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Diagnostic Comparison of Elevated Fecal Leukocytes and sTREM-1 in Children with Acute Diarrhea Caused by Bacterial Infection

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Abstract

Diarrhea is a health problem that most often occurs in children. Various etiologies of diarrhea can cause prolonged diarrhea and become malnourished (malnutrition). The etiology of diarrhea can be caused by a bacterial infection and requires antibiotics, so that detection is needed as early as possible. Examination of soluble triggering expressed receptors on myeloid cells-1 (sTREM-1) can predict bacterial infection in children with acute diarrhea. The study aims to know how much the diagnostic value of fecal leukocytes test compared to sTREM-1. A cross-sectional study of children aged 6-60 months with acute diarrhea without complications and other diseases. In the subjects, clinical manifestation was performed (fever, vomiting, abdominal pain), fecal leukocyte test and sTREM-1 test as a standard reference. Children, aged 6-60 months with acute diarrhea due to bacterial infections with sTREM-1 > 470 pg/mL as many as 2 of 64 subjects and fecal leukocytes > 10/HPF as many as 14 of 64 subjects, most male, normal nutritional status and had clinical manifestation of fever, vomiting and without abdominal pain. Increased fecal leukocytes > 10 / HPF has a sensitivity of 50%, specificity 79.1%, positive predictive value 7.1%, negative predictive value 98%, accuracy 78%, positive likelihood ratio 2.18 and negative likelihood ratio 0.63. Fecal leukocyte test > 10/HPF as a diagnostic confirmation is not good in diagnosing acute diarrhea due to bacterial infection.

Introduction

Acute diarrhea includes ongoing diarrhea, potentially 6-fold or about 15% of acute diarrhea can become persistent diarrhea and can cause various problems such as malnutrition and *stunting*. Acute diarrhea can become persistent diarrhea because gastrointestinal infections can be caused by a variety of pathogens, including viruses, bacteria and protozoa (Navaneethan & Giannella, 2008) The prevalence of diarrhea due to bacterial infections in China was found to be 19.4% in children under 5 years of age (Zhu et al., 2016). For research in Jakarta, Indonesia, it was found that the elevation of leukocytes in the stool was 25% with a division of 64.5% occurring in advanced diarrhea and 35.5% in acute diarrhea (Rahmat & Frimansyah, 2016)

The presence of bacterial infection can use several commonly used supports including leukocytes in the stool, increased C reactive protein (CRP) (Das et al., 2012; Simon et al., 2004), increased procalcitonin (Gomez et al., 2012; Tang et al., 2007) (PCT) , stool culture and increased *soluble triggering receptor expressed myeloid cells-1* (sTREM-1). Leukocyte examination in feces when more than 10 leukocytes per field of view (LPB) are found on stool microscopy examination. Fecal leukocyte elevation has a sensitivity between 25.8 - 66.9% while specificity is 63.6 - 96.5%. The sTREM-1 tool guide (*Quantikine® ELISA Human*

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TREM-1 Immunoassay, catalog number DTRM10C) indicates serum sTREM-1 values in healthy people of 133 - 471 pg/mL. An increase above 471 pg/mL may indicate a bacterial or fungal infection. Another study showed the possibility of bacterial infection in acute diarrhea with clinical features such as fever, abdominal pain, mucus in the stool, tenesmus, dehydration, vomiting and liquid diarrhea like rice washing (Bardhan et al., 2000).

The gold standard proving of acute diarrhea due to bacterial infection is done by stool culture but this examination requires longer results and there are still inconsistent results so sTREM-1 is considered to detect more quickly and accurately in assessing diarrhea due to bacterial infection. The fecal leukocyte test can be easily performed in primary health care settings. It is necessary to test between fecal leukocytes compared with sTREM-1 to assess bacterial infection in acute diarrhea. The aim of this study is to determine whether fecal leukocytes are good enough to detect bacteria in cases of acute diarrhea due to bacterial infection compared to the sTREM-1 test (Payne et al., 2013).

According to the WHO acute diarrhea is defined as diarrhea below 14 days while persistent or chronic diarrhea is above 14 days. Acute diarrhea tends to occur in children aged 6-24 months and peaks in the second half of life. Children who experience acute diarrhea in the first year of life have 2 times the risk of persistent diarrhea in pre-school age (Moore, 2021). Persistent diarrhea cases in developing countries are mostly caused by bacterial infections, which can sometimes be highly virulent and difficult to treat.

Furthermore, the multifactoriality of acute diarrhea can be seen in the following figure

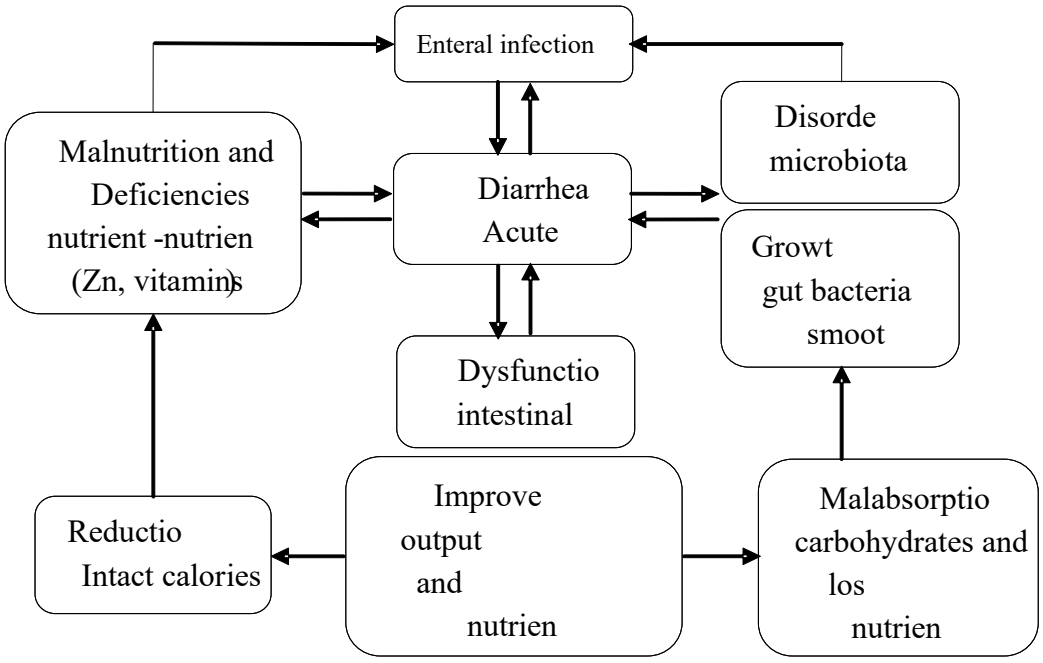

Figure 1. Multifactorial etiology of acute diarrhea

The pathogenesis of acute diarrhea is multifactorial and is essentially influenced by persistent damage of the gastrointestinal mucosa by infection or specific agents of different pathogens. It is further influenced by host factors such as micronutrients, vitamin deficiency, nutritional deficiencies and immunodeficiency. High mucosal permeability caused by the infectious process leading to malabsorption and microbiota disruption will add to the severity of the course of diarrhea. Acute diarrhea will cause shortened intestinal villi, decreased number and length of microvilli, dulled enterocyte layer, loss of glycocalyx, and *pseudomembranous* intestinal lining. In addition, there will also be changes in inflammatory markers including elevated interferon-gamma response, increased *fecal lactoferrin*, interleukin (IL)-8 and IL-1β and elevated $CD8^+$ T cells (Iyer et al., 2015). More than half of children who experience severe

acute diarrhea or continued diarrhea will experience enteropathic protein loss (Shane et al., 2017).

Although infection is thought to be the main cause of acute diarrhea, clear and conclusive evidence of the role of pathogens in inducing acute diarrhea is lacking. In developing countries, many pathogenic bacteria that cause acute diarrhea and dysentery cause persistent diarrhea. Invasive diarrhea caused by Shigella contributes to both acute and persistent diarrhea, and the prevalence of Shigella in children with acute and persistent diarrhea is higher (Fraser et al., 1998). *Enteropathogenic Escherichia coli* is found in at least 25% of children in lower and middle income countries (Abba et al., 2009).

Diagnosis of the cause of acute diarrhea, whether due to bacterial infection or not, is considered the cornerstone of diarrhea management. A correct diagnosis will prevent unnecessary antibiotics, hospitalization, and even death. Recent strategies in diarrhea management have been directed towards using a combination of clinical and laboratory information, such as peripheral whole blood, neutrophil count, and *C-reactive protein* or CRP concentration. However, there is a possibility of overlap between bacterial infection and non-bacterial infection at up to 40% so other approaches such as *soluble triggering receptor expressed on myeloid cells-1* or sTREM-1 are needed. *Soluble* triggering *receptor expressed on myeloid cells-1* or sTREM-1 is a soluble triggering receptor expressed on ELISA according to the manufacturer's instructions (*Quantikine® Human TREM-1 Immunoassay, R&D Systems, USA*), TREM-1 is measured by a commercially available human ELISA kit using a specific monoclonal antibody for humans (Stoll et al., 1983). *Triggering receptor expressed on myeloid cells* (TREM)-1 is a molecule that plays a role in monocytic activation and inflammatory responses. TREM-1 belongs to the natural killer cell receptor and is expressed by neutrophils, mature monocytes and macrophages. Inflammatory receptors mediated by stimulation of toll-like receptor-2 and -4 are amplified by association with TREM-1 (Bouchon et al., 2001). TREM-1 expression is controlled by nuclear factor-κB (NF-κB; activated by TLRs). With the incorporation of TREM-1, there is activation of several transcription complexes that synergize with NF-κB in order to transcribe proinflammatory genes. TREM-1 expression is enhanced on phagocytic cells in the presence of bacteria and fungi (Savola et al., 2001).

Fecal leukocytes are one of the criteria that need to be reviewed. Fecal leukocytes cannot be used in predicting the presence of *C. difficile*, nor are they useful in predicting the stool culture results of hospitalized patients. Stool culture and fecal leukocyte examination should not be routinely performed in hospitalized patients. Among outpatients, the presence of fecal leukocytes suggests the patient has bacterial diarrhea in cases where clinical symptoms are compatible (Carbonnelle, 2009).

Methods

This study is a cross-sectional design to assess the sensitivity, specificity, positive likelihood value, negative likelihood value, positive likelihood ratio and negative likelihood ratio of elevated leukocytes in stool compared to sTREM-1 in children aged 6-60 months suffering from acute diarrhea due to bacterial infection at Ciptomangunkusumo General Hospital, Salembembuso Central Jakarta, RSUD. Ciptomangunkusumo, Salemba, Central Jakarta, RSUD. Budhi Asih, Cawang, East Jakarta, Jatipadang Hospital, Pasar Minggu, South Jakarta, Jagakarsa Hospital, Jagakarsa, South Jakarta and Hasanah Graha Afiah Hospital, Depok, West Java. The examination of sTREM-1 will be carried out in the RSCM gastro laboratory while the examination of increased leukocytes in the stool will be carried out in the laboratories of Ciptomangukusumo Hospital, Budhi Asih Hospital, Jatipadang Hospital, Jagakarsa Hospital and Hasanah Graha Afiah Depok Hospital. The study was conducted from May 2019 - June 2019, after obtaining ethical approval from the Health Medicine Research Ethics Committee of the Faculty of Medicine, University of Indonesia with No. KET-

304/UN2.F1/ETIK/PPM.00.02/2019 dated March 25, 2019. Inclusion criteria Children aged 6 months to 60 months suffering from acute diarrhea. Exclusion criteria were children suffering from diarrhea who had received antibiotics 7 days before coming to the hospital, and children suffering from acute diarrhea associated with respiratory disease, neurological disorders, surgical conditions, bacterial infections not from the gastrointestinal tract and diarrhea due to immune deficiency. Patients who met the criteria had anamnesis of the clinical picture of fever, vomiting, and abdominal pain, physical examination, anthropometric examination to assess nutritional status and serum sTREM-1 examination > 471 pg/mL and fecal leukocyte examination > 10 / LPB to see the possibility of bacterial infection in children with acute diarrhea.

Result and Discussion

The study subjects were 64 children from 39 children in Budhi Asih Hospital Jaktim, 9 children in Jatipadang Hospital Jaksel, 5 children in Jagakarsa Hospital Jaksel and 11 children in Hasanah Hospital Graha Depok Jabar while in RSUP. Ciptomangunkusumo during the study period we did not find any study subjects who met the inclusion criteria. In this study, males had a greater number of acute diarrhea than females with 40 (62.5%) and 24 (37.5%) respectively, with a ratio of 1.7:1. The ages of the subjects with diarrhea were in the order of 6-24 months of age with 40 (62.5%) subjects and 25-48 months of age with 21 (32.8%) subjects with a median age of 17 months. For nutritional status, we found that 6 (9.4%) subjects were obese, 4 (6.2%) subjects were overweight, 47 (73.4%) subjects were normal and 7 (10.9%) subjects were underweight while malnutrition was included in our exclusion criteria. The examination of sTREM-1 > 471 pg/mL found 2 subjects out of 64 subjects or 3.1%. Only 1 child with sTREM-1 > 471 pg/mL had fecal leukocytes > 10/LPB, and had fever. Both children had symptoms of vomiting and abdominal pain and fecal pH ≥7. (Table 4.1).

Table 1. Characteristics of research data

Characteristics		Overall N=64 n (%)	sTREM-1 > 471 pg/mL N=2 n (%)	sTREM-1 < 471 pg/mL N=62 n (%)
Age, median (min-max),	Month	17 (6-59)	32 (6-59)	17 (6-59)
6-24 months 25-48 months 49-60 months		40 (62,5) 21 (32,8) 3 (4,7)	1 (50) 0 1 (50)	39 (62,9) 21 (33,9) 2 (3,2)
Gender (male)		40 (62,5)	2 (100)	38 (61,3)
Nutritional status	Obesity	6 (9,4)	1 (50)	5 (8,1)
	Excessive nutrition	4 (6,2)	0	4 (6,5)
	Normal nutrition	47 (73,4)	0	47 (75,8)
	Undernourished	7 (10,9)	1 (50)	6 (9,7)
Fever	Yes	51 (79,7)	1 (50)	50 (80,6)
	No	13 (20,3)	1 (50)	12 (19,4)
Vomiting	Yes	43 (67,2)	2 (100)	41 (66,1)
	No	21 (32,8)	0	21 (33,9)
Stomach pain	Yes	15 (23,4)	2 (100)	15 (24,2)
	No	49 (76,6)	0	47 (75,8)
Fecal leukocytes >10/LPB	Yes	14 (21,9)	1 (50)	13 (21,0)
	No	50 (78,1)	1 (50)	49 (79)
Fecal pH ≥7	Yes	8 (12,5)	2 (100)	8 (12,9)
	No	56 (87,5)	0	54 (87,1)

The diagnostic test comparing fecal leukocytes > 10 / LPB compared with sTREM-1 value > 471 pg/mL obtained a sensitivity of 50% and a specificity of 79.1% so that the fecal leukocyte test as diagnostic confirmation and the fecal leukocyte test as screening are poor in diagnosing

markers of bacterial infection in acute diarrhea (low sensitivity and specificity), but the fecal leukocyte test is good for excluding non-bacterial infectious diseases in acute diarrhea (specificity above 70%).

Table 2. Diagnostic test of fecal leukocytes >10/LPB and sTREM-1

		sTREM-1 > 471 pg/mL		**Total**
		Yes	**No**	
Fecal leukocytes > 10/ LPB	Yes	1	13	14
	No	1	49	50
Total		**2**	**62**	**64**

Sensitivity = 1 / (1+1) = 50 %

Specificity = 49 / (49+13) = 79,1 %

Accuracy = (1+49) / 64 = 78,0 %

NPP/PPV = 1 / (1+13) = 7,1 %

NPN/NPV = 49 / (49+1) = 98,0 %

Likelihood Ratio (+) = 50% / 22,9% = 2,18

Likelihood Ratio (-) = 50% / 79,1% = 0,63

The presence of bacterial infection can use several commonly used supports including leukocytosis in the stool, increased C reactive protein (CRP) (Simon et al., 2004), increased procalcitonin (Duong et al., 2018; Tang et al., 2007) (PCT) , stool culture and increased *soluble triggering receptor expressed myeloid cells-1* (sTREM-1). A study comparing several diagnostic tools in the detection of possible bacterial infection was conducted to compare stool culture with CRP, PCT and sTREM-1. This study showed that sTREM-1 had a sensitivity of 93.7% and specificity of 94.3% with a *cut off* value ≥ 12.4 ng/ml with an area under the ROC curve 95% CI 0.94 (0.84-0.99). PCT assessment had a sensitivity of 66.7% and specificity of 80% with a *cut off* value > 4.95 ng/ml and for CRP had a sensitivity of 100% and specificity of 80% with a *cut off* value > 46.0 mg/L (Gibot, 2005). Leukocytosis examination in feces when more than 10 leukocytes per field of view are found on stool microscopy examination (Al-Asy et al., 2017). The standard examination in acute diarrhea due to bacterial infection is done by stool culture examination.

The ability to identify pathogenic bacteria that require specific clinical management such as antibiotics in children with acute diarrhea is very important (Guerrant et al., 1985). A study showed that stool culture to identify enteropathogenic bacteria is not recommended to be routinely performed.' This is because acute diarrhea is most commonly caused by viral infections, the results take a long time or about 5-7 days and the cost of stool culture examination is quite expensive and there are still weaknesses that are inconsistent results and the way the culture works in detecting pathogens is still unknown (Schmutz et al., 2017). However, several diarrhea guidelines so far still recommend stool culture or microbiological testing for the possible presence of enteropathogenic bacteria. Other screening approaches are needed to detect possible bacterial or pathogenic infections.

Microscopic examination of feces in considering the presence of microbiology or infection in children with suspected enteropathogenic bacterial infection has varied results worldwide. However, it can be concluded that elevated fecal leukocytes have a sensitivity ranging from 25.8% to 66.9% while specificity is 63.6% to 96.5%. There is no guideline that is able to optimally provide a good picture. Most sensitivities can give false results in one third of cases proven to be diarrhea due to bacterial infection and most specificities can give false results in almost 75% of cases (Chiyangi et al., 2017).

A study showed that examination of leukocytes in feces > 3 / LPB had a sensitivity of 29% and specificity of 81%, fever sensitivity of 45.1% and specificity of 58%, tenesmus sensitivity of 32.2% and specificity of 76%. Detection of *Clostridium difficile* germs with fecal leukocytes > 1 / LPB has a sensitivity of 14% and a specificity of 90%, but when a stool culture is performed in these cases, a sensitivity of 52% and a specificity of 88% is found (Williams et al., 2018). Similar results were obtained when the fecal leukocyte value was >10/LPB. A 1983 study in developing country Bangladesh showed that fecal leukocytes >10/LPB had a sensitivity of 60% and specificity of 54%, a positive *likelihood* ratio of 1.3 and a negative *likelihood* ratio of 0.74. Another 1999 study in the developing country of Colombia showed that fecal leukocytes >10/LPB had a sensitivity of 47.1% and specificity of 91.9%, a positive *likelihood* ratio of 5.2 and a negative *likelihood* ratio of 0.59. From these two studies in developing countries, although they differed by more than 10 years when the research was conducted, they found similar results.

Systematic *review of* 14 meta-analysis studies found fecal leukocytes > 5/LPB in developing countries 73% sensitivity and 84% specificity, positive *likelihood* ratio 4.56, negative *likelihood* ratio 0.32 while in poor countries 50% sensitivity and 83% specificity, positive likelihood ratio (LR +) 2.94, and negative *likelihood* ratio (LR -) 0.60. In general, the usefulness of fecal leukocyte examination is low except when the fecal leukocyte result is below 5/LPB or an extreme increase above 100/LPB. Fecal leukocytes < 5/LPB sensitivity 93% and specificity 27%, positive *likelihood* ratio 1.3, negative *likelihood* ratio 0.25, and fecal leukocytes > 100/LPB sensitivity 62% and specificity 72%, and positive *likelihood* ratio 2.24 (Rahmat & Frimansyah, 2016).

One study showed the use of blood leukocytes (leukocytes above 10^9/L), neutrophil percentage (above 75%) and C-reactive protein (above 10 mg/L) in assessing the possibility of bacterial infection. This study also assessed the clinical features of fever, vomiting, abdominal pain, frequency of diarrhea and duration of diarrhea as an assessment in bacterial infection. This study found that fever, elevated blood leukocytes and elevated neutrophils can predict bacterial infection. Liquid diarrhea, vomiting and fever were the most common clinical features in children with acute diarrhea. Dehydration complications also occurred in about 28.57% of cases and almost 81.25% occurred in children under 2 years. In patients with Cryptosporidium cases found 100% of children with diarrhea, 70% with dehydration, 30% with vomiting and 20% with fever (Liu et al., 2017). Another study showed the possibility of bacterial infection in acute diarrhea by looking at clinical features such as fever, abdominal pain, mucus in the stool, tenesmus, dehydration, vomiting and liquid diarrhea like rice washing (Ruiz-Pelaez & Mattar, 1999).

In our study we found fecal leukocytes >10/LPB had a sensitivity of 50%, specificity of 79.1%, positive predictive value of 7.1%, negative predictive value of 98%, accuracy of 78%, positive likelihood ratio value of 2.81 and negative likelihood ratio value of 0.63. In addition, we did not find clinical features of fever, vomiting and abdominal pain that could support the possibility of bacterial infection except for the clinical features found fever before defecation suggesting the possibility of bacterial infection.

In our study, the incidence of possible bacterial infection in children aged 6-60 months with acute diarrhea based on the assessment of sTREM-1 > 471 pg/mL examination was only 3.1%. This supports previous data that children under 5 years are mostly due to viral infections so that the use of antibiotics in cases of acute diarrhea should be considered to maintain *antimicrobial resistance* (AMR). Studies in Zambia in children aged 0-59 months with acute diarrhea most organisms found during diarrhea are resistant to antibiotics due to the use of ampicillin and cotrimoxazole as empirical therapy (Gill et al., 2003). A Vietnamese study of 3166 children with acute diarrhea at a median age of 10 months (6.5-16.7 months) given

empiric therapy (*fluoroquinolones* and third generation *cephalosporins*) did not provide clinical benefit in treating diarrhea (Hatchette & Farina, 2011).

This study has limitations, especially in the technical examination of sTREM-1 and fecal leukocyte examination. The implementation of the sTREM-1 examination using the ELISA method is the first time in Indonesia so there are still difficulties in understanding the ideal workings of the tool, the ability of facilities and human resources of laboratory analysts who are quite reliable but not familiar with this sTREM-1 examination so that it can cause errors when analyzing the tool. In addition, the fecal leukocyte study, which is much influenced by the situation when the fecal sample is examined, is still a consideration for the risk of contaminant infection or the risk of inappropriate results. We aim to have all feces examined within the first hour.

Conclusion

In this study, children aged 6-60 months who suffered from acute diarrhea due to bacterial infection with fecal leukocytes > 10 / LPB and sTREM-1 > 471 pg/mL were 1 child out of 64 children, amounting to 1.56%. Subjects with a clinical profile of children aged 6-60 months suffering from acute diarrhea due to bacterial infection were dominated by patients aged 6-24 months, male gender, normal nutritional status, and had a clinical picture of fever, vomiting and no abdominal pain. Increased fecal leukocytes in acute diarrhea due to bacterial infection in children aged 6 months to 60 months have diagnostic value: sensitivity 50%, specificity 79.1%, positive predictive value 7.1%, negative predictive value 98%, accuracy 78%, positive likelihood ratio value 2.18 and negative likelihood ratio value 0.63. The diagnostic test of fecal leukocytes above 10 per LPB has a diagnostic value not comparable to the examination of sTREM-1 > 471 pg/mL in acute diarrhea due to bacterial infection so that fecal leukocytes > 10 / LPB are not well used in determining acute diarrhea due to bacterial infection.

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