ORIGINAL ARTICLE

Antibiotic Therapy for Invasive Bacterial Diarrhea

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ABSTRACT To evaluate the effectiveness of the standard practice of antibiotic prescribing in diarrheal diseases (DD) at Palembang General Hospital, we performed this single blind clinical trial. Subjects were children with DD, without *E. histolytica* or *G. lamblia* in their stool, 6 to 59 months of age, seen at the OPD from May 20, 1991 until March 31, 1992. Antibiotic treatment (AT) was given to the treated group (n=289), and was withheld from the control group (n=298). The effectiveness of antibiotic treatment was measured by rate of reconsultation, need for subsequent AT, duration of diarrhea, vomiting, and fever as measured by home visitors. The treated group has a significantly shorter duration of diarrhea and a significant difference in the need for additional AT. Subjects whose diarrhea persist more than 7 days were significant statistically only in bloody diarrhea and in subjects whose fecal leukocytes were more than 9 per high power field. Profuse diarrhea and mother's anxiety were the main reasons for further consultation, which were strikingly greater in control than in treated group. Mothers seeked reconsultation 12.5 times more often for bloody diarrhea and 19.5 times for mucoid diarrhea plus fever. This study reconfirmed that AT in DD shortens the duration of diarrhea, diminishes the rate of reconsultation, and need for subsequent antibiotics in bloody and mucoid diarrhea. **[Paediatr Indones 1993; 33:26-37]**

Introduction

Since 1980 WHO[1] has recommended resricting antimicrobial therapy in diarrheal diseases (DD) to the treatment of cholera, severe shigellosis, amebiasis, and giardiasis. In 1990 WHO[2] devised operational criteria for antibiotic therapy (AT), that are clinical diagnosis of cholera or bloody diarrhea. These criteria are based on the assumptions that from the public health point of view, the health hazard of invasive bacterial diarrhea (ID) is mainly due to shigellosis, and grossly bloody diarrhea is a sensitive and specific indicator for severe shigellosis. Since DD is very common in developing coun-

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tries, control of AT in DD will be of major benefit in controlling antibiotic abuse. The Indonesian CDD Program[3] has recommended AT for cholera, bloody diarrhea, presence of 'systemic manifestations' and the presence 10 or more fecal leukocytes per high power field (HPF). Although studies have shown that educational programs to use of oral rehydration (ORT) and appropriate feeding, and to discourage the use of antidiarrheal drugs[4-6] have been effective, the use of antibiotics is still inappropriately high.

We perceived a need for better data on the incidence of Shigella as a cause of dysentry and of the overall incidence of dysentry in Indonesia. If Shigella is not the major cause of dysentry it is necessary to determine if bloody diarrhea caused by other agents may benefit from AT. Only then can appropriate recommendations regarding AT be developed.

At the Department of Child Health, Palembang General Hospital, the indications for AT in DD include bloody diarrhea, mucoid diarrhea plus fever, high fever, clinical diagnosis of cholera, 10 or more fecal leukocytes per HPF, and 'systemic manifestations'. These are based on clinical experiences and the impression of the physicians that they can predict shigellosis and ID or cholera by these criteria. This study aimed to evaluate the effectiveness of these criteria.

Methods

Design

The study was a single blind clinical trial. Subjects were assigned randomly to treated and control groups. The treated group, using the above criteria for AT, received antibiotics. AT was withheld from the control group; instead, placebo was given. The investigators knew which subjects received AT, but the parents or care givers did not.

Randomization

Subjects were assigned to either treated or control group by every '2 days' of their presentation to the OPD, i.e., on two consecutive days all children were assigned to the treated group and on the following two days all the children were assigned to the control group.

Definitions

Diarrhea is defined as 3 or more watery stools with or without mucus or blood, or 3 or more loose stools with mucus and / or blood. Diarrhea was classified into 3 categories; watery diarrhea is defined as diarrhea with no blood or mucus, mucoid diarrhea is defined as diarrhea with mucus but no blood, bloody diarrhea is difined as diarrhea with blood.

Fever is classified into reported fever, i.e., fever as reported by care giver; and measured fever, i.e., rectal temperature 37.5°C or more.

As the guidelines for home visitors to asses the clinical course of DD and the criteria for follow up AT, the progress of patients were considered 'more severe' if diarrhea or vomiting became more frequent and profuse, if body temperature has risen to 39.5°C or more, or other serious clinical manifestations such as convulsion or severe abdominal distention occurred. Patients were considered unimproved if the frequency, consist-

ency, and quantity of diarrhea and vomiting were stable for 2 days. Patients were considered improved if the frequency and quantity of vomiting and diarrhea diminished or consistency of stools became more solid. Patients were considered cured if there was no diarrhea, fever and vomiting, or had fever which can be explained by other causes.

Subjects

Infants and children with diarrhea from age 6 to 59 months seen at the outpatient clinic of Palembang General Hospital (OPD), from 20 May 1991 up to end of March 1992 who had diarrhea within 24 hours prior to the visit were eligible to this study.

Patients were excluded from the study if there was an immediate need for hospitalisation, if the diarrhea had lasted for more than 14 days, if there was an indication for antibiotic therapy for other diseases, if patients were unavailable for follow up, or if there was *G. lamblia* or *E. histolytica* found in microscopic examination of the stools. To optimise follow up, only the first 4 eligible patients were recruited for the study each day.

Procedures

Routine history and physical examination were conducted by the OPD attending physician. The physicians are senior pediatric residents working in OPD. They were trained by the investigators to identify DD patients who were eligible for the study, assigned them to treated or control groups and prescribed AT according to the study protocol. Normatively, they should render AT according the Hospital's standard regiment in treating DD, where the indications for AT in DD are: bloody diarrhea, mucoid diarrhea plus fever, high fever, the clinical diagnosis of cholera, 10 or more fecal leucocytes per HPMF and the presence of 'systemic manife :tations'.

The attending physicians prescribed antibiotics for the treated group as indicated. Alternately on 'control days', antibiotics were not prescribed although there were indications according to the standard criteria. Placebo, powdered multivitamin, was given instead. In addition, paracetamol or cough mixture were prescribed as indicated. Antibiotics routinely available and used for common infections including DD are: ampicillin, chloramphenicol, and co-trimoxazole. The choice of antibiotic depended on the attending physician's perception which was based on history of antibiotic use, clinical manifestations, and the availability of antibiotics.

In addition, the routine DD treated management used at the OPD was followed. This included education of all care givers about ORT; administration of ORS to the child while waiting; dispension of ORS packages and education regarding appropriate feeding. If a child was severely dehydrated but could tolerate ORT, the child was observed for 2-4 hours during administration of ORT. Anti diarrheal drugs were not used.

Thorough history and physical examination were carried out by investigators to gather data including: age and sex, the first symptoms and signs appeared, the time lapsed in hours since the first symptom / sign, first abnormal stool, first vomiting, onset of fever, frequency and type of stool passing, frequency of vomiting, signs of dehydration, signs of abdominal pain, previous feeding regimen and treatment. General pediatric examination was performed as usual.

Stool (either spontaneously passed, catheterized, or obtained by rectal swab) was examined under light microscope and was cultured. The gross presence of blood or mucus was used to confirm the history of mucoid or bloody diarrhea. Microscopic examination was conducted immediately at OPD by a laboratory technician under the supervision of the investigator. Direct examination of the stool was done with eosin and lugol stain looking for worm eggs, *Giardia lamblia* and *Entamoeba histolytica*, and white blood cells (WBC) and red blood cells (RBC) were counted per HPF. Specimens were plated to relevant media immediately in OPD by a microbiologic technician to isolate *Salmonella, Shigella, Campylobacter jejuni, Yersinia enterocolitica, Vibrio cholerae* and *parahaemolyticus, E. coli, Aeromonas*, and *Pleisiomonas*.

Each day the investigators planned and coordinated home visits with the home visitors. Follow up was done by nurses who were trained to identify and differentiate more severe, unimproved, improved, and cured patients. Every subject in the treated or control group was visited on day 1, 2, 3, 5, and 7. Patients whose DD became more severe were referred to the private clinics of the investigators, or to the OPD during working hours, or to on duty resident at Department of Child Health, whichever was the most feasible. The unimproved cases before the result of stool culture and sensitivity test were available, were referred according to emotional condition of the care giver. After microbiologic examination results were available, all unimproved subjects were referred. On the fifth day, improved subjects who still had fever were referred. On the seventh day all uncured subjects were referred.

During the investigators meeting with the home visitors, follow up AT prescribed for the subjects at home were dispensed. Antibiotics were given to all subjects who met the criteria for follow up AT. The criteria were: 1) any subject referred for reconsultation from either the treated or the control group who had fever more than 38°C or met OPD's criteria for AT. Before the results of stool culture available, nalidixic acid 50 mg/kg BW was prescribed. 2) any unimproved subject, either from treated or control group who had enteric pathogen (except *E. coli*) isolated were treated with nalidixic acid. 3) on day five, any improved subject who still had fever were given antibiotic, either nalidixic acid or another antimicrobial according to the stool culture results. 4) on day 7, improved subject who had any stool pathogens except *E. coli*, were treated with antibiotic according to the stool culture. 5) any subject hospitalized was given gentamicin if AT was needed.

Data management and analysis

The investigators checked the thoroughness, clarity, and contradictory data in all forms and cross checked anecdotally. Data were processed and analysed by Epi-Info[7] application program.

Subjects were excluded from analysis if they were loss to follow-up, or could not be followed up more than 2 times, or did not take the prescribed medicine more than 3 times.

Measures of efficacy of AT included the need for consultation/hospitalization of further AT; and duration of diarrhea, fever and vomiting. Duration of the symptoms was divided into total duration and duration after treatment. For the purpose of analysis, if the diarrhea became persistent, the duration of diarrhea after treatment was regarded as 240 hours.

The difference of outcome in treated and control groups for continuous data were tested by Student's t test, and for discrete data by chi square test using Yate's correction, or Fisher's exact test.

Consent

Written consent was obtained after sufficient explanation of the purpose, nature, and the procedures of the treatment during the trial.

Results

There were 701 DD subjects eligible for the study, 82 patients were excluded. Of 619 of the assigned subjects, 32 had *E. histolytica* in their stools and were excluded from the analysis. Of the 587 subjects entered to the study, 289 were treated subjects and 298 were controls.

Characteristics of the subjects at the time of enrollment is shown in Table 1. There were no significant differences in the clinical findings in treated and control groups.

Table 2 shows the isolation of bacterial enteric pathogens, except for *E. coli;* 30% of the *Shigella* isolated were sensitive to ampicillin, 28% to chloramphenicol, 85% to co-trimoxsazole, 11% to erythromycine, 65% to gentamicin, and 98% to nalidixic acid.

Tables 3 and 4 show the mean duration of diarrhea after treatment and the mean of total duration of diarrhea in the treated and control groups, according to the sub-set of subjects in line with the indication of AT. There was no subject whose rectal temperature was more than 39.4°C (high fever) or who showed the 'systemic manifestation' on enrollment. The proportion of treated subjects with watery diarrhea, mucoid diarrhea, and bloody diarrhea whose diarrhea persisted more than 5 days after treatment, respectively, were 7.5%, 11.0% and 6.1%. Of the control group 13.5% of watery diarrhea, 16.9% of mucoid diarrhea and 37.5% of bloody diarrhea persisted for 5 days. The difference between the treated and control group was significant only in bloody diarrhea (p = 0.005). The subjects whose total duration of diarrhea were more than 7 days were shown in Table 5.

Table 6 shows the administration of follow up AT in the sub-set of subjects according to the indication of AT and in all subjects. There was a discrepancy between the number of treated group subjects who are eligible for AT according to the pre-determined criteria and the number of subjects who actually got AT on enrollment. The reason for this discrepancy was: the decision for AT was undertaken by the physician in charge, whilst the clinical findings are recorded by investigators. All follow up AT was given based on clinical course as described in the methods section, no antibiotics were given by stool culture results alone. Of 90 subjects who got follow up AT, 85 were prescribed during reconsultation or hospitalization, 5 based on observation on home visits.

Two subjects, 1 treated and 1 control were hospitalized at a private hospital because of profuse diarrhea with mild and moderate dehydration. Both were treated with combination of antibiotics and prolonged IV fluids. The diarrheal episode from the treated group became prolonged.

Nine additional cases were admitted to out hospital. One subject of 7 months old was admitted with watery diarrhea, high fever and presumed endotoxic shock. After receiving IV fluid, ampicillin and gentamycin in hospital, the patient died at day 4 of hospitalisation. One child was admitted with high fever and moderate dehydration, 3 children with severe dehydration, 4 children with profuse diarrhea and profuse vomiting. Five subjects from the control group were admitted, 1 with high fever and moderate dehydration, and 4 with severe dehydration.

The need for hospitalization in treated was not significantly different than that seen in control group. Except for the one who died, all recovered uneventfully.

Of 94 subjects who practiced reconsultation, 31 were of the treated group, 63 were of the control group. The reasons for consultations in both groups were shown in Table 7. Table 8 shows the odds ratio for needing reconsultation between the treated and control group.

Of 205 subjects who vomited at home, the mean of total duration of vomiting for both cases and controls were 55 hours. The mean duration of vomiting after enrollment was 19 hours vs 18 hours for cases and controls. This difference was not statistically significant (p=0.9). These parameters were also not different for the sub-set of subjects according to indication for AT.

Of 360 subjects who reported fever, the mean of the total duration of fever in the treated and control groups were 3.20 vs 2.89 days. The mean duration of fever after enrollment were 0.55 vs 0.53 days. These differences were not statistically significant. These parameters were also not different for the sub-set of subjects according to indication for AT.

Discussion

The general characteristics, history, physical examination, pattern of treatment at home, feeding practice before and during diarrhea, and microscopic laboratory examination of the stools of the subjects on enrollment of the treated and control groups were not different. The isolation of *Shigella* in treated group was relatively higher, in agreement with the relatively higher proportion of bloody diarrhea in the treated group.

In differentiating the efficacy of AT, 4 indicators were used: duration of diarrhea, duration of vomiting, duration of fever, need for further AT, and number of reconsultation. Since the number of hospitalisation was so small, we did not consider it as an indicator.

Table 1. Characteristics ofstudy subjects

		Treated n=289 (%)	Control n=298 (%)
Age (months)	Range	6-59	6-59
	Mean	18.9	17.1
Sex	Female	43.9	45
Nutritional status	< 59	2.8	1.0
% BW for age	60-69	10.0	10.4
	70-79	32.5	32.2
	80-109	54.6	56.4
Kind of diarrhea	Watery	60.2	61.7
	Mucoid	28.4	29.9
	Bloody	11.4	8.1
Durat. of diarrhea	Hours	57.9	51.5
Reported fever	Positive	57.1	63.1
Temp. > =37.5°C	Positive	29.8	27.2
Reported vomiting	Positive	33.4	32.9
Measles in last 6 mo	Positive	14.5	13.8
Sign of vit. A def.	Positive	2.1	2.3
Dehydration	Mild	3.1	1.0
	Moderate	1.4	1.3
	Severe	0.3	0.0
Still breastfed	Positive	67.5	62.4
Treatment at home	Self med	38.8	49.9
	T. healer	2.1	0.67
	M. person	39.1	33.2
AT at home	Positive	10.4	11.1
WBC > 9 / HPF	Positive	11.1	9.1

*) T. healer = traditonal healer; M. person = medical personnel; AT = antibiotic treatment; WBC = white blood cells;

Table 2. Isolation of enteric bacterial pathogen

	treated n=289	(%)	control n=298	(%)
Vibrio cholerae	1	0.3	4	1.3
Shigella	23	8	19	6.4
Salmonella	1	0.3	2	0.7
Campilobacter	6	2.6	5	1.7
Yersinia	0	0	0	0
Aeromonas	1	0.3	1	0.3
Vibrio non-agl.	0	0	1	0.3
Plesiomonas	0	0	1	0.3
		p=0.896		

The treated group, in general, and in the sub-set of subjects who are classified according to fulfillment to the criteria for AT, had a significant shorter duration of diarrhea after treatment compared with the control group, except for the sub-set who fulfilled the criteria 'fecal leukocyte' 10 or more per HPF (Table 3). This last finding may be due to the small sample size, and only 19 out of 32 eligible subjects had received AT on enrollment.

The data also show that there was a significant difference in the need for additional antibiotic therapy in cases compared to controls, except for the subset of subjects whose fecal stool leukocyte were 10 or more per HPF, although its odds ratio was high (OR=5.26 - Table 6). However, the proportion of subjects whose total duration of diarrhea persisted more than 7 days were significant statistically only in bloody diarrhea and in subjects whose fecal leucocyte were more than 9 per HPF. This fact might

Table 3. Duration of diarrhea after treatment in treated and control groups according to characteristic of diarrhea*

	Treated				*p*	Control		
	n	Received AB	Duration of diarrhea (hrs)			n	Duration of diarrhea (hrs)	
			Mean	SD			Mean	SD
Bloody diarrhea	33	32	64	36	0.002	24	102	52
Mucoid+fever	48	44	63	44	0.029	63	90	69
Mucoid+ temp.> 37.5°C	23	22	55	40	0.019	31	87	55
Fecal leukocyte > 9/HPF	32	19	56	31	0.076	27	72	39
Either above criteria	75	60	60	41	0.001	88	86	62
All subjects	288	119	63	49	0.000	298	80	52

*one subject of treated group was missing value; HPF = high power field

Table 4. Total duration of diarrhea in treated and control groups according to characteristic of diarrhea*

	Treated				*p*	Control		
	n	Received AB	Total duration of diarrhea (hrs)			n	Total duration of diarrhea (hrs)	
			Mean	SD			Mean	SD
Bloody diarrhea	33	32	145	36	0.582	24	161	52
Mucoid+fever	48	44	117	60	0.026	63	135	84
Mucoid+ temp.> 37.5°C	23	22	101	53	0.072	31	132	66
Fecal leukocyte > 9/HPF	32	19	106	58	0.140	27	131	73
Either above criteria	+ 75	60	115	61	0.082	88	135	81
All subjects	288	119	120	49	0.046	298	131	52

*one subject of treated group was missing value

Table 5. Total duration of diarrhea which persist for more than 7 days, in treated and control groups, according to characteristic of diarrhea*

	Control			OR	p	Treated		
	n	Received AB	> 7 days			n	Received AB	> 7 days
Bloody diarrhea	24	0	16	4.00	0.026	33	32	11
Mucoid+fever	63	0	11	0.71	0.635	48	44	11
Mucoid+ temp. > 37.5°C	31	0	4	0.42	0.294	23	22	6
Fecal leuc. > 9/HPMF	27	0	12	4.35	0.032	32	19	5
Either above criteria	88	0	23	1.20	0.741	75	60	17
All subject	298	0	76	1.28	0.254	288	119	61

* one subject of treated group was missing value

Table 6. Follow up antibiotics therapy in control and treated group

	Control group			OR	p	Treated group		
	n	Received AB on enrollment	Received AB on follow up			n	Received AB on enrollment	Received AB on follow up
Bloody diarrhea	24	0	11	8.33	0.004	33	32	3
Mucoid+fever	63	0	19	4.76	0.010	48	44	4
Mucoid+ temp. > 37.5°C	31	0	10	22.95	0.030	23	22	0
Fecal leukocyte> 9/HPF	27	0	4	5.26	0.169	32	19	1
Either above criteria	88	0	24	5.26	0.001	75	60	5
All subject	298	0	62	2.44	0.000	288	120	28

Table 7. Reason for reconsultation

Reason	Total n=94		
	treated n=31	control n=63	p = 0.001
			OR = 0.51
Profuse diarrhea	24	44	
High fever	5	4	
Bloody diarrhea	0	2	
Mucoid diarrhea	0	1	
Restlessness	0	1	
Mother's anxiety	4	15	
Did not known	1	1	

support that the widely accepted criteria for AT (bloody diarrhea and fecal stool leucocyte 10 or more per HPMF) are more relevant compared with other criteria used in this study.

Profuse diarrhea was the main reason for reconsultation. This is supported by the fact that there was no significant difference of duration of fever and vomiting in the treated and control groups. Mother's anxiety was the next most common reason for re-consultation and this was strikingly greater in the control group than the treated group. Even though it might be argued that the overall difference in duration of diarrhea after treatment, although significant statistically, was actually only 38 hours longer for bloody diarrhea not treated with antibiotics and 17 hours for all subjects. Mothers were concerned about their children so as to seek re-consultation 12.5 times more often for bloody diarrhea and 19.5 times for mucoid diarrhea plus fever.

It is presumed that appropriate AT prevent the severe complications of diarrhea, earlier improvement of clinical manifestations, diminish malnutrition, and may shortened the duration of shedding of enteric pathogen. It is well known that antibiotic therapy will reduced the case fatality of shigellosis in the community in Bangladesh,[8] shorten the clinical course of shigellosis,[9] and lessen the nutritional impact of shigellosis.[10]

Although watery and mucoid diarrhea, and even more, a lot of bloody diarrhea will subside without AB, this study agrees with others that antibiotics can shorten the duration of diarrhea. As this is often the main concern of the care taker of the patients, it is possible that antiobiotics could lessen the need for further consultation to health car providers.

Since AT was withheld for bloody diarrhea subjects in the control group, it can be assumed that the differences of the outcomes indicators were mainly due to the difference of treatment in bloody diarrhea subjects. However, our findings show that these significant differences were also found in mucoid diarrhea subjects. Nevertheless, the main impact of AT was observed in bloody diarrhea.

In analyzing why antibiotic usage rate in treating DD is still high in Indonesia, we predict that conceptually clinicians are willing to accept that not all bacterial diarrhea need AT. However, they are still hesitant to accept the current indications for antibiotic therapy, that is only for cholera and bloody diarrhea. It is still difficult for the health providers to accept the reasoning for the guidelines which are recommended by WHOas mentioned above.

Table 8. Reconsultation in control and treated group according to characteristic of diarrhea

	Control group					Treated group		
	n	Received AB on enrollment	Received AB on follow-up	OR	p	n	Received AB on enrollment	Received AB on follow-up
Bloody diarrhea	24	0	11	12.5	0.001	33	32	2
Mucoid+fever	63	0	18	3.45	0.04	48	44	5
Mucoid+ temp. > 37.5°C	31	0	9	19.84	0.007	23	22	0
Fecal leuc. > 9/HPMF	27	0	4	2.63	0.398	32	19	2
Either above criteria	88	0	23	3.45	0.001	75	60	7
All subjects	298	0	63	2.22	0.001	288	120	31

The data in this study are not intended to contradict the previous studies or the current WHO recomendations that certain bacterial diarrheas can be managed without antibiotics.[11,12] Our data support the current indication of AT in DD that bloody diarrhea resolves more quickly with antibiotics whether or not it is caused by Shigella. However, this study also suggests it is possible that the rate of reconsultation due to prolonged diarrhea and mothers anxiety may be high enough to counteract the benefits of withholding antibiotics initially for mucoid diarrhea as well.

There is a need to better understanding of the etiology, pathogenesis and clinical course of mucoid diarrhea so that we might better determine whether this diarrheal syndrome is best managed with antibiotics, as bloody diarrhea or with ORT alone as watery diarrhea or if a new management scheme needs to be developed for mucoid diarrhea.

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