BLOODY DIARRHEA AMONG FILIPINO CHILDREN: ETIOLOGY AND OUTCOME OF THERAPY USING WHO CASE MANAGEMENT

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ABSTRACT

A descriptive, prospective study was conducted to determine etiology and outcome of bloody diarrhea in children according to WHO guidelines. Forty five patients ages 3 mos. to 14 yrs. with bloody diarrhea (mean 17.50 mos.) were included. M:F ratio was 34:11. The associated symptoms observed were fever (51.1%), vomiting (26.7%), convulsions (2.2%), and abdominal pain (37.8%). The mean weight was 8.53 kg. and only one was <70% of the weight for height. Majority, 32 (71.1%), came in with no signs of dehydration while 12 (26.7%) with some dehydration and only 1 (2.2%) with severe. On stool microscopy 51.1% had >5-10 wbc/hpf and all had RBC's in the stool. Enteropathogens isolated in pure culture were E. histolytica (6), Salmonella (4), Shigella (2), EPEC (2), Vibrio cholera (2), ETEC (1), Aeromonas (1), Cryptosporidium (1) and Rotavirus (1). Mixed cultures were seen in 20.0%. Treatment with cotrimoxazole alone showed improvement in 36/41, and of those who did not improve, 1 improved with nalidixic acid and 4 with metronidazole given subsequently. Four patients given metronidazole initially due to documented E. histolytica on admission improved within 48 hrs. Thus, it is important to consider treatment of E. histolytica in patients with bloody diarrhea who do not respond within 48 hrs. to cotrimoxazole therapy.

Key words: bloody diarrhea, enteropathogen, stool microscopy, *E. histolytica*, *Shigella*

INTRODUCTION

Bloody diarrhea accounts for 10-15% of diarrheal episodes among children less than 5 years of age[1]. Unlike acute watery diarrhea, however, which can be effectively managed by fluid and feeding therapy, dysentery requires special attention in that anti-microbial therapy do have a significant impact on its clinical course. In addition, intensive nutritional management may also be required due to resulting nutritional disturbance[2].

A number of organism have been found in dysentery cases and more than one pathogenic organism are the bacterial enteropathogens of acute diarrhea, namely *Shigella*, *Salmonella*, *Campylobacter*, *ETEC*, *EPEC*, *EIEC*, and *Aeromonas*. *Entamoeba histolytica*, a parasite, has likewise been thought of as an important cause of dysentery. However, studies have shown that they are present in nearly the same percentage on non-diarrheic controls[3]. In Bangladesh, *Shigella* has been found to be the most frequent organism in acute bloody diarrhea, accounting for as much as 30 to 60% of all cases[1,2]. A survey done by Ablaza et al at the PGH and the RITM among children with bloody diarrhea have reported a 30% combined isolation rate for *Shigella*, *Salmonella*, and *E. histolytica*[4]. This study, however, limited the survey to these three organisms and included children with previous antibiotic therapy and with duration of diarrhea more than five days.

Dysentery is responsible for up to 25% of diarrheal deaths[1]. It has a much greater adverse effect on the child's growth and nutrition than an episode of acute watery diarrhea. Moreover, the presence of dysentery has a greater tendency than acute diarrhea, to become persistent, perpetuating the vicious cycle of diarrhea, malabsorption and malnutrition.

Dysentery has a different clinical course. It does not respond to ORT alone. Thus the treatment, expectations and prognosis will vary and will depend on prevailing circumstances, particularly the epidemiologic and environmental setting. Even among developing countries, effective treatment for Shigella may differ since the prevalent Shigella strains in a particular locality may not respond to the usual antibiotics[5].

In many instances, practitioners use a combination of treatments to cover various possibilities and then see what happens. If the patient gets better, well and good, and if not, an alternate drug is used. This approach is practical in a way but it does not identify the type of organisms we are dealing with an leaves us mystified. In the final analysis, this can also be very expensive and deleterious to the patient.

Since bloody diarrhea is usually associated with a pathogen that necessitates treatment with an antimicrobial agent and because laboratory facilities are not usually available, it is essential:

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1. to establish simple but sensitive criteria for diagnosis and management and

2. to establish a community-based algorithm for physicians and other secondary level health providers.

The World Health Organization (WHO) has proposed an algorithm for bloody diarrheas. However, since antimicrobial management is complicated by the high prevalence of multiresistant strains of Shigella in many communities and amebiasis incidence varies from one community to the other, an algorithm to be recommended for a particular setting must be periodically evaluated[6].

There has been no validation of the WHO algorithm in the Philippine setting. Thus, if a patient who does not respond to initial therapy for shigellosis, poses the question on treatment for *Entamoeba histolytica* infection be started or should the patient be presumed to be infected with a Shigella strain resistant to the initial therapeutic choice and therefore be treated accordingly? The answers are not well defined at present.

The current recommendation by the WHO is to treat a diarrheic patient for Shigella infection in the presence of bloody stools. (See Appendix A - Algorithm for Therapy of Bloody Stools). This suggestion is being followed in our local setting, since a well-controlled study has not been conducted which justifies the use of cotrimoxazole and validates the algorithm for case management of bloody diarrhea in children. Furthermore, all possible enteropathogens associated with bloody diarrhea among Filipino children have not yet really been thoroughly investigated. Likewise the antimicrobial susceptibility of these organisms should be identified in order to make firm recommendations regarding proper empiric antimicrobial therapy.

OBJECTIVES

General Objective

To validate the case management of bloody diarrhea (dysentery) in children according to WHO guidelines for the Philippine setting.

Specific Objectives

1. to determine the etiologic agents associated with acute bloody diarrhea among Filipino children;

2. to determine the epidemiologic, clinical characteristics and laboratory features of patients with bloody diarrhea;

3. to describe the antimicrobial sensitivity of the enteropathogens isolated from patients with bloody diarrhea; and,

4. to determine the outcome of patients with bloody diarrhea treated according to WHO protocol or guidelines, as measured in terms of duration of diarrhea, and disappearance of bloody stools.

MATERIALS AND METHODS

This study was conducted at the Department of Pediatrics of the UP-PGH. Patients were screened from those consulting at the Pediatric Emergency Room and at the Sick Child Clinic of the Out Patient Department. This is a descriptive, prospective study conducted from January 1, 1993 to December 30, 1994.

The inclusion criteria were patients aged 3 months to 14 years, male or female with presence of diarrhea defined as >3 episodes of loose bowel movement in the last 24 hours with blood streaking and visible blood as confirmed by the investigators. Excluded were those with antimicrobial intake in the preceeding 24 hours prior to consultation, presence of signs and symptoms suggestive or indicative of a surgical condition like ileus, obstructions, presence of severe systemic illness like septicemia, bronchopneumonia, miningitis which may indicate a DIC, presence of anal fissure, and presence of blood dyscrasia, bleeding defects or malignancy.

On admission, information as to the epidemiologic data and clinical symptomatology of the patient were gathered and written down on the data form. A complete physical examination was done with emphasis on the nude weight, length, temperature, nutritional assessment and degree of dehydration and rectal examination.

Stool specimens were collected and labelled for processing. The first stool specimens were placed in stool vials with Cary Blair medium and sent to the laboratory for standard bacteriologic, microscopic and virologic studies. Those who did not defecate within 24 hours will be withdrawn from the study. Stool microscopy was immediately done and the following investigated;

1. Gross examination
   - 1.1 bloody or non-bloody
   - 1.2 mucoid or non-mucoid

2. Microscopic examination (to be reported as quantitative count) using methylene blue staining and direct fecal smear
   - 2.1 white blood cell count (per hpf)
   - 2.2 red blood cell count (per hpf)
   - 2.3 macrophages (per hpf)

3. Presence of ova or parasites employing trichome staining method using two preservatives - formalin and PVA
   - 3.1 *Entamoeba histolytica*
   - 3.2 *Giardia lamblia*
   - 3.3 *Trichuris*
   - 3.4 Hookworm

4. Acid-Fast staining for the presence of Cryptosporidium

The watery portion of the stool collected using disposable plastic bags, were examined for stool pH with the use of pH indicator paper (Riedel de Haen, pH 0-14) and for the presence of reducing substances using Clinitest tablets (Miles Laboratory, Ames Division).

A specimen for stool culture was placed in a Cary Blair transport medium and stored at 4/C until processed for bacteriologic examination of the following organisms, using standard microbiologic examination of the following organisms, using standard microbiologic techniques:

Shigella

Salmonella

Campylobacter

Enterotoxigenic E. coli

Enteropathogenic E. coli

Aeromonas

Plesiomanas

Vibrio cholera

Vibrio parahemolyticus

Another stool specimen was set aside for rotavirus antigen detection using Enzyme-Linked Immunosorbent Assay (ELISA Dakopatts, Denmark).

Blood specimens were extracted from the patient for hematocrit, red blood cell count, white blood cell count with differentials and platelet count using venous or capillary puncture. Antimicrobial sensitivity pattern of the enteropathogens isolated were also determined using standard disc inhibition techniques. A stool sample was collected on the third and fifth day for repeat stool microscopy and culture for those positive for Salmonella, Shigella, Entamoeba histolytica and other significant enteropathogens.

Initial therapy was given using Cotrimoxazole and following WHO guidelines. For those with persistent diarrhea and for those whose diarrhea did not improve after 5 days of initial therapy, treatment was given according to protozoal, bacteriologic and susceptibility studies: Guidelines for treatment is seen in accompanying chart.

Guidelines for Treating Patients with Bloody Stools

If blood is present

Treat for 5 days with an oral antibiotic recommended for Shigella in your area.

Teach the mother to feed the child as described in Plan A

See the child again after 2 days if:

under 1 year of age
initially dehydrated
there is still blood in the stool
not getting better

If the stool is still bloody after 2 days, change to a second oral antibiotic recommended for Shigella in your area. Give it for 5 days.

Antimicrobial agents used in the treatment of bloody diarrhea

Shigella dysentery: Trimethoprim (TMP) - Sulfamethoxazole (SMX)

children : TMP 5 mg/kg and SMX 25 mg/kg twice a day for 5 days
: Nalidixic Acid (2nd oral antibiotic recommended for Shigella)
children : 15 mg/kg 4 times a day for 5 days

Amoebiasis: Metronidazole

children : 5 mg/kg 3 times a day for 5 days

Follow-up of all patients was done two days after discharge. Nude weights and other anthropometric measures were taken. All possible complications and new developments were noted down in the subsequent follow-up of the subjects.

RESULTS

A total of 45 patients had been gathered and entered in the study with the age range of 4 months to 7 years (mean age of 17.5 months) and a male to female ratio of 34:11. The mean onset of diarrhea was 121.8 hours prior to consult. The symptoms which were associated with diarrhea were fever in 23 patients (51.1%), vomiting in 12 (26.7%), convulsions in 1 (2.2%), and abdominal pain in 17 out of the 45 patients (37.8%). (Table 1)

Table 1

Symptoms associated with bloody diarrhea in the 45 patients

Fever	23	(51.1%)
Vomiting	12	(26.7%)
Convulsions	1	(2.2%)
Abdominal Pain	17	(37.8%

Table 2 shows 36 of the 45 patients (80.0%) were being given milk formula while only 1 (2.2%) was purely breastfed and 8 (17.8%) of these patients were on mixed feeding. There was a history of contact with persons who have diarrhea in the household in 5 (11.1%) of the patient population and neighbors who have diarrhea in 3 (6.7%). The other 37 patients (82.2%) have had no history of contact with persons having diarrhea.

Table 2

Feeding patterns of 45 patients with dysentery

Breastfeeding	1	(2.2%)
Formula feeding	36	(80.0%)
Mixed feeding	8	(17.8%))

On physical examination, the mean weight obtained for all the 45 patients was 8.53 kg and the mean height was 71.18 cm with the nutritional status having a mean of 96.71% in weight for height. Only 1 (2.2%) of the patients fell under 70% of the ideal weight for height. Table 3 shows most of the patient population, 32 out of 45 (71.1%) came in with no signs of dehydration, 12 (26.7%) with some dehydration, and 1 (2.2%) came in with severe dehydration.

Table 3

Hydration status on admission on 45 patients with dysentery

No dehydration	32	(71.1%)
Some dehydration	12	(26.7%)
Severe dehydration	1	(2.2%)

The laboratory parameters taken showed a mean hematocrit of 34.70 and a mean WBC count of 12.86. On stool microscopy, 23 of the 45 patients (51.10%) showed greater than 5-10 wbc/hpf and all of the 45 (100%) had RBCs. Table 4 shows of the enteropathogens isolated with E. histolytica was in 6 (13.3%), *Salmonella* in 4 (8.9%), *Shigella* in 2 (4.4%), *Enteropathogenic E. coli* in 2 (4.4%), *Vibrio cholera* in 2 (4.4%), *Enterotoxigenic E. coli* in 1 (2.2%), *Aeromonas* in 1 (2.2%), *Rotavirus* in 1 (2.2%) and *Crytosporidium* in 1 of the 45 patients (2.2%). There were 9 (20.0%) patients with mixed cultures while 16 (35.5%) of the 45 patients had no organisms isolated.

Table 4 *Enteropathogens Isolated in 45 Patients with Bloody Diarrhea*

Organism	No. of Patients
A. Pure Cultures	
E. histolytica	6 (13.3%)
Salmonella	4 (8.9%)
Shigella	2 (4.4%)
EPEC	2 (4.4%)
Vibrio cholera	2 (4.4%)
ETEC	1 (2.2%)
Aeromonas	1 (2.2%)
Cryptosporidium	1 (2.2%)
Rotavirus	1 (2.2%)
B. In mixed cultures	9 (20.0%)
C. No enteropathogen	16 (35.5%)

Outcome of therapy showed 36 of the 41 patients (87.8%) to improve on co-trimoxazole alone. Of the 5 patients who did not improve with co-trimoxazole, one was given metronidazole after having found out to be positive for *E. histolytica* on the second day, one improved after being given nalidixic acid while the other three who still did not respond to nalidixic acid were given metronidazole and subsequently improved. There were four patients given metronidazole initially because of the presence of E. histolytica on stool microscopy and they improved after 48 hrs. (Figure 1).

Sensitivity patterns for Shigella and Salmonella are shown in Table 5A & B.

Table 5A

Sensitivity Patterns for Shigella Flexneri isolated in 2 Patients

	No. Sensitive
Trimethoprim-sulfa	2 (100%)
Nalidixic acid	2 (100%)
Kanamycin	1 (50%)
Norfloxacin	2 (100%)
Ampicillin	1 (50%)
Amoxicillin	1 (50%)

Table 5B

Sensitivity Patterns for Salmonella isolated in 4 patients

	No. Sensitive
Trimethoprim-sulfa	4 (100%)
Nalidixic acid	4 (100%)
Amikacin	4 (100%)
Norfloxacin	4 (100%)
Kanamycin	4 (100%)
Tetracycline	2 (50%)
Chloramphenicol	2 (50%)
Ampicillin	2 (50%)

DISCUSSION

With the WHO Case Management Protocol, it is expected that 90 to 95% of the patients with acute diarrhea will be treated successfully with ORT alone. In the presence of bloody diarrhea or

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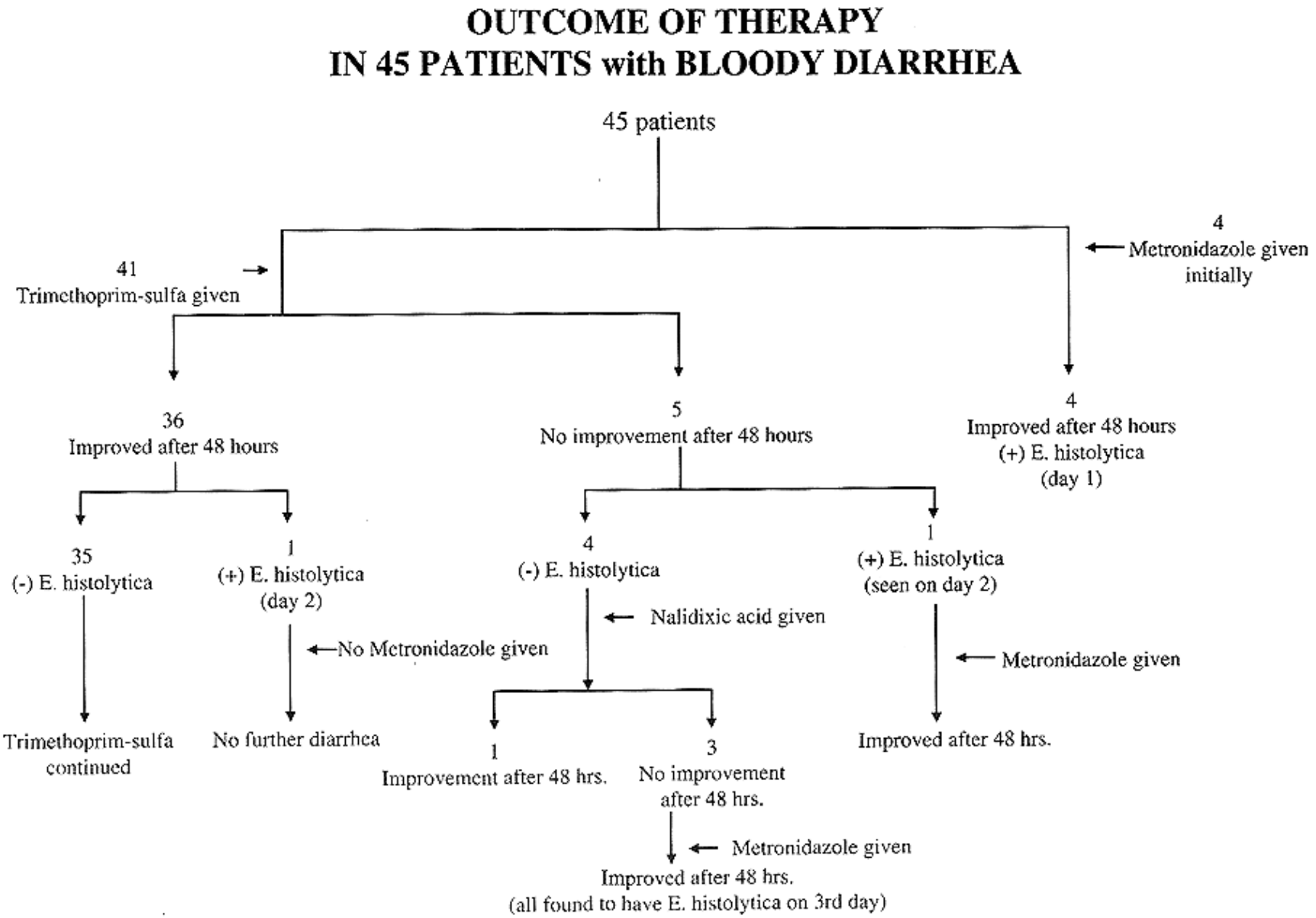
Figure 1



dysentery, however, the use of antimicrobial is recommended to treat for Shigella which is believed to be the most likely pathogen in this condition. This was based on studies in Bangladesh which reveal 60% of the etiologic agents in bloody diarrhea are Shigella[1,2]. It is presently becoming evident that this may not be so in other countries like the Philippines where a greater number of *E. histolytica* was seen among pediatric patients with bloody diarrhea. 13.3% of the patients in our study had *E. histolytica* which comprised the highest frequency among the other enteropathogen. Although other studies on bloody diarrhea revealed the presence of Shigella, this was still much less than the expected number compared to other countries[1,2]. The empiric treatment being recommended may prove to be inadequate and may cause delay in proper diagnosis and therapy. One aspect that was noted in this study is that *E. histolytica* in the stools was not seen in the initial examination but on subsequent stool microscopy. It is therefore necessary to do serial microscopy to confirm absence or presence of *E. histolytica* in bloody diarrheas.

Another important enteropathogen that appears significant in our present study is *Salmonella*. It should be noted that although there was no complication observed among our patients, Salmonella has been previously proven to be quite invasive and has caused septicemia, enteric fever and even death in very young infants[3]. The presence of bloody stools could alert the clinician on the possibility of a severe *Salmonella* infection and antimicrobial therapy could be beneficial. The sensitivity patterns should be monitored as this may vary from one area to another. Multiple antimicrobial resistance has been shown with Salmonella sp. in many occasions both locally and abroad. Equal frequency was seen with Enteropathogenic *E. coli, Shigella, Vibrio cholera* which is quite unexpected. *V. cholera* would not have bloody stools as this is secretory in nature. However, it has been shown previously that even in asymptomatic patients *V. cholera* has been isolated (0.1%). No *Enterohemmorhagic E. coli* (EHEC) was seen but 2 cases of *EPEC* were isolated. Previous study by Paje-Villar have shown *EHEC* to be present in about 2% of patients with acute diarrhea[7]. Perhaps; the finding in our series is too small to reveal the presence of EHEC among our population. *Shigella* which was expected to be the predominant organism proved to be small in number in our series to justify the empiric therapy of bloody diarrhea according to WHO Case Management protocol. The cases were collected over a 24 month period, with no epidemics of bloody diarrhea being noted. This could imply that at least in our country the Philippines, there should be further work-ups and studies to prove and validate the proper diagnosis and treatment of dysentery or bloody diarrhea.

The presence of other organisms, *Aeromonas, rotavirus, ETEC,* and *Cryptosporidium* are expectedly small in numbers and the presence of mixed cultures of 20% have also been shown in other studies.[4] No enteropathogen was isolated in 35.5%, which also follows the usual pattern in our local studies on acute diarrheal diseases[4,8].

The clinical characteristics of our patients with bloody diarrhea did not differ significantly with other patients with acute diarrhea. Majority were bottlefed and were not severely malnourished. Most of them had no dehydration when they were seen in the hospital which may be due to the extensive information campaign for treating diarrhea at home i.e. giving extra fluids and feeding the patient. It has been noted that in recent years, there has been a significant improvement in the mortality due to diarrhea mainly because of the Control of Diarrheal Disease Program (CDD) of the government.

The administration of cotrimoxazole as empiric therapy for bloody diarrhea should now be analyzed in the light of the present findings. At least 15-20% may have a delay in diagnosis and treatment of Amoebiasis if this is carried out without proper stool microscopy. It is also noteworthy that the initial microscopy may not reveal the presence of *E. histolytica* and would therefore necessitate repeated examinations. Cultures may also become necessary especially if patients do not show improvement within 48-72 hours. Although sensitivity of Shigella and Salmonella to cotrimoxazole was proven in this series, still the numbers are too small and the in-vivo therapy has shown at least 2 cases of bloody diarrhea improving with nalidixic acid after using cotrimoxazole.

E. histolytica has been considered a rare pathogen in children below 3 years of age. It is a food and water borne disease that can cause not only gastroenteritis but extra-intestinal complications of liver hepatitis, liver abscess or pulmonary infiltrations. Characteristically the infection is manifested by tenesmus, vomiting, abdominal pain and presence of bloody to mucoid stools. Once diagnosed, antimicrobial therapy particularly metronidazole is indicated. In our present study, Amoebiasis was found to be the most frequently occurring in pediatric patients with bloody diarrhea or dysentery and should therefore be considered in the work-up and proper therapy of these conditions. Empiric treatment of cotrimoxazole resulted in about 80% of improvement within 48 hrs. This is still a favorable factor for the use of the WHO Case Management Protocol especially in areas with limited facilities for doing stool microscopy and cultures. However after 48 hrs. and no improvement is seen, the

presence of Amoebiasis should be considered and metronidazole could be instituted. Waiting for another 48 hrs. or using another drug for *Shigella* may delay recovery or pose some complications. The present sensitivity of the pathogens, *Shigella and Salmonella* to cotrimoxazole appears to be good with no need to use alternative drugs for these organisms.

CONCLUSIONS

A total of 45 patients with bloody diarrhea whose age ranged from 4 months to 7 years were recruited in the study. The most common etiologic agent found was *E. histolytica* 6 (13.3%), followed by *Salmonella* 4 (8.9%), *E. coli* 2 (4.4%), *Shigella* 2 (4.4%) and *V. cholera 2 (4.4%).* Mixed cultures were seen in 20.0% while no enteropathogen was seen in 35.5%. Majority of patients were on milk formula 80.0% and did not have a history of exposure to diarrheic persons. 71.1% had no signs of dehydration, 12 (26.7%) with some and only 1 (2.2%) had severe dehydration.

Outcome of therapy revealed that using cotrimoxazole as empiric therapy for bloody diarrhea resulted in only about 80.0% success rate with 11.1% showing no improvement within 48 hours. Four patients (8.9%) had *E. histolytica* seen on stool microscopy on the 1st day and was given metronidazole initially with subsequent improvement. In 4 cases, confirmation of *E. histolytica* was seen on repeated examinations, 1 on the 2nd and 3 on the 3rd day. One patient was found to have *E. histolytica* on day two but initially improved on cotrimoxazole, and was not treated with metronidazole. It is recommended therefore to obtain stool cultures and do serial stool examinations for *E. histolytica* on patients with bloody diarrhea whenever possible for early detection and therapy of amoebiasis with prevention of possible complications.

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