

ANTIMICROBIAL USE IN CHILDREN UNDER FIVE YEARS WITH DIARRHEA IN A CENTRAL REGION PROVINCE, THAILAND

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Abstract. This cross-sectional study aimed to estimate the prevalence of appropriate antimicrobial prescribing for treating childhood diarrhea within the public hospital system in a central region province, Thailand. Reported are findings of a prospective clinical audit of 424 cases treated by 38 physicians. Appropriate use of antimicrobials was defined as prescribing antimicrobials for managing an invasive bacterial-type, bloody diarrhea or not prescribing antimicrobials for managing a watery-type or non-bloody diarrhea. Among 424 cases with diarrhea, 12.5% were invasive bacterial-type. Of the 66 diarrheal episodes in which stool samples were cultured, 7 stool specimens were positive, two with *Shigella sonnei*, two with *Vibrio cholerae* Ogawa and three with *E.coli*. Based on the presence of mucus and blood in stools, 27.4% of 424 cases received appropriate antimicrobial drugs. Cotrimoxazole was the most commonly prescribed drug (51%), followed by colistin sulfate (15.3%), norfloxacin (11%), and nalidixic acid (0.5%). The average number of antimicrobials per case of inpatients was higher than outpatients (1.15 vs 0.84, $p < 0.001$). There was a trend toward prescribing norfloxacin in childhood diarrhea. The Ministry of Public Health should continue providing effective interventions aimed at improving physicians' knowledge of diarrhea treatment. Similar efforts should be directed toward improving caretakers' knowledge about home care for childhood diarrhea and encouraging widespread correct use of oral rehydration therapy (ORT) in the community. Hopefully, such activities will help reduce the inappropriate use of antimicrobial agents in treating diarrheal disease.

INTRODUCTION

Diarrheal disease continues to be a common problem for Thai children. The mortality rate for children aged less than five years due to diarrhea steadily declined between 1990 and 1999, from 20 to 5.2 deaths per 100,000 population. However, the surveillance data collected during the same period suggests an increasing prevalence of the morbidity rate, from 5,113.2 to 7,140 cases per 100,000 population. Diarrhea also accounts for a major proportion of hospital admissions when associated with dehydration. Nearly 40% of all diarrhea cases and 26% of deaths due to diarrhea were in children less than 5 years of age (Division of Epidemiology, 1999; Choprapawon, 2000).

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Suboptimal prescribing for childhood diarrhea has been reported in many developing countries, with under use of effective measures, such as oral rehydration salts (ORS) and over use of marginally effective or ineffective drugs such as adsorbents and antimicrobials (Harris and Black, 1991). Inappropriate drug use leads to treatment failure, spread of disease, increased antibiotic resistance, high health care costs, and side effects (Bojalil and Calva, 1994; Hoge *et al*, 1998). Since 1990, the Thai Ministry of Public Health has disseminated guidelines throughout the country for the treatment of childhood diarrhea, which were slightly modified from the guidelines recommended by the WHO (World Health Organization, 1990a; 1992; Ministry of Public Health, 1992; Action Program on Essential Drugs, 1993). However, the doctors who do the prescribing are scarcely acknowledged officially, especially in the management of childhood diarrhea.

To gain a better insight into the problem, we conducted a survey to estimate the prevalence of

appropriate antimicrobial usage on children less than 5 years of age with diarrhea in ten public hospitals of a central region province.

MATERIALS AND METHODS

This study was a part of a Health Facility Survey conducted in two general and eight community hospitals providing residential care in a Central Thailand province in 1995. The scope of this paper focuses on an audit of antimicrobials prescribed according to the standard treatment guidelines (World Health Organization, 1990a; 1992; Ministry of Public Health, 1992; Action Program on Essential Drugs, 1993). This paper uses the data from a prospective clinical audit of the management of 424 cases of children under 5 years, sampled from all 38 doctors treating diarrhea in those ten public hospitals.

While waiting to see the doctors, 424 caretakers were interviewed by the investigators (it is beyond the scope of this paper to deal with data collected through the caretakers' interviewed). Caretakers refer to mothers, fathers, relatives or other persons who brought the child with diarrhea for care to the hospitals during the study period. The survey instrument was adapted from the WHO Health Facility Survey instrument (World Health Organization, 1990a). It consisted of 13 questions covering the child's medical history, signs and symptoms, caretakers' home-based management for their children including diet and fluid since onset of diarrhea, source of medical advice prior to seeking care at the public hospital. The children were examined for degree of dehydration and nutritional status using the WHO criteria (World Health Organization, 1990a). Laboratory results were also collected if the patient was ordered to receive a stool culture. The questionnaires were reviewed and pre-tested; necessary modifications were made before conducting the survey.

The research protocol was submitted and approved by the Deputy Director-General, Department of Communicable Diseases, Ministry of Public Health, and the Deputy Provincial Chief Medical Officer of the studied province. Verbal consent was obtained from the Medical Director of each hospital and from each individual doctor

to collect information from medical records. Verbal consent for interviewing and examining the children was gained from caretakers while they were waiting to see the doctors.

Operational definitions

The following definitions were adapted based on the Thai Ministry of Public Health (1992) and World Health Organization (1992) diarrheal treatment guidelines.

Diarrhea was defined as the passing of three or more loose stools of watery consistency or one stool with blood or mucus in a 24 hour period.

Appropriate use of antimicrobials was defined as prescribing antimicrobials for managing an invasive bacterial-type, bloody diarrhea or not prescribing antimicrobials for managing a watery-type or non-bloody diarrhea.

The inappropriate use of antimicrobials was defined as prescribing antimicrobials in a watery, non-bloody diarrhea or not prescribing antimicrobials for an invasive bacterial-type or bloody diarrhea.

Statistical analysis

The difference between means were tested using the *t* test. The significance level was set at $\alpha \leq 0.05$. The sample size of 424 cases in this study was calculated to estimate the prevalence of ORS and antimicrobial prescribing for a 95% confidence interval to be within +/- 5% of point estimate. When the proportion of antimicrobial use was 60%, the sample size required for the study was at least 369 cases.

RESULTS

Among the 38 physicians, 70% were males, 87% were aged less than 45 years, and 71% had not received postgraduate training. The remainder of the physicians were trained in pediatrics and other specialties. Only 13% received updated training on diarrhea case management. Fifty percent had practiced medicine less than 6 years. About 63% had his/her own private clinics or worked part-time in private hospitals.

Of the 424 caretakers interviewed, 94.6% were female. The ages ranged from 16 to 66 years with a mean age of 30 years. Of these, 77.4% were aged between 21-40 years, 94.6% were the

Table 1
Stool culture requested by place of treatment (outpatient vs inpatient).

Stool culture ^a	% of patients		
	Outpatients n = 275 (%)	Inpatients (day 1) n = 149 (%)	Total n = 424
Done :	11 (4.0)	55 (36.9)	66 (16.0)
Result :	n = 11	n = 55	n = 66
No growth/negative	11 (100.0)	48 (87.3)	59 (89.0)
<i>Shigella sonnei</i>	0 (0.0)	2 (1.3)	2 (3.0)
<i>Vibrio cholerae</i> Ogawa	0 (0.0)	2 (1.3)	2 (3.0)
<i>E. coli</i>	0 (0.0)	3 (2.0)	3 (4.5)

^aStool culture was performed for bacterial pathogens only.

mothers of the treated children.

Among the 424 children examined, 65% were outpatients, and 56% were male. The mean age was 20.5 months (SD=16.8 months), 45% were aged 1-12 months and 21.7% aged 13-24 months. Regarding children's signs and symptoms, 52% had experienced the illness for less than one day. Only 4.0% were ill for more than 7 days. Nearly 26% passed watery stool more than 10 times in the last 24 hours prior to consulting the doctor. Based on the presence of mucus and blood in stools, 12.5% of cases were of an invasive bacterial-type. About 5.4% had decreased urine. More than half of the children experienced sickness associated with their diarrhea, such as fever, vomiting, cough and runny nose. Approximately 1.2% had convulsions before consulting the doctor. Concerning the degree of dehydration, 66% had none or mild dehydration. Only 1.4% had severe dehydration, which required intravenous fluid therapy (IV). In terms of nutritional status, 16.5% were classified as 1st degree malnutrition and 3.8% were 2nd degree malnutrition.

Diagnosis was given as acute diarrhea in 74.3%, bloody diarrhea in 6%, infectious diarrhea in 4.5%, severe diarrhea (cholera) in 0.5%, diarrhea with other complications, such as an upper respiratory infection, vomiting, pyrexia, convulsions in 14.2% and chronic diarrhea in 0.5%.

Stool culture

Of the 424 cases, 66 patients had a stool culture ordered. Seven of the 66 stool specimens

were positive, two with *Shigella sonnei*, two with *Vibrio cholerae* Ogawa, and three with *E.coli* (Table 1).

Number of antimicrobial drugs prescribed per episode

Table 2 shows that the number of antimicrobials prescribed ranged from 0 to 3 drugs. About 76.4% of cases received at least one antimicrobial drug. Approximately 14.4% received no antimicrobial drugs during the episode of diarrhea. About 22% of inpatients received two or more antimicrobials during the first day of therapy. The average number of antimicrobials per case of inpatients was higher than outpatients (1.15 vs 0.84, $p < 0.001$).

Types of antimicrobials prescribed

Nine types of antimicrobials were prescribed in this study (Table 3). Cotrimoxazole was the most commonly prescribed drug (51%), followed by colistin sulfate (15.3%), the quinolone group, - norfloxacin (11%), and nalidixic acid (0.5%). Only 2.4% of cases were prescribed two types of antimicrobials, ampicillin plus gentamicin.

Use of antimicrobials

Table 4 shows that 116 (27.4%) cases were appropriately managed while 308 (72.6%) cases were inappropriately treated according to treatment guidelines. These 308 episodes were further analyzed in terms of inappropriate treatment patterns. No cases of bloody diarrhea were underprescribed in relation to antimicrobials. The proportion of appropriate antimicrobial use among pediatricians was higher than general prac-

Table 2
Number of antimicrobials prescribed per episode of diarrhea by place of treatment
(outpatient vs inpatient).

No. of antimicrobials	% of patients ^a		
	Outpatients n = 275	Inpatients (day1) n = 149	Total n = 424
0	17.8	8.0	14.4
1	80.0	69.8	76.4
2	2.2	21.5	9.0
3	0.0	0.7	0.2
Mean ^b	0.84	1.15	0.95
Median	1	1	1

^aFirst day therapy only considered.

^bA significant difference between the means was identified by *t*-test ($p < 0.001$).

Table 3
Types of antimicrobials prescribed for the treatment of diarrhea by place of treatment
(outpatient vs inpatient).

Types of antimicrobials ^b	% of patients ^a		
	Outpatients n = 275	Inpatients (day1) n = 149	Total n = 424
No antimicrobial prescribed	17.8	8.0	14.4
Cotrimoxazole	55.3	43.0	50.9
Colistin sulfate	16.4	13.4	15.3
Norfloracin	8.0	16.8	11.1
Ampicillin	0.7	4.7	2.1
Gentamicin	0.4	5.4	1.9
Amoxicillin	1.5	1.3	1.4
Metronidazole ^c	1.5	0.0	0.9
Nalidixic acid	0.4	0.7	0.5
Erythromycin	0.0	0.7	0.2
Ampicillin + gentamicin	0.0	6.7	2.4

^aFirst day therapy only considered; ^bSome patients received >1 antimicrobial drugs / encounter.

^cIn this study defined as an antimicrobial drug.

Table 4
Antimicrobial usage^a in 424 diarrheal cases.

Antimicrobial usage	Number	%
Appropriate	116	27.4
Given antimicrobial for bloody diarrhea	53	12.5
Given antimicrobial for severe diarrhea	2	0.5
Not given antimicrobial for non-bloody diarrhea	61	14.4
Inappropriate	308	72.6
Not given antimicrobial for bloody diarrhea	0	0.0
Given antimicrobial for non-bloody diarrhea	308	72.6

^aFor inpatients, first day therapy only considered.

Table 5
Antimicrobial usage in 424 diarrheal cases by physician's specialty.

Physician's specialty	No. of prescriptions	Antimicrobial usage			
		Appropriate		Inappropriate	
		n	%	n	%
General practitioner (n=27)	289	77	26.6	212	73.4
Pediatrician (n=5)	84	28	33.3	56	66.7
Other specialty (n=6)	51	11	21.6	40	78.4

tioners and other specialties (33.3% vs 26.6%, 21.6% respectively) as showed in Table 5.

DISCUSSION

Two possible sources of error in the prescription audit may be present. First, the audit was based on the history reported by caretakers, and observations and assessments by the investigator according to WHO guidelines. An independent assessment by an outside physician may have produced different categorizations of the cases from those of the observer. Second, the diarrheal cases studied included those with bloody and non-bloody diarrhea in outpatients and inpatients. However, some cases also had other complications, which may have required treatment other than that specified in the guidelines. The rigorous WHO guidelines for treatment of diarrhea in children may not always be appropriate due to the complexity of some diarrhea cases. For example, in some non-bloody diarrhea cases with high fever, lethargy, and a complete blood count that shows the white blood cells were >10 cells/HPF, especially in children aged less than 6 months, doctors have to prescribe antimicrobials such as ampicillin and gentamicin or cefotaxime for treating suspected sepsis while waiting for hemo-culture results. Another limitation was that appropriate use of antimicrobials relied on prescribing or not prescribing such drugs. These criteria did not involve the appropriate choices, the correct dosage and right duration of antimicrobial use.

On the basis of the rigorous WHO guidelines for the treatment of diarrhea, 72.6% of children received inappropriate antimicrobials. The

high level of antimicrobial prescriptions in this study were similar to the studies reported from Bangladesh (99%), Indonesia (94%), Mexico (79%), Pakistan (65%), India (64%) and Peru (58%) (Gani *et al*, 1991; Aguila and Brown, 1993; Chowdhury *et al*, 1993; Gutierrez *et al*, 1994; Singh *et al*, 1995; Nazami *et al*, 1996).

The 27.4% prevalence of appropriate use of antimicrobials in our study was lower than the 73.8% figure reported by Osatakul and Tangadullart (1999), who reviewed the medical records of 529 children with 749 acute diarrheal episodes at Songklanagarind Hospital, a teaching hospital in Southern Thailand. The substantial difference in the rate might be due to the difference in study subjects. Our study included both inpatients and outpatients, whereas the Southern Thai study included only outpatients. Inpatients may require treatment other than specified in the guidelines. Another reason may be that the prescriptions in our study were spread over 38 physicians in ten public hospitals, while the comparison study was conducted in a teaching hospital and included an unspecified number of medical instructors, internists, and medical students. Usually, the patients who seek care at teaching hospitals tend to be more severe cases than patients seeking care at community hospitals. Osatakul and Tangadullart (1999) noted that among 263 diarrheal episodes in which stool samples were cultured, *Salmonella* was detected in 16.7%, *Shigella* in 2.3%, and other pathogens in 7.3%. This contrasts with our study in which only 7 out of the 66 specimens were positive. The prescriptions for antimicrobials tended to meet the audit criteria. Furthermore, a higher proportion of doctors at Songklanagarind Hospital may have received

updated training on diarrhea case management.

Although there might be some error due to using only the presence of mucus and blood in stools as the only indication, the antimicrobial use in our study was still high. According to Levine (1986), the use of antimicrobials in outpatients was justified in only about 5-10% of cases. This observation is consistent with the findings of Osatakul and Tangadullart (1999): 12% of diarrhea cases in their study were of the invasive bacterial-type that required antimicrobials. In our study, considering only outpatients, 82.2% (226/275) received antimicrobials, and 10.9% (30/275) were an invasive bacterial-type that required antimicrobials.

Countries differ in the most commonly prescribed antimicrobials and employ different drugs as first-line treatments (Gani *et al*, 1991; Aguila and Brown, 1993; Chowdhury *et al*, 1993; Gutierrez *et al*, 1994; Singh *et al*, 1995; Nazami *et al*, 1996). This might depend on drug resistance features which differ between countries and also on the guidelines provided by the government. The most commonly prescribed antimicrobial in our study was cotrimoxazole (50.9%) as was the case in Pakistan (18.2%) (Nazami *et al*, 1996). The equivalent popularly prescribed drug in Mexico (Gutierrez *et al*, 1994) was ampicillin (20%).

In Osatakul and Tangadullart's (1999) report, among 749 diarrheal episodes, 33.3% (250/749) received antimicrobials, and the most commonly prescribed antimicrobial was norfloxacin (20.6%; 154/749), followed by cotrimoxazole (12.3%; 92/749). Osatakul and Tangadullart (1999) reported that 100% of *Shigella* and *Samonella* were sensitive to norfloxacin, while 100% of *Shigella* and 33% of *Samonella* were resistant to cotrimoxazole.

Our study also found a trend toward prescribing norfloxacin in childhood diarrhea. The reasons might be due to the problem of drug resistance to cotrimoxazole, while nalidixic acid might be inconvenient to take in comparison to a smaller tablet of norfloxacin. Moreover, the physicians may prescribe antimicrobials to prevent secondary infection and because of uncertainty about the diagnosis of the child's underlying condition [Howteerakul *et al* (2003) analysis of physicians

rationales of adhering and not adhering to treatment guidelines for childhood diarrhea].

In Thailand, metronidazole is used little, (1%), but its use is markedly higher in Bangladesh (65%), Mexico (28%), and Pakistan (15%) (Chowdhury, 1993; Gutierrez *et al*, 1994; Nazami *et al*, 1996). Since amebiasis and giardiasis are uncommon in Thailand, few doctors prescribe metronidazole [the study in Mexico (Gutierrez *et al*, 1994) defined metronidazole as an antiparasitic; in Pakistan (Nazami *et al*, 1996) it is defined as an antiamebics].

Conclusion

In conclusion, most doctors recruited in this investigation prescribe antimicrobials even with non-bloody diarrhea. Our Thai physicians did not rely only upon the presence of blood as an indication for prescribing antimicrobials. There was a trend toward prescribing norfloxacin in treating childhood diarrhea. Overall, inpatients received more antimicrobials than outpatients. The results support the Thai Ministry of Public Health efforts to continue re-orientating physicians about diarrhea case management with an emphasis on avoiding antimicrobial use in cases of non-bloody diarrhea. Another educational point is awareness that prescribing norfloxacin in treating childhood diarrhea as been show to cause bone cartilage damage in young animals (World Health Organization, 1990b; Stahlmann *et al*, 1993), although there is currently no clinical evidence to suggest that quinolones cause joint damage in children or adolescents (Rosenstiel and Adam, 1994). Caretakers should be re-oriented and encouraged to use acceptable ORT. Only 14% of children received WHO-ORS or acceptable commercial ORT before seeking care at the hospital (data not shown). This may indicate that caretakers do not know how to manage children with diarrhea at home and may not have a positive attitude toward ORT use. It is possible that caretakers expect the physicians to prescribe medicines, including antimicrobials, for their children (Howteerakul *et al*, 2003). Therefore, we recommend expanded interventions to improve the doctors' and caretakers' knowledge about treatment and to encourage the wider correct use of ORT in the community to help reduce antimicrobial prescribing rates in children with diarrhea.

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