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Research Paper

The Efficacy of Single Antibiotic And Combination Antibiotics Therapy in Pediatric Patients With Typhoid Fever

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Abstract
Typhoid fever is a systemic infectious disease caused by Salmonella typhi. Cases of typhoid fever in the Special Region of Yogyakarta in 2016 became the 5th most common with a prevalence of 3.820 cases. Antibiotic therapy is the main therapy for typhoid fever patients. This study aims to determine the effectiveness of a single antibiotic (ceftriaxone) compared to a combination antibiotic (ampicillin-chloramphenicol) in pediatric typhoid fever patients at the hospital. Private, Yogyakarta.
The research method used is a quasi-experimental design with an after and before with control group (prospective) conducted from May 2018 to October 2018. The study was divided into two groups, namely 26 patients receiving ceftriaxone antibiotics and 26 patients receiving ampicillin-chloramphenicol antibiotics. Parameters of clinical conditions measured were fever (temperature), abdominal pain, nausea, vomiting, diarrhea and length of hospitalization. The data obtained were statistically analyzed using Chi Square test and independent t-test with 95% confidence level.
The results showed that there was no significant difference between the two groups (p>0.05) in clinical improvement of fever (temperature), abdominal pain, nausea, vomiting and diarrhea. The mean±SD length of stay in the ceftriaxone group (4.11±0.58 days)/(75.07±15.02 hours) and the ampicillin-chloramphenicol group (4.07±0.62 days)/(73 .53±14.31 hours) with p>0.05.
Based on the results of this study, it can be concluded that there is no significant difference between the effectiveness of ceftriaxone and ampicillin chloramphenicol against fever (temperature), abdominal pain, nausea, vomiting, diarrhea and length of hospitalization.
Keywords*: Typhoid fever, ceftriaxone antibiotic effectiveness, ampicillin-chloramphenicol combination, clinical improvement, length of hospitalization*

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I. INTRODUCTION

Typhoid fever is a gram-negative bacterial infection with Salmonella typhi in the intestinum[1]. The main symptoms are continuous fever[2] and other clinical problems such as abdominal pain, nausea, vomiting, pallor, headache, dirty tongue, diarrhea, cough, anorexia and constipation[3].

Typhoid fever generally occurs in children aged <15 years with a case of 180.3/100,000 population[4]. The incidence of typhoid fever worldwide is around 17 million per year, with a mortality rate of 600,000 per year in Asia and in Indonesia there are 900,000 cases with a mortality rate of 20,000 per year. Typhoid fever cases in the Special Region of Yogyakarta became the 5th most common occurrence with a prevalence of 3,820 cases[5].

Antibiotics are the main therapy for typhoid fever patients and supportive therapy[6]. The use of antibiotics in typhoid fever raises new problems, namely the emergence of resistance, thereby increasing disease morbidity and mortality[7].

The existence of antibiotic resistance causes several problems such as drug availability, efficacy, cost factors and recurrence[4]. Combination antibiotic therapy has several advantages, namely preventing bacterial

resistance to antibiotics, increasing effectiveness, preventing polybacterial infections[8], eliminating side effects from other drugs[9]. This study used ceftriaxone antibiotic therapy and ampicillin-chloramphenicol combination.

II. MATERIALS AND METHODS

The design of this study was a quasi-experimental after and before with control group. The subjects of this study were pediatric patients aged 0-18 years who were diagnosed with typhoid fever. Data collection of pediatric typhoid fever patients was prospectively carried out in the population in the inpatient ward of the hospital. Private, Yogyakarta during the period from May to October 2018. This study was approved by the health research ethics committee of the Dr. Moewardi with No. 482/IV/HREC/2018. The informed consent obtained contains a signature of approval from the patient's guardian.

Inclusion criteria were pediatric patients under 18 years of age with a diagnosis of typhoid fever (ICD-10: A01.0) and receiving ceftriaxone antibiotic therapy or ampicillin-chloramphenicol combination. Patients who had discontinued or changed antibiotics were excluded from this study.

Accurate clinical improvements were temperature, abdominal pain, nausea, vomiting, diarrhea, and length of hospital stay.Comparison of therapeutic efficacy between the antibiotic ceftriaxone and ampicillin chloramphenicol was statistically analyzed. Statistical tests were performed using the Chi Square test and independent t-test.

III. RESULTS

Table I. Characteristics and Presenting Symptoms Patients Children with Typhoid Fever

Characteristics	Ceftriaxone (n=26)	Ampicillin-chloramphenicol (n=26)	*p*
Gender			
Male	15 (57,7%)	12 (46,2%)	0,579
Female	11 (42,3%)	14 (53,8%)	
Age	5,55±2,55	4,97±2,70	
	2±10	1±10	
< 5 years old	11 (42,3%)	13 (50,0%)	0,781
> 5 years old	15 (57,7%)	13 (50,0%)	
Fever			
Yes	13 (50,0%)	14 (53,8%)	1,000
No	13 (50,0%)	12 (46,2%)	
Abdominal pain			
Yes	14 (53,8%)	13 (50,0%)	1,000
No	12 (46,2%)	13 (50,0%)	
Nausea			
Yes	5 (19,2%)	5 (19,2%)	1,000
No	21 (80,8%)	21 (80,8%)	
Vomiting			
Yes	4 (15,4%)	9 (34,6%	0,199
No	22 (84,6%)	17 (65,4%)	
Diarrhea			
Yes	7 (26,9%)	8 (30,8%)	
No	19 (73,1%)	18 (69,2%)	1,000
Anorexia			
Yes	15 (57,7%)	14 (53,8%)	
No	11 (42,3%)	12 (46,2%)	1,000
Cough			
Yes	17 (65,4%)	15 (57,7%)	0,776
No	9 (36,6%)	11 (42,3%)	
Constipation			
Yes	1 (3,8%)	1 (3,8%)	1,000
No	25 (96,2%)	25 (96,2%)	

Table 1 describes the Characteristics and Presenting Symptoms Patients Children with Typhoid Fever. There were 52 pediatric patients under 18 years old who were diagnosed with typhoid fever in the pediatric ward of the hospital. Private, Yogyakarta. Patient demographic data can be seen in table 1 in the analysis using the Chi Square test. The number of incidences of typhoid fever in male patients was 27 (51.9%) more than female patients in 25 (48.1%). The number of pediatric patients with typhoid fever was higher in the age group (>5 years) 28 (53.8%) than in the age group (<5 years) 24 (46.2%).

Table II. Laboratory test results

Laboratory Value	Ceftriaxone(n=26)	Ampicillin-Chloramphenicol (n=26)	*p*
Leukosit (sel/mm^3)	9208±4295	10968±6484	
	3400-17700	3980-30740	0,328
< 4000	1 (3,8%)	1 (3,8%)	
4000-11000	19 (73,1%)	14 (53,8%)	

> 11000	6 (23,1%)	11 (42,4%)	
Laboratory Diagnostics			
Widal test	8 (30,8%)	6 (23,1%)	0,755
Thypidot test	18 (69,2%)	20 (76,9%)	

Table II describes the laboratory test results related to leukocyte values and laboratory Diagnostics. This numerical data was analyzed using the independent t-test to determine the difference between patients receiving ceftriaxone and ampicillin-chloramphenicol therapy. The above results are supported by other parameters in the form of measuring the patient's body temperature which is shown in figure 1.The results in figure 1 show that the temperature on the first day averaged 37.62 ^{0}C and 37.48 ^{0}C and the next day the temperature of typhoid fever patients was normal.

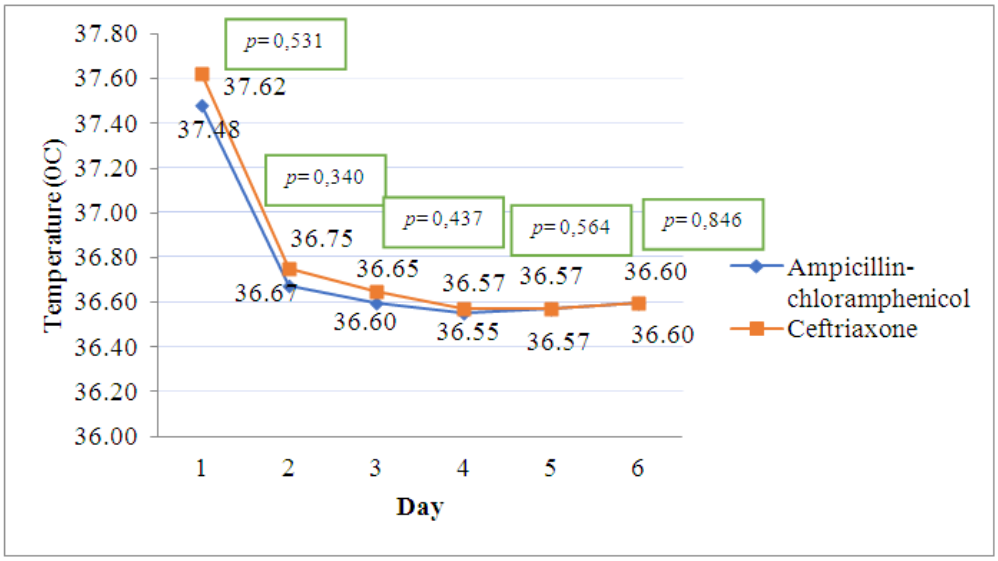

Figure 1. Graph of the average temperature change of typhoid fever patients in a private hospital, Yogyakarta on day 1 to day 6.

If it is associated with the patient's clinical complaints on day 1 to day 6, it is shown in figure 2. Figure 2 shows clinical improvement of abdominal pain by numerical (scoring). Day 1 abdominal pain averaged 1.31 and 1.04. on the 4th day, statistically, abdominal pain in the control group of typhoid fever patients still occurred compared to the treatment group. The results of this numerical data analysis showed that there was no significant difference between the ceftriaxone and ampicillin chloramphenicol groups in the improvement of temperature and abdominal pain therapy (p>0.05).

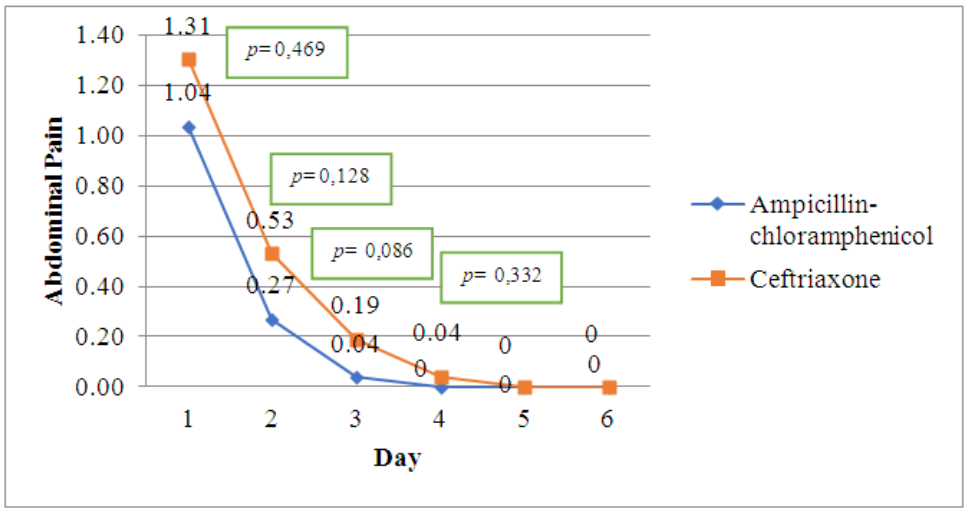

Figure 2. Graph of the average clinical changes in abdominal pain in patients with typhoid fever in a private hospital, Yogyakarta on day 1 to day 6.

The effectiveness of antibiotic therapy on clinical improvement numerical data (scoring), namely nausea and vomiting, can be seen in figures 3 and 4. These numerical data were analyzed using independent t-test, respectively. Figures 2 and 3 show that there was a change in the clinical improvement of nausea and vomiting on day 1 to day 3, but statistically on day 4 the control group still had nausea (0.04 times/day) and vomiting (0.04 times/day). 0.08 times/day) compared to the treatment group. Clinical improvement of nausea and vomitingafter therapy in both groups showed no significant difference (p>0.05).

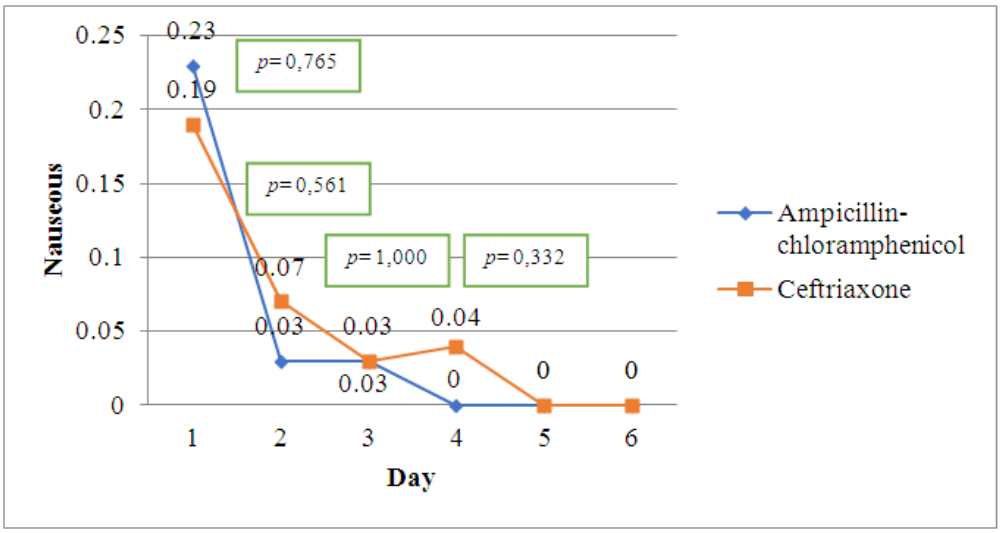

Figure 3. Graph of the average clinical change in nausea of typhoid fever patients in in a private hospital, Yogyakarta on day 1 to day 6.

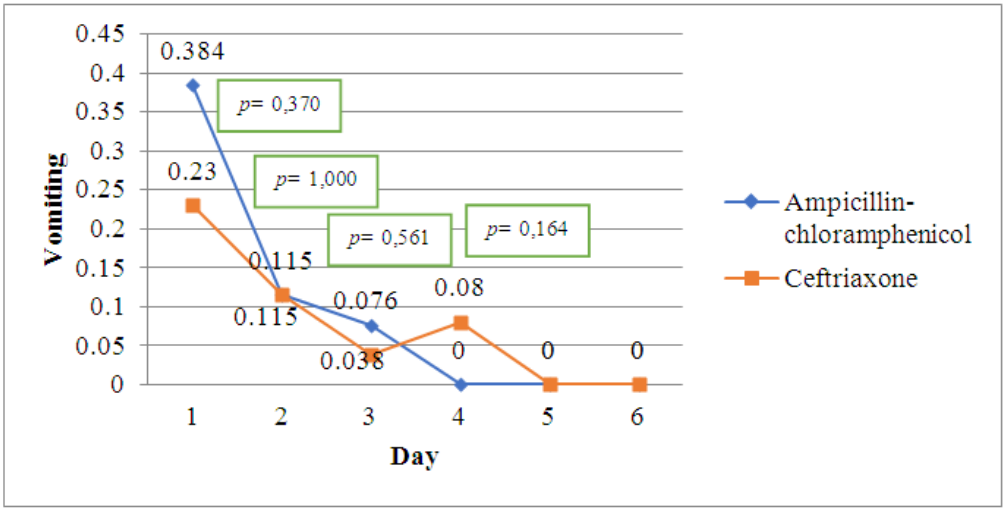

Figure 4. Graph of the average clinical change in the vomiting of typhoid fever patients in a private hospital, Yogyakarta on day 1 to day 6.

The effectiveness of antibiotic therapy on clinical improvement can be seen the numerical data (scoring) namely the frequency of diarrhea in figure 5 and anorexia in figure 6. These numerical data were analyzed using independent t-test. Figure 5 shows changes in clinical improvement on day 1 with an average of (0.3 times/day) and (0.26 times/day) and on day 5 clinical symptoms of diarrhea resolved. The length of hospitalization data is numerical data which was analyzed using independent t-test.

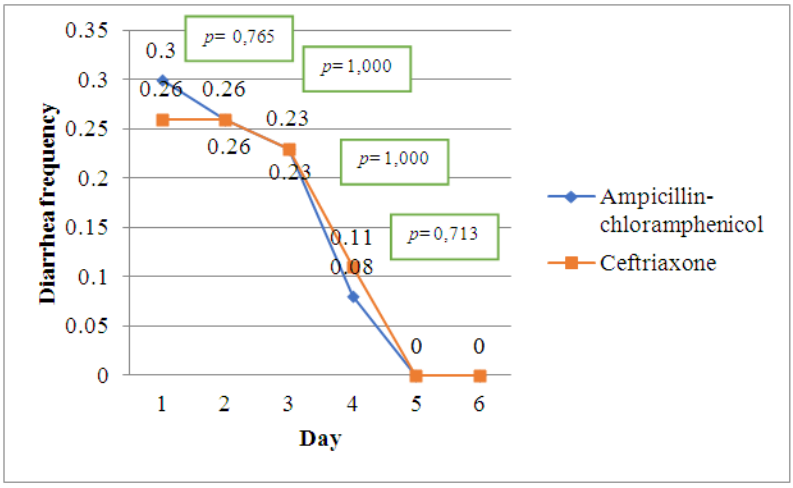

Figure 5. Graph of the average clinical change in diarrhea of typhoid fever patients in a private hospital, Yogyakarta on day 1 to day 6.

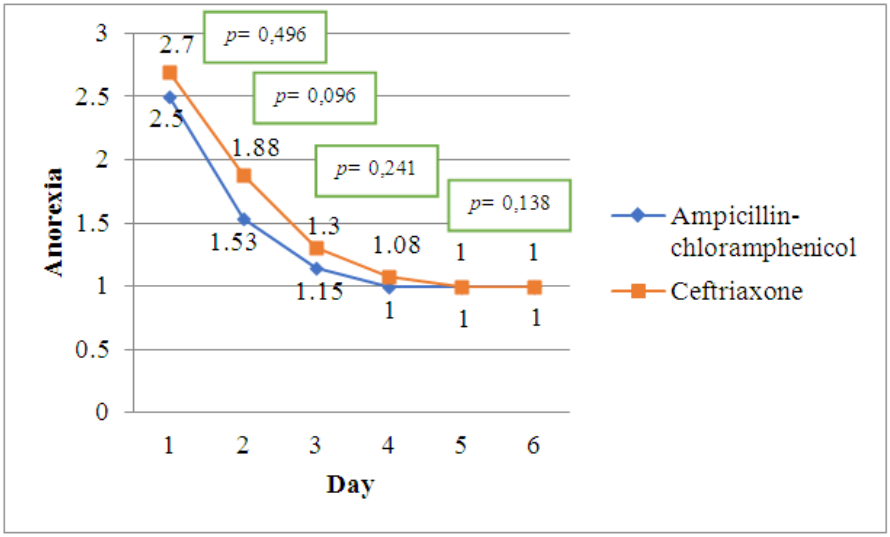

Figure 6. Graph of the average clinical changes of anorexia in typhoid fever patients in a private hospital, Yogyakarta, from day 1 to da 6.

Table III. Effectiveness on clinical improvement after being given ceftriaxone therapy (n=26), ampicillin-chloramphenicol combination (n=26).

Day		1	2	3	4	5
Fever (temperature)	Ceftriaxone	37,63±0,811 36,40-39,40	36,75±0,315 36,40-37,80	36,65±0,274 36,20-37,50	36,57±0,151 36,20-36,80	36,56±0,057 36,50-36,60
	Ampicillin-chloramphenicol	37,48±0,770 36,20-38.80	36,67±0,256 36,50-37,60	36,60±0,163 36,40-37,20	36,55±0,094 36,30-36,70	36,57±0,050 36,50-36,60
	p	0,531	0,340	0,437	0,562	0,846
Abdominal pain	Ceftriaxone	1,307±1,435 0-4	0,538±0,706 0-2	0,192±0,401 0-1	0,040±0,200 0-1	-
	Ampicillin-chloramphenicol	1,038±1,215 0-4	0,269±0,533 0-2	0,038±0,196 0-1	-	-
	p	0,469	0,128	0,086	0,332	-
Nausea	Ceftriaxone	0,192±0,401 0-1	0,076±0,271 0-1	0,038±0,196 0-1	0,040±0,200 0-1	-
	Ampicillin-chloramphenicol	0,230±0,514 0-2	0,038±0,196 0-1	0,038±0,196 0-1	-	-
	p	0,765	0,561	1,000	0,332	-
Vomiting	Ceftriaxone	0,230±0,651 0-3	0,115±0,325 0-1	0,038±0,196 0-1	0,080±0,276 0-1	-
	Ampicillin-	0,384±0,571	0,115±0,431	0,076±0,271	-	-

	chloramphenicol	0-2	0-2	0-1		
	p	0,370	1,000	0,561	0,164	-
Diarrhea frequency	Ceftriaxone	0,269±0,452 0-1	0,269±0,452 0-1	0,230±0,429 0-1	0,115±0,276 0-1	-
	Ampicillin-chloramphenicol	0,307±0,470 0-1	0,269±0,533 0-2	0,230±0,514 0-2	0,083±0,282 0-1	-
	p	0,765	1,000	1,000	0,713	-

Table III showed that there was no significant difference between the administration of ceftriaxone therapy and the combination of ampicillin chloramphenicol on clinical improvement. Table IV shows that the length of stay in the ceftriaxone group (n=26) was 4.11±0.58 (3-6 days) or 75.07±15.02 (56-128 hours) while the ampicillin chloramphenicol group (n= 26) is 4.07±14.21 (3-6 days) or 73.53±14.31 (48-120 hours). Value of length of stayafter therapy in both groups showed no significant difference (p>0.05).

Table IV. Length of stay (LOS)

	Ceftriaxone (n=26)	Ampicillin-chloramphenicol (n=26)	*p*
Mean±SD	75,07±15,02*	73,53±14,21*	0,707*
Min-Max	56-128 jam	48-128 jam	
Mean±SD	4,11±0,58**	4,07±0,62**	0,821**
Min-Max	3-6 days	3-6 days	

IV. Discussion

Distribution of Antibiotics are the main therapy for typhoid fever patients and supportive therapy[6]. Some research literature and prescribing patterns of combination antibiotic combinations in typhoid fever are ampicillin chloramphenicol[10,11], azithromycin ofloxacin[12], cefixime azithromycin[13]. The antibiotics used in this study were ceftriaxone and ampicillin chloramphenicol. The results of this study showed that there were more male patients suffering from typhoid fever with a percentage of 51.9%. Typhoid fever can affect anyone, there is no difference in sex between men and women[14]. The number of pediatric typhoid fever patients was higher in the age group > 5 years with a percentage of 53.8%. Typhoid fever often occurs in the age group 3-19 years[4.] It is suspected that age is susceptible to food or drink contaminated with Salmonella typhi bacteria.

Some clinical symptoms that can be found in typhoid fever patients are fever, abdominal pain, nausea, vomiting, diarrhea, cough, anorexia, dirty tongue, headache, constipation[3]. Observation of clinical improvement of fever was seen by the patient's temperature, abdominal pain scoring (Numeric Branch Scale) which was a score of 0 (no pain), a score of 1-3 (mild pain), a score of 4-6 (moderate pain) and a score of 7-10 (severe pain). , scoring for nausea, vomiting, diarrhea (normal=0, 1-3 times/day=mild, 4-5 times/day=moderate and 6 times/day=severe)[16].

The results of the analysis of this study showed that there was no significant difference between the administration of ceftriaxone therapy and the combination of ampicillin chloramphenicol on clinical improvement (see table III). Fever (temperature), abdominal pain, nausea, vomiting and diarrhea (p>0.05). Patients with typhoid fever are free from fever after 3 days or less of antibiotics. Improvements in clinical symptoms of abdominal pain resolved on the 2nd day. This is because the activity of antibiotics in inhibiting Salmonella typhi bacteria releases pain mediators[18].

Improvements in clinical symptoms of nausea, vomiting, and diarrhea occur on average on day 2. Antibiotics improve intestinal motility by reducing intestinal hyperperistalsis. The length of hospitalization is also one of the things that can be used to determine the effectiveness of an antibiotic. The results of the analysis of length of stay concluded that there was no significant difference between the two groups (p>0.05).

V. Conclusion

Based on the results of this study, it can be concluded that there is no significant difference between the effectiveness of ceftriaxone and ampicillin chloramphenicol against fever (temperature), abdominal pain, nausea, vomiting, diarrhea and length of hospitalization.

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