The benefit of co-trimoxazole treatment in the management of acute watery diarrhea caused by invasive bacterial infection

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Abstract

Background World Health Organization (WHO) states that antimicrobials are reliably helpful only for children with bloody diarrhea (probable shigellosis), suspected cholera with severe dehydration, and symptomatic infection caused by *Giardia lamblia*. The benefit of antimicrobial treatment in management of acute watery diarrhea caused by invasive bacterial infection is still debated.

Objective To prove the benefit of co-trimoxazole treatment in the management of acute watery diarrhea caused by invasive bacterial infection in patients age 2–24 months.

Methods This was a randomized, double blind clinical trial involving infants and children aged 2–24 months with acute watery diarrhea caused by invasive bacterial infection without co-morbidity or complications. Invasive bacterial infection was defined by fecal leukocytes greater than ten cells (+2) per high power field on stool. Subjects were assigned to receive either co-trimoxazole or placebo. The duration and frequency of diarrhea between two groups were compared.

Result Of 70 patients (co-trimoxazole, n=35; placebo, n=35), 42 (60%) were children aged 12–24 months, of whom 61% were undernourished. Males were affected 1.2 times as much as females. The clinical manifestations were mild-moderate dehydration (64%), mucus in the stool (100%), fever (24%), vomiting (10%), fever with vomiting (56%) and lactose malabsorption (53%). Duration of diarrhea in placebo group (mean 117.0 [SD 28.1] hours) was not significantly different (P=0.43) compared to that in co-trimoxazole group (mean 122.5 [SD 30.1] hours). Frequency of diarrhea per day in placebo group (mean 5.23 [SD 1.48] times) was not significantly different either (P=0.37) compared to that in co-trimoxazole group (mean 5.64 [SD 2.20] times).

Conclusion It is concluded that co-trimoxazole therapy provides no benefit to patients with acute watery diarrhea caused by invasive bacterial infection. This disorder seems to be self-limited.[Paediatr Indones 2007;47:104-108].

Keywords: invasive bacteria, diarrhea, fecal leukocyte, antimicrobial.
any benefit in shortening the clinical course. Proulx et al.\(^6\) also reported the same result in those with \textit{E. coli} O157:H7 infection. On the other hand, DuPont et al.\(^7\) found that the administration of TMP-SMX to patients with acute diarrhea caused by \textit{E. coli} and \textit{Shigella} infection shortened the duration of diarrhea. Thoren et al.\(^8\) reported the same result in those with Enteropathogenic \textit{E. coli} (EPEC) infection. Grisaruso et al.\(^9\) found that 80% of children with \textit{Salmonella} spp bacteremia previously had a history of acute diarrhea. Therefore, in our department, patients with acute watery diarrhea caused by invasive bacterial infection confirmed by the finding of numerous fecal leukocytes were given co-trimoxazole treatment routinely.

While the benefit of antimicrobial in diarrhea treatment is still debated, we presume that antimicrobial has benefits in the treatment of invasive bacterial diarrhea. The purpose of this study was to prove the benefit of co-trimoxazole administration in management of acute watery diarrhea caused by invasive bacterial infection in patients aged 2–24 months in Pediatric Department, Cipto Mangunkusumo Hospital, Jakarta.

### Methods

A randomized, double blind, clinical trial was carried out on outpatients and inpatients infants and children with acute watery diarrhea caused by invasive bacterial infection treated at the Pediatric Department, Cipto Mangunkusumo Hospital. This study was performed from 25 August to 30 December 2005. Infants and children aged from 2 to 24 months with acute watery diarrhea caused by invasive bacterial infection were eligible for this study. Invasive bacterial infection was defined by finding of leukocytes greater than ten cells (+2) per high power field on stool (preferably mucus) smear. Informed consent was obtained from parents. We excluded patients with diarrhea more than 72 hours, those who suffered from dysentery, cholera or had co-morbidity such as severe infection, immune deficiency or severe malnutrition, or a history of antimicrobial administration before admission and those who were sensitive to sulphonamide, were excluded from the study.

The total sample needed was 70 subjects. Subjects were randomly assigned to either receive co-trimoxazole or placebo. The duration and frequency of diarrhea per day were observed and recorded into a form by one of the authors and parents. The duration and frequency of diarrhea between two groups were compared and analyzed. The stools were also collected for bacterial culture with appropriate media (MacConkey agar and SS agar) and for antimicrobial sensitivity test at Pramita Laboratory Jakarta. Subjects that were considered suffered from adverse reactions such as dermatologic reactions (pruritis, skin rash) or prolonged diarrhea (more than 7 days) were considered as failure of therapy and received a specific treatment based on the etiology.

Student’s t-test (2-tailed) and linear regression analysis with a level of significance <0.05 were performed using SPSS 12 for Windows program. The study was approved by the Committee for Medical Research Ethics of the Faculty of Medicine, University of Indonesia.

### Results

Seventy patients were enrolled and divided into two groups (co-trimoxazole, n=35; placebo, n=35). The characteristics between two groups were similar (Table 1). Forty two subjects (60%) were children aged 12–24 months, of whom 61.4% were undernourished. Males were affected 1.2 times as much as females.

Table 2 shows that the clinical manifestations were mucus in the stool (100%), fever (24%), vomiting (10%), fever with vomiting (56%), and without fever or vomiting (10%).

Table 3 shows the comparison of duration and frequency of diarrhea per day between the two groups. Duration of diarrhea and frequency of diarrhea per day in placebo in co-trimoxazole group were not significantly difference. There was no failure of therapy reported during the study.

From the 70 stool specimens, EPEC was identified in 8.6% and \textit{Salmonella arizonae} in 7.1% of the diarrheagenic pathogen but no \textit{Shigella} spp. specimens were isolated. Twenty percent of the specimens were other non-diarrheagenic bacteria, such as \textit{Enterobacter sakazakii}, \textit{Enterobacter cloacae}, \textit{Serratia odorifera}, \textit{Klebsiella pneumoniae}, \textit{Acinetobacter calcoaceticus} and \textit{Staphylococcus epidermidis}. Non pathogenic \textit{E.coli} was found 64.3% from all speci-
Discussion

There were several limitations of our study. Globally, the major cause of infectious diarrhea in infant and children is rotavirus\(^3,10,11\). We did not search for rotavirus as the etiology of diarrhea, but we assumed that all stool specimens with more than ten leukocytes per high power field were considered invasive bacterial infection.\(^12\) Nevertheless, the rotavirus co-infection in bacteria caused diarrhea could occur.\(^11\) Because of laboratory investigation limitation we could not identify other invasive bacteria such as Enteroinvasive E.coli and Campylobacter jejuni which are often found in the developing country as the diarrheagenic bacteria.\(^3,11\)

Forty two subject (60\%) were children aged 12–24 months (Table 1), this finding is similar to previous study. Diniz-santos et al\(^13\) reported that the incidence of bacteria caused diarrhea increases in children more than 1 year of age, the period when children contact with environmental pathogen increases dramatically. Males were affected 1.2 times as much as females (Table 1) which is similar to results of previous studies.\(^8,13,14\) Until know, we have not been able to find any literature which explain the gender-specific difference in bacteria caused diarrhea. The most clinical manifestations in acute watery diarrhea caused by invasive bacteria were fever with vomiting (55.7\%) besides mucus...
in the stool (100%) (Table 2). This finding is similar to Guandalini’s report that fever with vomiting (68%) is the most frequently found clinical manifestations in bacterial diarrhea, besides the mucus in stool.11

Robins-Browne et al15 reported that duration of diarrhea in placebo group of *Campylobacter jejuni* gastroenteritis was 144 hours, while DuPont et al7 found that the duration of diarrhea in placebo group of uncomplicated *Shigella* gastroenteritis was 109.6 hours. Our study has a similar results to previous studies, that clinical course in placebo group of uncomplicated acute watery diarrhea caused by invasive bacteria whereas no antimicrobial treatment was 116.97 hours (Table 3). The clinical course seems to be self-limited since no co-morbidity or other complications occur. Administering antimicrobial in such patients should not be given routinely except for children with bloody diarrhea (probable shigellosis) or suspected cholera with severe dehydration.3,10

Duration of diarrhea in placebo group was not significantly different compared to those in co-trimoxazole group. Frequency of diarrhea per day in placebo group was also not significantly different compared to those in co-trimoxazole group (Table 3). Disadvantages of antimicrobial benefit in bacteria caused diarrhea management are also shown on previous studies.5,6,14,15,18 Co-trimoxazole susceptibility test (Table 4) shows that most of diarrheagenic bacteria are resistant to this antimicrobial. The increase of this antimicrobial resistant and probable co-trimoxazole associated diarrhea may cause disadvantage to the clinical course in this study.19

*Enteropathogenic E. coli* was identified in 8.6% of all stool specimens which is similar to Diniz-Santos’s study (7.3%) of acute bacterial diarrhea in children in Brazil.13 *Salmonella arizonae* was isolated 7.1% of the diarrheagenic pathogen, and this finding is similar to those in developing country reported by WHO (1-5%).3 We have failed to isolate *Shigella spp.* This negative finding probably because patients with bloody diarrhea (probable shigellosis) which obviously need the antimicrobial treatment were excluded. The subjects age in our study ranged 2–24 months, meanwhile the highest incidence of shigellosis is usually occur in children between 4–10 years of age.13 Finally, the laboratory investigation limitation may also cause this negative finding.

All of *Enteropathogenic E. coli* isolated (100%) were found to be resistant to co-trimoxazole (Table 4), much higher than that of Pracoyo et al20 and Soelaeman et al21. The overuse of co-trimoxazole in diarrhea management in general population probably causes the increase of antimicrobial resistance.

We conclude that co-trimoxazole provides no benefit to patients with acute watery invasive bacterial diarrhea. This clinical course seems to be self-limited since no co-morbidity or other complications occur. Administering antimicrobial in such patients should be discontinued.

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