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Etiological pathogen causes of diarrhea in children

Patógenos etiológicos causantes de diarrea en niños

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SUMMARY

Introduction: *The incidence of diarrhea in early childhood in developing countries has a mortality rate of nearly one million each year. This study aims to determine the pathogens that cause diarrhea in children based on their groups.*
Methods: *Information was obtained using several relevant keywords through search engines or online databases such as PubMed, Google Scholar, and SINTA websites with keywords "etiology", "pathogen", "causes", and "diarrhea in the child". The publication years were 2010 to 2020 with the minimum publication category indexed by Scopus and SINTA 4.*
Results: *There were three groups of pathogens found, including viruses, bacteria, and parasites. The most common type of virus found in 6 articles is Rotavirus. Four articles mention Escherichia coli as the bacterial pathogen in the bacterial group that causes the most diarrhea. In comparison, the most types of parasites found in five journals were Cryptosporidium sp. The age range of children who were more frequently sampled was 0-5 years. Many cases of diarrhea are found at the age of 0-5 years because the immune system in infants and toddlers (under five years old) is still learning to recognize and protect the body from incoming pathogens so that they are more susceptible to infection. Of the 12 research articles identified, Polymerase Chain Reaction was used.*
Conclusion: *The most common type of virus was Rotavirus. In the bacterial group, E. coli is the bacterial pathogen that causes the most diarrhea. In comparison, the most type of parasite found was Cryptosporidium sp.*

Keywords: *Diarrhea, etiology, pathogens.*

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RESUMEN

Introducción: *La incidencia de diarrea en la primera infancia en los países en desarrollo tiene una tasa de mortalidad de casi un millón cada año. Este estudio tiene como objetivo determinar los patógenos que causan diarrea en los niños en función de sus grupos.*
Métodos: *La información se obtuvo utilizando varias palabras clave relevantes a través de motores de búsqueda o bases de datos en línea como PubMed, Google Scholar y sitios web SINTA con las palabras clave "etiología", "patógeno", "causas" y "diarrea en*

el niño". Los años de publicación fueron 2010 a 2020 con la categoría de publicación mínima indexada por Scopus y SINTA 4.
Resultados: *Se encontraron tres grupos de patógenos, incluidos virus, bacterias y parásitos. El tipo de virus más común encontrado en 6 artículos es el rotavirus. Cuatro artículos mencionan a Escherichia coli como el patógeno bacteriano, en el grupo bacteriano, que causa más diarrea. En comparación, la mayoría de los tipos de parásitos encontrados en cinco revistas fueron Cryptosporidium sp. El rango de edad de los niños que fueron muestreados con mayor frecuencia fue de 0 a 5 años. Muchos casos de diarrea se encuentran entre los 0 y los 5 años porque el sistema inmunológico de los bebés y niños pequeños (menores de cinco años) todavía está aprendiendo a reconocer y proteger el cuerpo de los patógenos entrantes para que sean más susceptibles a las infecciones. De los 12 artículos de investigación identificados, se utilizó la reacción en cadena de la polimerasa.*
Conclusión: *El tipo de virus más común fue el rotavirus. En el grupo bacteriano, E. coli es el patógeno bacteriano que causa más diarrea. En comparación, el tipo de parásito más encontrado fue Cryptosporidium sp.*

Palabras clave: *Diarrea, etiología, patógenos.*

INTRODUCTION

The incidence of diarrhea in early childhood in developing countries has a mortality rate of nearly one million each year (1). Diarrhea is one of the significant foodborne in children (2). It is a leading cause of dehydration in infants and children age five, and over mild to moderate diarrhea can result in missed school days and may require treatment by a health care provider. Diarrhea that is more severe and lasts longer will require hospitalization (3-5). Therefore, Mortality Research and Basic Health Research states that diarrhea is still the leading cause of child mortality in Indonesia for years (6).

It is well known that the majority of diarrheal episodes are self-limiting. Although oral rehydration therapy can normally be used to treat dehydrated patients, it would be better if it could also be used to prevent diarrhea in children (3-5). This is due to the results of the 2013 Basic Health Research (Riskesdas) report that diarrhea is still the most common cause of infant mortality in Indonesia, namely 46 %, while the cause of death for children aged 1-4 years is caused by diarrhea as much as 25 % (7). Numerous prevention methods, such as improving water sanitation, implementing basic hygiene practices, and ensuring the hygiene of milk bottle-feeding, are easy to implement (2,8,9). Another study also suggests improving women's empowerment as an important strategy to prevent diarrhea (10).

The etiology of diarrhea is divided into two factors, including infection and non-infection (11). Infectious diarrhea can be caused by viruses, bacteria, parasites, and fungi (12). Infection is depending on the variation of bacterial virulence, host genetics, and/or environmental factors (13). Meanwhile, non-infectious diarrhea is caused by allergies, food intolerance, colitis, celiac disease, and poisoning. Diarrhea caused by infection has more cases and a number of deaths than non-infectious diarrhea. Several laboratory examination methods diagnose pathogens that cause infectious diarrhea, including culture, serological tests, polymerase chain reaction (PCR), and microscopic examination. Several pathogens that infect the digestive system itself can produce toxins, causing inflammation and damage to the mucus and intestinal microvilli. Damage to the intestine itself can be characterized by diarrhea with blood. In the above conditions, if not handled immediately, it is leading to death (14).

Numerous experiments have been performed in countries around the world to assess if one or more pathogens are present in diarrhea stool. Although isolated studies on specific pathogens can yield valuable information, it is difficult to determine the relative importance of different pathogens without considering the entire spectrum of agents. As such, this study aims to collect data on the annual incidence and mortality rates of a number of potential pathogens in this age group.

METHODS

Online databases such as PubMed, Google Scholar, and 6 SINTA was searched using the following several relevant keywords: "Etiology", "Pathogen", "Causes", and "diarrhea in the child" with the publication year of 2010 to 2020, with

the minimum publication category indexed by Scopus and SINTA 4. Analyzing the data was carried out through bibliographic annotation analysis.

The author first reviewed journal titles and abstracts for the suitability of the screening process based on relevant keywords and sort by concurrently identified broad-spectrum pathogens so that it did not include research journals based on specific pathogens. The information cited relates to the study population, study setting, definition of diarrhea, prevalence of each pathogen, and information on diarrhea pathogens required to be included in the literature review. Furthermore, analyzing the data was carried out through annotated bibliography analysis (annotated bibliography). Bibliographic annotation can be concluded as a list of sources used in a study, where each source is given a conclusion related to what is written in it.

RESULTS

The authors list several articles that are used as references for writing literature reviews in the form of Table 1.

Table 1 shows that there are three groups of pathogens found, namely viruses, bacteria, and parasites. The most common type of virus found in six articles was Rotavirus. In the bacterial group, four articles mention *Escherichia coli* as the bacterial pathogen that causes the most diarrhea. While the most types of parasites found in the 5 articles were *Cryptosporidium sp*. The group of fungal pathogens was not found in the 12 articles.

Table 2 shows diarrhea pathogens based on several studies. Of the 12 research articles identified using PCR, six research articles only used PCR to identify viruses, bacteria, and parasites at once. In four research articles, PCR examination was combined with culture examination, and three research articles combined PCR with the serological examination. The classification of pathogens and pathogenesis of pathogens in causing diarrhea varies depending on the species of the pathogen. This literature review realizes that national-level community-based hospital and surveillance reports will enable a country to better understand the level of local disease through pathogens and can serve as a reference for better prevention programs. In addition, the age range of children who were more frequently sampled was 0-5 years. Of the 11 studies, a sample aged 0-5 years was used. Only one study used a sample of 0-17 years old.

DISCUSSION

The most common type of virus found in 6 articles was Rotavirus. Morbidity peaked in 2003, and the virus mostly affects children under the age of three. Rotavirus requires only a small number of infectious virions to cause disease in susceptible hosts. Rotavirus infection will cause malabsorption of carbohydrates and loss of fluid from digestion because the death of enterocyte cells will release the cytoplasm into the intestinal lumen. Also, changes in function in the villi caused by the virus induce an increase in intestinal motility, worsening the situation (15,16).

In the bacterial group, 4 articles mention E. coli as the bacterial pathogen that causes the most diarrhea. The evolution of pathogenic E. coli, which culminated in the development of distinct pathotypes capable of colonizing the gastrointestinal tract, urinary tract, and meninges, demonstrates how genetic strains can adapt to a variety of host environments. The process of evolution has produced highly capable species capable of colonizing, multiplying, and destroying diverse environments. Due to the ability of various *E. coli* virulence factors to affect a broad variety of cellular functions, various toxins, effectors, and cell surface structures have been used to gain a deeper understanding of these fundamental eukaryotic processes (17).

The most type of parasite found in the 5 articles was *Cryptosporidium sp*. Cryptosporidium can survive in the environment as oocysts containing four sporozoites, which are a form of the infectious parasite. The incubation period following exposure ranged from two to ten days, with an average of seven days. Following ingestion, the oocyst migrates to the small intestine, where it produces sporozoites. The sporozoites colonize the small intestine and multiply asexually in the extra cytoplasmic parasitophorous vacuoles (18).

Table 1

Bibliographical Annotation Analysis in Journals Identifying the Pathogens Widely

Title	Author(s)	Years	Groups of pathogens			
			Virus	Bacteria	Parasite	Fungi
Etiology of Diarrhea, Nutritional Outcomes, and Novel Intestinal Biomarkers in Tanzanian Infants	Gosselin, et al	2017	Rotavirus 8.9 % (11)	*E. coli* 5 % (5), *Shigella* 5.7 % (7), *Campylobacter* (1)	*Cryptosporidium* 7.3 % (9)	-
Detection of Acute Gastroenteritis Etiology in Hospitalized Young Children: Associated Factors and Outcomes	Jamie M, et al	2017	Rotavirus 33 % (70)	*C difficile* 9.8 % (10); *Shigella* (2); *Salmonella* (9); *Campylobacter* (2)	-	-
Etiology of Severe Acute Water Diarrhea in Children in the Global Rotavirus Surveillance Network Using Quantitative Polymerase Chain Reaction	Operario DJ, et al	2017	Rotavirus, Norovirus, Adenovirus, Astrovirus	*Shigella*. *Salmonella, Campylobacter*. *E. coli*	*Cryptosporidium*	-
Use of quantitative molecular diagnostic methods to assess the etiology, burden, and clinical characteristics of diarrhea in children in low-resource settings: a reanalysis of the MAL-ED cohort study	Platts-Mills, et al	2018	Adenovirus, Astrovirus, Norovirus, Rotavirus,	*Campylobacter, E. coli, Shigella,*	*Cryptosporidium*	-
Potential Diarrheal Pathogens Common Also in Healthy Children in Angola	Pelkonen T, et al	2018	Adenovirus 7 (4 %), Astrovirus 7 (4 %), Norovirus 43 (22 %), Rotavirus 40 (21 %), Sapovirus 22 (11 %)	*E. Coli* 100 (52 %), *Shigella* 29 (15 %), *Campylobacter* 29 (15 %), *Salmonella* 2 (1%)	*Giardia* 27 (14 %), *Cryptosporidium* 22 (11 %), *Entamoeba* 7 (4 %)	-
Bacterial and viral etiology of childhood diarrhea in Ouagadougou, Burkina Faso	Bonkoungou IJ, et al	2013	Rotavirus 85 (30 %), Adenovirus 14 (5 %),	*Shigella* 16 (6 %). *Salmonella* 24 (9 %), *Campylobacter* 5 (25). *E. coli* 67 (24 %)	-	-
Pathogen-specific burdens of community diarrhea in developing countries (MAL-ED): a multisite birth cohort study	Platts-Mills, et al	2015	Astrovirus, Norovirus, Rotavirus	*Campylobacter*, *E. coli*, *Shigella* -	*Giardia, Cryptosporidium*	
Etiology and Epidemiology of Diarrhea in Hospitalized Children from Low Income Country: A Matched Case-Control Study in Central African Republic	Breurec S, et al	2016	Adenovirus 37 (11.1 %), Astrovirus 48 (14.4 %) Norovirus 46 (13.8 %), Rotavirus 145	*E. coli* 72 (21.6 %), *Shigella* 94 (28.2 %), C	*Cryptosporidium* 51 (15.3 %), *Entamoeba* 11 (3.3), *Giardia* 29 (8.7 %)	-
Etiology of diarrheal disease and evaluation of viral–bacterial coinfection in children under 5 years old in China: a matched case–control study	Li L, et al	2016	Rotavirus 40.6 %, Norovirus 24.7 %, Adenovirus 10.9 %,	*Shigella* (18.6 %), *Salmonella, Campylobacter*	-	-
Real-time PCR identification of agents causing diarrhea in Rwandan children less than 5 years of age	Kabayiza JC, et al	2014	Rotavirus (42 %), adenovirus (39 %),	*E. coli* (21 %), *shigella* (13 %), *campylobacter* (14 %)	-	-
Real-Time PCR Threshold Cycle Cutoffs Help To Identify Agents Causing Acute Childhood Diarrhea in Zanzibar	Elfving K, et al	2014	Norovirus (19 %), rotavirus (9.1 %)	*Shigella* (20 %), *E. coli* (16 %)	*Cryptosporidium* (25 %),	-
Detection of 23 Gastrointestinal Pathogens among children who present with diarrhea	Stockmann C, et al	2017	Adenovirus (7 %), sapovirus (6 %), rotavirus (4 %), astrovirus (2 %)	*Clostridium difficile* (16 %), *E. Coli* (15), *Salmonella* (2 %), *Campylobacter* (1 %).	*Giardia* (4 %)	-

PCR: Polymerase Chain Reaction

Table 2

Diarrhea Pathogens Group

Virus	Bacteria	Parasite
-Rotavirus	-*Shigella spp*	-*Giardia lambia*
-Norovirus	-*Salmonella spp*	-*Cryptosporidium spp*
-Adenovirus	-*Campylobacter spp*	-*Entamoeba histolytica*
-Sapovirus	-*Escherichia coli*	
-Astrovirus	-*Clostridium difficile*	

Each cell multiplies rapidly, forming thick-walled oocysts capable of being excreted in the stool and surviving in the environment. Additionally, they create thin-walled oocysts that can automatically infect the patient. Three suggested mechanisms account for the symptoms: inflammatory cell invasion of the lamina propria: increased epithelial permeability, villous atrophy, and cell death, and malabsorption due to bowel architecture failure. Cryptosporidium can alter the host immune response to prevent infected cells from undergoing apoptosis, thus allowing the infection to continue (18).

The fungal pathogen group was not found in these 12 pieces of literature, but another study states that the cause of diarrhea in the fungal group is *Candida albicans*. *C. albicans* is rarely found because it causes canker sores more often than gastrointestinal infections. *C. albicans* are more easily infected when normal immunity is compromised (5).

The dominant study samples were less than five years old. Many cases of diarrhea are found at this age because the immune system in infants and toddlers (under five years old) is still learning to recognize and protect the body from incoming pathogens so that they are more susceptible to infection with the disease. Whereas in adolescents and adults, the immune system has recognized the type of pathogen and immediately responds when the pathogen will infect the body. Therefore, parenting, food hygiene, and children's nutrition play an essential role in preventing diarrhea (19,20).

To prove the etiology of the pathogen causing diarrhea requires accurate examination. In 12 research journals, only three laboratory tests were found, namely, PCR, culture, and serological tests. This microscopic examination is not used because microscopic examination can only see the presence of parasites and ova (eggs, cysts) in the feces. This makes fecal microscopic examination of high subjectivity, namely only in the parasite pathogen group, so it is rarely used to look for pathogens that cause diarrhea (21).

The PCR examination method is most widely used to determine the etiology of diarrhea in the research literature. PCR is a laboratory technique used to amplify specific DNA segments for a variety of laboratory and/or clinical applications. The main components of PCR are templates, primers, free nucleotide bases, and the DNA polymerase enzyme. PCR uses complementary base pairs, double-stranded properties, and the melting temperature of the DNA molecule. This process involves cycles through 3 sequential loops of temperature-dependent reactions: DNA fusion (denaturation), annealing, and enzyme-driven DNA replication (elongation) (22).

The authors expect that further research can be grouped by region, economy, geography, or risk factors so that they can draw more complete conclusions. The authors also hope that this literature review can be used as a contribution to medical science in the future.

CONCLUSION

In this study, it was found that the most common type of virus was Rotavirus. In the bacterial group, *Escherichia coli* is the bacterial pathogen that causes the most diarrhea. At the

same time, the most type of parasite found was *Cryptosporidium sp*. The age range of children who were more frequently sampled was 0-5 years. Of the 12 research articles identified, Polymerase Chain Reaction was used.

REFERENCES

1. Sima LC, Ng R, Elimelech M. Modeling risk categories to predict the longitudinal prevalence of childhood diarrhea in Indonesia. Am J Trop Med Hyg. 2013;89(5):884-891.
2. Syahrul F, Wahyuni CU, Notobroto HB, Wasito EB, Adi AC, Dwirahmadi F. Transmission media of foodborne diseases as an index prediction of diarrheagenic *Escherichia coli*: Study at elementary school, Surabaya, Indonesia. Int J Environ Res Public Health. 2020;17(21):1-13.
3. Guarino A, Aguilar J, Berkley J, Broekaert I, Vazquez-Frias R, Holtz L, et al. Acute gastroenteritis in children of the world: What needs to be done? J Pediatr Gastroenterol Nutr. 2020;70(5):694-701.
4. Guarino A, Lo Vecchio A, Dias JA, Berkley JA, Boey C, Bruzzese D, et al. Universal recommendations for the management of acute diarrhea in nonmalnourished children. J Pediatr Gastroenterol Nutr. 2018;67(5):586-593.
5. DeFilippis EM, Sokolow R, Barfield E. Health Care Maintenance for the Pediatric Patient With Inflammatory Bowel Disease. Pediatrics. 2016;138(3).
6. Kemenkes RI. Profil Kesehatan Indonesia Tahun 2015. Jakarta; 2016.
7. Indonesia Ministry of Health. Riset Kesehatan Dasar (RISKESDAS) Tahun 2013. Jakarta; 2013.
8. Krisnana I, Pradanie R, Mustika DA. Impact of complementary foods and environmental sanitation on the incidence of diarrhea in children aged 6-24 months in sidoarjo, Indonesia. Syst Rev Pharm. 2020;11(5):778-782.
9. Lanida BP, Farapti F. The prevention strategy against the incidence of diarrhea in toddlers through hygiene of milk bottles-feeding. J Berk Epidemiol. 2018;6(3):244-251.
10. Astutik E, Efendi F, Sebayang SK, Hadisuyatmana S, Has EMM, Kuswanto H. Association between women's empowerment and diarrhea in children under two years in Indonesia. Child Youth Serv Rev. 2020;113.
11. Sudarmo SM, Shigemura K, Athiyyah AF, Osawa K, Wardana OP, Darma A, et al. Genotyping and clinical factors in pediatric diarrhea caused by rotaviruses: One-year surveillance in Surabaya, Indonesia. Gut Pathog. 2015;7(1).
12. Imanadhia A, Ranuh IGMRG, Nuswantoro D. Etiology based on clinical manifestation of acute diarrhea incidence of children hospitalized in Dr. Soetomo General Hospital Surabaya Period 2011-2013. Biomol Heal Sci J. 2019;2(1):31-35.
13. Waskito LA, Miftahussurur M, Lusida MI, Syam AF, Suzuki R, Subsomwong P, et al. Distribution and clinical associations of integrating conjugative elements and cag pathogenicity islands of *Helicobacter pylori* in Indonesia. Sci Rep. 2018;8(1):6073.
14. Martiza I, Juffrie M, Oswari H, Arief S, Rosalina I. Buku ajar gastroenterologi-hepatologi. Jakarta: Badan Penerbit IDAI; 2012.
15. LeClair CE, Budh DP. Rotavirus. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2020.
16. Narkeviciute I, Tamusauskaite I. Peculiarities of norovirus and rotavirus infections in hospitalized young children. J Pediatr Gastroenterol Nutr. 2008;46(3):289-292.
17. Ameer MA, Wasey A, Salen P. Escherichia Coli (E Coli 0157 H7). In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2020.
18. Ryan U, Hijjawi N. New developments in Cryptosporidium research. Int J Parasitol. 2015;45(6):367-373.
19. Takele K, Zewotir T, Ndanguza D. Risk factors of morbidity among children under age five in Ethiopia. BMC Public Health. 2019;19(1):942.
20. Ygberg S, Nilsson A. The developing immune system - from foetus to toddler. Acta Paediatr. 2012;101(2):120-127.
21. Amin HA, Ali SA. Evaluation of different techniques of stool examination for intestinal parasitic infections in Sulaimani City-Iraq. Int J Curr Microbiol Appl Sci. 2015;4(5):991-996.
22. Ghannam MG, Varacallo M. Biochemistry, Polymerase Chain Reaction.[Updated 2020 Jul 10]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2020.