substantial decline of 67% (with a range of 18-84%). Furthermore, there was a notable decrease of 42% (with a range of 3-64%) in the number of deaths caused by diarrhea in general [11, 15, 16]. The demographic composition of individuals affected by rotavirus sickness has experienced alterations, primarily observed among unvaccinated children aged 6 to 16 and individuals aged 70 years and above [17]. There have been observed alterations in seasonal patterns, characterized by a postponement in the initiation of the rotavirus season, abbreviated durations of seasons, and diminished intensity of seasonal peaks [18].

Finally, the author considers that the prevention of AGE can be efficiently achieved through physical factors. It has been observed that the implementation of barrier measures mandated by the government subsequent to the emergence of SARS-CoV-2 in France has also exerted an influence on the transmission of the etiological agents responsible for Acute Gastroenteritis (AGE). The implementation of physical distancing measures and the imposition of lockdowns have been shown to effectively mitigate the risk of acquiring acute gastroenteritis (AGE). Regular handwashing with soap and water is considered to be one of the suggested preventive methods against acute gastroenteritis (AGE).

5. Conclusion

This study employs a literature review methodology to investigate the disparities in microbiome composition between those diagnosed with AGE and those who are considered to be in good health. This article also presents an overview of prevalent viral infections that are associated with Acute Gastroenteritis (AGE) and explores preventive measures. The research overviewed relevant studies that employed quantitative molecular diagnostic techniques, metagenomic analysis using the Linear discriminant analysis Effect Size (LEfSe) approach, and Next-Generation Sequencing (NGS) to assess the identification of etiological factors responsible for diarrhea in children and the composition of the microbiota in patients with Acute Gastroenteritis (AGE). However, the paper discussed in this publication still possesses several limitations. The study lacks comprehensive investigation into the many causes of diarrhea in underdeveloped nations, as well as limited examination of the microorganisms involved. Additionally, the number of patients analyzed in the study is restricted, which can be compensated in future studies.

DOI: 10.54254/2753-8818/15/20240467

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