CONCISE COMMUNICATION

Antimicrobial-Resistant Bacterial Diarrhea in Rural Western Kenya

Roger L. Shapiro,[1,2] Lata Kumar,[1] Penny Phillips-Howard,[3,4] Joy G. Wells,[1] Penny Adcock,[1,2] John Brooks,[1,2] Marta-Louise Ackers,[1,2] John Benjamin Ochieng,[4] Eric Mintz,[1] Susanne Wahlquist,[3] Peter Waiyaki,[4] and Laurence Slutsker[1]

[1]Foodborne and Diarrheal Diseases Branch, National Center for Infectious Diseases, [2]Epidemic Intelligence Service, Epidemiology Program Office, and [3]Division of Parasitic Diseases, National Center for Infectious Diseases, Centers for Disease Control and Prevention, Atlanta, Georgia; [4]Kenya Medical Research Institute, Vector Biology and Control Research Center, Kisumu, Kenya

Bacterial diarrheal diseases cause substantial morbidity and mortality in sub-Saharan Africa, but data on the epidemiology and antimicrobial susceptibility patterns of enteric bacterial pathogens are limited. Between May 1997 and April 1998, a clinic-based surveillance for diarrheal disease was conducted in Asembo, a rural area in western Kenya. In total, 729 diarrheal specimens were collected, and 244 (33%) yielded ⩾1 bacterial pathogen, as determined by standard culture techniques; 107 (44%) *Shigella* isolates, 73 (30%) *Campylobacter* isolates, 45 (18%) *Vibrio cholerae* O1 isolates, and 33 (14%) *Salmonella* isolates were identified. *Shigella dysenteriae* type 1 accounted for 22 (21%) of the *Shigella* isolates. Among 112 patients empirically treated with an antimicrobial agent and whose stool specimens yielded isolates on which resistance testing was done, 57 (51%) had isolates that were not susceptible to their antimicrobial treatment. Empiric treatment strategies for diarrheal disease in western Kenya need to be reevaluated, to improve clinical care.

Diarrhea is a major cause of morbidity and mortality in the developing world [1]. After acute respiratory illnesses, childhood diarrhea is the most important cause of disability-adjusted life years lost [2], and diarrhea has the single greatest adverse effect on children's growth and development [3]. Approximately 5 episodes of diarrhea per child per year occur among children <5 years old, and ~0.2% of the cases are fatal [4]. Sub-Saharan Africa is among the regions with the highest morbidity and mortality from diarrheal diseases [1]; however, detailed population-based surveillance data and antimicrobial susceptibility patterns of specific bacterial diarrheal pathogens for the area are lacking.

In 1997, the Centers for Disease Control and Prevention (CDC) and the Kenya Medical Research Institute (KEMRI) established ongoing clinic-based surveillance for diarrheal disease in Asembo, a rural, 200-km^2 area in the Siaya District of western Kenya, which borders Lake Victoria. The 53,000 residents of Asembo live in ~79 villages and are primarily subsistence farmers and fishermen. Most residents do not have electricity or running water. It is estimated that the annual mortality rate in the region for children <5 years old is ~53/1000 (CDC and KEMRI, unpublished data). Health facilities in Asembo include 10 government clinics, 3 private or mission clinics, and 1 mission hospital.

Methods

Surveillance and specimen collection. Between 1 May 1997 and 30 April 1998, enhanced surveillance for diarrheal illness among clinic attendees was conducted at 3 sites in Asembo (2 government health clinics and a mission clinic and hospital), in conjunction with a randomized, controlled trial on the efficacy of insecticide-treated bed nets on child mortality and morbidity (CDC and KEMRI, unpublished data). A stool specimen and information on patient demographics, medication use before the clinic visit, and reported symptoms were obtained from patients with diarrhea (defined as ⩾3 loose stools in a 24-h period, at any time within the preceding 5 days). Specimens were collected every weekday at the mission hospital site and on alternate days at the 2 government clinics. In addition, a fourth, daily collection site was added in October at a small private clinic in Asembo. Among children <12 years old, all visits to the 14 clinic or hospital sites in the region were recorded; of those children with symptoms of diarrheal disease, ~21% were seen at 1 of the 4 surveillance clinics and had a stool specimen cultured for bacterial enteric pathogens.

If the patient was unable to produce a whole stool specimen, a rectal swab was obtained. All specimens (including a swab of each whole stool specimen) were placed immediately in Cary Blair transport medium and were kept in a refrigerator or on ice for same-day

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The study protocol was reviewed and approved by the institutional review boards at the Centers for Disease Control and Prevention and the Kenya Medical Research Institute.

Reprints: Foodborne and Diarrheal Diseases Branch, Centers for Disease Control and Prevention, MS A-38, 1600 Clifton Rd., Atlanta, GA 30333. Correspondence: Dr. Roger Shapiro, Harvard AIDS Institute, 651 Huntington Ave., FXB 401, Boston, MA 02115 (rshapiro@hsphx.harvard.edu).

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transport to the CDC/KEMRI Microbiology Laboratory near Kisumu. All specimens arrived at the laboratory within 6 h of collection and were processed the same day. Culture results and antimicrobial susceptibility results were returned to the clinic officers at each health facility within 1 week of specimen collection and were used by health care providers to evaluate treatment decisions.

Demographic data and stool specimens also were collected from 100 patients who did not have diarrhea during the previous 30 days. Children were targeted selectively to provide these specimens, to control for pathogens such as *Campylobacter* and *Salmonella,* which commonly are shed for long periods of time during childhood. These specimens were obtained at the 4 sites during both the dry and rainy seasons between December 1997 and April 1998.

Laboratory procedures. All stool specimens were cultured at the CDC/KEMRI Microbiology Laboratory for *Shigella* species, *Salmonella* serotype Typhi, and other *Salmonella* and *Campylobacter* species. In addition, stool specimens from patients with watery diarrhea were cultured for *Vibrio cholerae* O1 and O139, and the first 100 specimens from patients with bloody diarrhea were tested for *Escherichia coli* O157:H7, using sorbitol-MacConkey agar and O157 latex reagent. Testing for other Shiga toxin–producing *E. coli,* enterotoxigenic *E. coli,* enteropathogenic *E. coli,* enteroaggregative *E. coli,* rotavirus, and parasites was done on selected pathogens, and the results will be presented elsewhere.

Antimicrobial susceptibility testing was done at the CDC/KEMRI Microbiology Laboratory on all bacterial pathogens (excluding *Campylobacter* species) by use of the disk diffusion method. Susceptibility to the following antimicrobial agents was tested: ampicillin, amoxicillin–clavulanic acid, ceftriaxone, chloramphenicol, ciprofloxacin, gentamicin, kanamycin, nalidixic acid, streptomycin, sulfisoxazole, tetracycline, and trimethoprim-sulfamethoxazole [5]. The National Committee for Clinical Laboratory Standards has established interpretive criteria for *V. cholerae* for the following drugs: ampicillin, chloramphenicol, sulfisoxazole, tetracycline, and trimethoprim-sulfamethoxazole. Criteria established for the *Enterobacteriaceae* were used to interpret results of other susceptibility tests. Antimicrobial susceptibility results were confirmed at CDC in Atlanta. Isolates of *Campylobacter* species were tested at CDC by the Etest (AB Biodisk) method for susceptibility to ciprofloxacin, chloramphenicol, clindamycin, erythromycin, nalidixic acid, tetracycline, and trimethoprim-sulfamethoxazole [6, 7]. Interpretive criteria for susceptibility testing have not been established for *Campylobacter* species.

Results

Overall, 729 stool specimens were collected from patients with diarrhea at the 4 surveillance sites during the 1-year period, and 244 (33%) yielded *Shigella, Campylobacter, Salmonella,* or *Vibrio* species. In 14 specimens, >1 such pathogen was identified, for a total yield of 258 bacterial pathogens isolated from the 729 specimens (table 1). The median age among all clinic patients who provided specimens was 11 years (range, 1 month to 80 years), and 46% were <5 years old. Forty-eight percent of patients were male. The median age among persons who provided control specimens was 5 years (range, 1 month to 51 years). Among all patients meeting the case definition, fever was reported by 76%, nausea by 62%, vomiting by 48%, and abdominal cramps by 80%. Seventeen percent of specimens were bloody, and these were from patients whose median age was 25 years (range, 3 months to 73 years), an age significantly older than that for patients with nonbloody specimens (median age, 4 years; range, 1 month to 80 years; $P < .05$).

Table 1. Bacterial enteric pathogens found in 729 diarrheal specimens from patients with diarrhea and in stool specimens from 100 clinic attendees without diarrhea: Asembo, Western Kenya, 1 May 1997 to 30 April 1998.

Bacterial pathogen	No. (%) of specimens		*P*
	Patients with diarrhea	Clinic attendees without diarrhea	
Shigella species	107 (15)	3 (3)	.001
S. dysenteriae type 1	22	—	—
S. dysenteriae, other	25	—	—
S. flexneri	51		
S. sonnei	7	—	—
S. boydii	2	—	—
Campylobacter species	73 (10)	8 (8)	.52
C. jejuni	57		
C. coli	6		
C. lari	6		
C. jejunilcoli	4		
Nontyphoidal *Salmonella* species	32 (4)	2 (2)	.26
Salmonella serotype Typhi	1 (0)	—	—
Vibrio cholerae O1 (El Tor, Ogawa)	45 (6)	—	—
Escherichia coli O157:H7	—	—	—
Total no. of pathogens[a]	258	13	<.0001

[a] Stool samples from some patients yielded >1 pathogen.

Among all patients with diarrhea, *Shigella* species were the most common pathogens isolated, followed by *Campylobacter* species and *V. cholerae* O1. Among children <5 years old, *Campylobacter* species were the most common pathogens isolated. Fifty-six (45%) of 124 bloody stool specimens yielded *Shigella* species, whereas only 4 bloody specimens (3%) yielded *Campylobacter* species. A cholera outbreak in western Kenya reached Asembo in October 1997, and after that time, *V. cholerae* O1 was the most commonly isolated pathogen: among bacterial pathogens isolated between 22 October 1997 and 30 April 1998, 45 (34%) of 133 were *V. cholerae* O1.

Resistance to antimicrobial agents was common among all pathogens (table 2). Among 70 *Campylobacter* species isolate susceptibilities determined by Etest, 95% were below the standard resistance breakpoints for chloramphenicol, ciprofloxacin, clindamycin, erythromycin, and tetracycline; 76% were below the breakpoint for nalidixic acid; and 46% were below the breakpoint for trimethoprim-sulfamethoxazole.

Among tested primary isolates from 241 patients, 216 (90%) were not susceptible to ⩾1 antimicrobial agent tested, and 178 (74%) were not susceptible to ⩾3 agents tested. Among *Shigella* species, multi-agent antimicrobial resistance was common. All *Shigella dysenteriae* type 1 (Sd1) isolates tested were resistant to ⩾6 agents (chloramphenicol, trimethoprim-sulfamethoxazole, tetracycline, ampicillin, sulfisoxazole, and streptomycin). *V. cholerae* O1 was generally susceptible to tetracycline, the

Table 2. Antimicrobial susceptibility patterns among 181 *Shigella*, *Salmonella*, and *Vibrio* isolates tested: Asembo, Western Kenya, 1 May 1997 to 30 April 1998.

Pathogen (no. tested)	Percentage of susceptible isolates (percentage moderately or intermediately susceptible)												
	Chl	TMP-SMZ	Tet	Cpfx	NA	Amp	SSZ	Stm	Km	Gm	Ctri	Amox-CA	Fur
Shigella species (106)	24	6	3	100	98	12	12	0	100	100	100	28 (34)	ND
S. dysenteriae type 1 (22)	0	0	0	100	100	0	0	0	100	100	100	14 (59)	ND
S. dysenteriae, other (24)	46	0	8	100	96	4	17	0	100	100	100	50 (29)	ND
S. flexneri (51)	10	12	2	100	98	6	18	0	100	100	100	12 (31)	ND
S. sonnei (7)	100	0	0	100	100	100	0	0	100	100	100	100	ND
S. boydii (2)	100	0	0	100	100	100	0	0	100	100	100	100	ND
Salmonella, nontyphoidal (29)	76	59	41 (24)	100	93	55	34 (10)	38 (6)	79	79	100	52 (28)	ND
Salmonella serotype Typhi (1)	100	100	100	100	100	100	100	100	100	100	100	100	ND
Vibrio cholerae serotype O1 (45)	7 (73)	0	98	100	0 (4)	93	0	0	98	98	100	84 (13)	0

NOTE. Amox-CA, amoxicillin–clavulanic acid; Amp, ampicillin; Chl, chloramphenicol; Cpfx, ciprofloxacin; Ctri, ceftriaxone; Fur, furazolidone; Gm, gentamicin; Km, kanamycin; NA, nalidixic acid; ND, not done; SSZ, sulfisoxazole; Stm, streptomycin; Tet, tetracycline; TMP-SMZ, trimethoprim-sulfamethoxazole.

most commonly used antimicrobial for suspected cholera in western Kenya; however, one isolate collected in February 1998 was resistant to tetracycline.

Antimicrobial agents (penicillin, ampicillin, trimethoprim-sulfamethoxazole, tetracycline, nalidixic acid, metronidazole, or gentamicin) were prescribed for 76% of children diagnosed at clinics in Asembo with gastroenteritis, diarrhea, or dysentery. Before seeking treatment at the health clinic, 12% reported taking ⩾1 antimicrobial agents. Information on antimicrobial agents administered at the clinic was available for 112 patients who were treated empirically with ⩾1 antimicrobial agents and whose stool specimen yielded an isolate for which resistance testing was done. Of these patients, 57 (51%) received only antimicrobial agents to which their isolate was later found to be nonsusceptible. Among patients with *Shigella* species, 37 (84%) of 44 for whom information was available had been given only ineffective agents.

Discussion

Antimicrobial-resistant bacterial diarrhea is a significant public health problem throughout the developing world [8–10]. In western Kenya, our finding that more than half of all pathogens were not susceptible to empiric therapy demonstrates the magnitude of the problem. Ineffective treatment has multiple potential consequences: (1) it delays the time until effective treatment is offered to patients when antimicrobial agents are indicated, (2) it creates a false sense of security for both patients and health care providers, (3) it adds significantly to the cost of treating diarrheal illness, especially relative to per capita income in Kenya, and (4) it contributes to the development of further resistance of both enteric and nonenteric bacterial pathogens. The development of antimicrobial resistance limits treatment options available for potentially fatal epidemics of Sd1 and *V. cholerae* O1 [11].

In western Kenya, as in many developing countries, antimicrobial agents are widely available; most are sold without prescription at chemist shops, and many are even sold by vendors in market stalls. At government health clinics, antimicrobial agents are dispensed according to an algorithm, and indications include suspected bacillary dysentery and severe dehydrating diarrhea (i.e., suspected cholera). However, our results demonstrate that, in practice, most of the children (76%) who sought treatment in health clinics in Asembo during our study period for either gastroenteritis, diarrhea, or dysentery received ⩾1 antimicrobial agents. The failure of current treatment programs to deliver effective antimicrobial agents for diarrheal disease in areas such as Asembo indicates the need for tighter restrictions on the availability of antimicrobial agents, standardization of treatment practices among clinical officers and physicians, and programs aimed at the primary prevention of diarrheal diseases (i.e., the provision of safe drinking water and improved sanitation). In addition, selection of effective antimicrobial agents, when indicated as part of optimal case management, could be improved by expanding laboratory-based antimicrobial susceptibility testing at selected sentinel sites.

Sd1 is an endemic pathogen in this region, and the potential exists for periodic Sd1 epidemics during favorable conditions, as occurred in Asembo in 1995 [11] and early 1997 during the dry season and at the beginning of the rainy season (CDC and KEMRI, unpublished data). The high level of antimicrobial resistance among Sd1 isolates has been observed in previous studies in Africa [10]. Although all isolates were susceptible to nalidixic acid and ciprofloxacin, chromosomal resistance to these agents is easily transferred [12, 13], and experience in other parts of the world has confirmed that resistance to these agents arises rapidly once selective pressure is exerted through intensive use of quinolones and fluoroquinolones [12, 13].

A cholera epidemic began in Asembo in October 1997, and the first known case in Siaya District was detected through this surveillance system [14]. In February 1998, the first isolate resistant to tetracycline—the antimicrobial agent used most commonly to treat cholera in the region—was detected. Monitoring antimicrobial susceptibility for *V. cholerae* O1 is useful, since antimicrobial therapy is recommended as an important adjunct to rehydration [15].

Our findings show that a high percentage of cases of diarrhea in rural western Kenya is caused by antimicrobial-resistant bac-

teria, thus illustrating the effect of longstanding, unregulated antimicrobial use. Most enteric pathogens easily share genes for antimicrobial resistance, and the continuous selective pressure applied by the over-the-counter availability of these agents, as well as the prescription of these agents at most clinic visits, has potentially lethal consequences for a region plagued by epidemics of Sd1 infection and cholera. Judicious use of antimicrobial therapy requires the education of health workers and patients, adequate laboratory diagnostic capabilities, and government regulation. Antimicrobial susceptibilities must be monitored, to effectively treat pathogens such as Sd1 and *V. cholerae* O1. Finally, emphasis should be placed on primary preventive measures, such as ensuring sewage management and safe drinking water in underdeveloped regions like Asembo. The long-term benefits of such investment in infrastructure are highlighted by the failure of antimicrobial therapy to effectively treat diarrheal diseases in the developing world.

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