Does Treatment of Bloody Diarrhea due to *Shigella dysenteriae* Type 1 with Ampicillin Precipitate Hemolytic Uremic Syndrome?

Diarrhea-associated hemolytic uremic syndrome (HUS), the most common cause of acute renal failure in infancy and childhood, is often associated with infection by organisms producing Shiga toxin (ST) or Shiga-like toxin (SLT), mainly verocytotoxin-producing *Escherichia coli* (VTEC O157:H7) and *Shigella dysenteriae* type 1 (1,2). Although antibiotics are believed to be essential in treating shigellosis, treatment of *S. dysenteriae* type 1 patients with antibiotics to which the organism is resistant has been considered a risk factor for HUS (3,4).

Until 1993, HUS was rarely reported from Saudi Arabia. Four cases of diarrhea-associated HUS due to *S. dysenteriae* type 1 were identified in 1989 (J. Hibbs and A. Mishkas, unpublished report), and one case of HUS attributed to plasma transfusion was documented in 1988 (5).

In May 1993, four dysentery-associated HUS cases in two families were reported from northwestern Saudi Arabia (Tabuk). *S. dysenteriae* type 1 was isolated from the stool of each HUS patient. The organism was also isolated from 6 of the other 10 members of the two families who had dysentery. All isolates were resistant to trimethoprim-sulfamethoxazole, chloramphenicol, tetracycline, and ampicillin but sensitive to nalidixic acid. The two families had just returned from a 1-week visit to relatives in two neighboring villages in Gizan. This densely populated region in southwestern Saudi Arabia has about 1.2 million people living in more than 4,000 villages; the population is relatively poor and uneducated, and environmental sanitation is generally inadequate.

We defined a case of HUS as any case of bloody diarrhea (BD) that had all of the following: acute renal failure (serum urea nitrogen, 18 mg/dL (or 6.3 mmol/L); or creatinine, 1.3 mg/dL (or 115 mmol/L)); thrombocytopenia (platelet count 130,000/mm^3); and hemolytic anemia (hemoglobin level less than 10 g/dL; or hematocrit less than 30%; or appearance of fragmented red cells on direct microscopy). We standardized the treatment of BD in the Gizan region as follows: No antibiotics were given for treatment of BD at the primary health care centers (PHCCs) before a stool specimen was taken for culture and sensitivity testing. After reviewing the preliminary results, we either recommended use of nalidixic acid for treatment of BD or were guided by the results of the stool culture. This protocol was followed for management of BD in the entire region.

Parasitologic, bacteriologic, and biochemical tests and drug treatment regimens were obtained for all patients admitted with BD or HUS to the regional referral hospital or five district hospitals in the outbreak area. BD cases were identified through hospital admission records, visits to PHCCs in the affected villages, interviews with family members of the identified patients, and school visits. We visited the houses of all HUS and BD patients and interviewed family members to ascertain which antibiotic was used to treat the BD patients; mothers were shown bottles and boxes of antibiotics and were asked to identify the antibiotic used for treating the children with BD.

We identified 233 cases of BD occurring from February through July 1993 among 79 families scattered over 19 contiguous villages. Affected villages were predominantly in southern Gizan region near the Yemeni border. One hundred ninety patients (81.5%) consulted PHCCs; of those, 97 (51%) were referred to hospitals, and 81 (43%) were admitted. Thirty-four other BD patients were admitted directly to hospitals (a total of 115 admissions). In nine BD cases patients did not seek medical care including seven (3%) who used traditional treatment (the Wicka plant). In 23 (10%) patients, 13 male and 10 female, BD developed into HUS. Four isolates of *S. dysenteriae* type 1 that showed the same antibiotic susceptibility described earlier were obtained from four patients with BD in different villages in the middle of the outbreak. We used Cary-Blair transport medium for transporting stool specimens collected before antibiotic treatment from newly recognized patients with BD. However, community- and hospital-based interviews showed that the sequence of symptoms was almost identical in all of the 233 BD cases: the condition started with colicky abdominal pain and tenesmus (69%), followed by watery diarrhea (60%), which rapidly became only

mucus and blood (83%) or blood-streaked (17%). Seven patients (3.0%) had rectal prolapse. *S. dysenteriae* type 1 was not isolated from any of the 23 HUS patients; however, all stool specimens were taken during antibiotic treatment.

Most BD cases (92.3%) were among Saudis; the remaining 7.7% were among Yemeni patients. No HUS case occurred among patients over 11 years of age. The male/female ratio for both BD and HUS was 1.3:1. Three boys and three girls with confirmed HUS died (case-fatality rate = 26.1%); none of the patients with uncomplicated BD cases died.

Of the 23 HUS patients, 18 (78%) became ill with the disease 2 to 14 days after hospital admission for uncomplicated BD. This compares with a hospital admission rate of 40 (27%) of 147 for children of the same age with BD from the same villages (odds ratio = 9.6, 95% confidence interval 3.1-35). Five children, aged 8 to 16 months, got HUS either before or on the day of hospital admission; all had received oral ampicillin at home for 5 to 7 days before their illness progressed to HUS. In comparison, two of nine children of the same age, with BD, who were not hospitalized, received ampicillin at home (OR = infinite, p value = 0.02, Fisher's exact test).

Eighteen HUS cases occurred after the patients were admitted to Samtah and Abu-Arish, two out of five district hospitals. The demographic, clinical, and laboratory profiles of BD and HUS cases are shown in Table 1A-C. Six different antibiotics were used in various combinations for treating BD

Table 1.

A. Profiles of children admitted to hospitals with bloody diarrhea (BD) or hemolytic uremic syndrome (HUS)

	Places of hospitalization of BD and HUS cases				
	Samtah	Abu-Arish	KFH	Bysh	Sabia
No. of BD cases	43	42	13	9	8
No. of HUS cases	8	14	-	-	1[a]
Percentage of HUS cases	18.8	33.3	0	0	12.5
Median age in years: BD cases	4.0	5.0	7.0	4.0	4.0
HUS cases	1.8	2.8	-	-	0.8
Mean (±SD) of duration (in days) between onset of symptoms and admission to hospital:					
BD	3.8 (1.9)	5.5 (1.6)	4.5 (0.4)	3.7	3.9 (2.0)
BD complicated with HUS	5.2 (2.6)	4.5 (2.5)	-	-	-
HUS diagnosed on admission	13.0 (2.8)	7.5 (0.7)	-	-	6.0 (0.0)

B. Percentage of 110 BD patients treated with antibiotics[b,c]

Ampicillin	36.6	70.0	15.4	11.1	100.0
Metronidazole	14.6	55.0	7.7	0	100.0
Gentamicin	22.0	22.5	0	55.6	42.9
Nalidixic acid	70.7	57.5	61.5	66.7	0
Claforan	2.4	20.0	0	11.1	0
Amikacin	9.8	0	7.7	22.2	28.6

C. Laboratory values of children hospitalized with BD or HUS

Laboratory test made on the day of admission to the hospital[d]	Non-HUS cases		HUS diagnosed 2-14 days after admission to hospital		HUS diagnosed on admission to hospital	
	Mean (N)[e]	SD	Mean (N)	SD	Mean (N)	SD
Serum creatinine	60 (16)	46	63 (3)	79	279 (3)	94
Blood urea nitrogin (BUN)	5.4 (23)	5.8	15.3 (3)	12.0	23.0 (3)	6.1
Serum sodium	129 (33)	9	137 (3)	4.6	127 (3)	14
Serum potassium	3.8 (47)	0.8	3.9 (7)	1.1	4.6 (5)	1.1
(Leukocytes [WBC] count)	14.2 (48)	6.0	34.0 (6)	24.7	41.2 (5)	18.8
Hemoglobin	11.3 (50)	2.3	12.0 (1)	1.5	6.8 (4)	2.5
Hematocrit	36.1 (13)	3.9	NA	NA	15 (2)	7.1
Thrombocytes (platelets)	322 (5)	250	154 (1)	-	NA	NA
(Body temperature on admission)	37.8°C (75)	0.8	37.9°C (18)	0.8	37.9°C (5)	0.9

[a] Community case of HUS. [b] Percent of cases receiving the corresponding antibiotics. A patient may receive more than one antibiotic. Totals do not add up to 100%. [c] This table does not include 5 cases diagnosed as HUS on admission and treated as cases of BD. [d] Creatinine in mg/dL, blood urea nitrogen in mg/dL, sodium in mmol/L, potassium in mmol/L, WBC (white blood cell count) in thousands/µm, hemoglobin level in g/dL, hematocrit, platelets in thousands/mm^3. Values shown are for children under 12 years of age only. [e] N = number of cases of BD diagnosed in the hospital. NA = not available.

Table 2. Risk of developing hemolytic uremic syndrome (HUS) by antibiotic combination used for treatment of bloody diarrhea (BD), Gizan, Saudi Arabia, 1993

Antibiotic combination group	Antibiotic combinations	Dysentery patients		BD cases admitted to Samtah and Abu-Arish Hospitals	HUS rate (%)	Risk ratio	95% confidence Interval[a]
		Total (N = 110)	Developing HUS (N = 18)				
Nalidixic acid with or without other antibiotics, but no ampicillan[b]	N(3/23), N+G (0/7) G+N+C+A (0/1), M+N (0/1), M+N+C (0/2), N+C (0/4)	41	3	28	7.3	1	0.23–4.34
No antibiotic	No antibiotic (0/12)	12	0	6	0.0	NC[c]	p value = 0.629[d]
Antibiotic other than nalidixic acid or ampicillin	A (0/1), C (1/0), G (0/1). M+G (0/1)	4	1	4	25.0	1.58	0.22–11.58[e]
Ampicillin with or without other antibiotics but no nalidixic acid		28	10	19	35.7	6.90	0.98–48.68
Ampicillin only	P (3/3)	6	3	5	50.0	6.11	1.31–28.54
Ampicillin with other antibiotics but no nalidixic acid	P+G (1/2), P+M (2/3), P+M+A (0/2), P+M+C (1/0) P+M+G (3/8)	22	7	14	31.8	10.50	0.54–205.39
Ampicillin and nalidixic acid with or without other antibiotics	P+M+G+N (1/1), P+M+N 0/10), P+M+N+C (1/0). P+N (1/8), P+N+A (1/2)	25	4	24	16.0	1.77	0.31–10.21

HUS rate (%) calculated from total number of BD in the five district hospitals using corresponding antibiotic .[a] Mantel-Haenszel weighted relative risk adjusted to hospital (Epi Info, version 6.02). Analysis restricted for data from Samtah and Abu-Arish hospitals. HUS was not reported from the other three district hospitals. [b] Reference group. A = amikacin, C = claforan, g = gentamicin, N = nalidixic acid, M = metronidazole, P = ampicillin. Numbers between parentheses in the second column (antibiotic combination) indicate the (number of patients with HUS who took the corresponding antibiotic combination number or patients with BD who took the same antibiotic combination but did not develop HUS in the five district hospitals). [c] NC = not calculated. [d] One-tailed Fisher's exact test. [e] Adjusted Mantel-Haenszel relative risk could not be calculated.

patients in these hospitals Table 1B. Treatment with ampicillin prescribed alone or with other antibiotics except nalidixic acid (Table 2), was associated with development of HUS. However, three BD patients who received nalidixic acid developed HUS. Of 12 BD patients (including eight children under 12 years of age) who received no antibiotic therapy, none got HUS.

These results support the implication from Bangladesh and from a parallel investigation in Saudi Arabia that inpatient antibiotic treatment of children with dysentery due to *S. dysenteriae* type 1 may precipitate HUS. We have extended these observations to show the same association for antibiotic treatment at home. Although Abu-Arish and Samtah hospitals received similar numbers of BD patients, more HUS cases were reported from Abu-Arish hospital, which used ampicillin to treat patients with BD. The various combinations of antibiotics used to treat BD patients could be explained by the presence of doctors from parts of the world that have different prescription practices. Three BD patients got HUS despite the use of nalidixic acid. Resistance to nalidixic acid among *S. dysenteriae* isolates was reported from Bangladesh; resistance increased from 2.1% in 1986 to 57.9% in 1990 (6).

We recommend a laboratory-based surveillance system to identify and promptly contain emerging outbreaks. Physicians need to be informed continuously about emerging resistant strains of bacteria and be cautious when using antibiotics to treat patients with dysentery unless the causative organism and the resistance pattern have been identified. Parents of children with BD need to be educated to take their children to the nearest health facility as soon as possible.

S. dysenteriae is a delicate bacterium that does not withstand adverse conditions (e.g., heat and dryness); prompt plating, preferably at bedside, is recommended (7). Failure to isolate *S. dysenteriae* type 1 from dysenteric stool specimens during this outbreak could be attributed to delayed plating of specimens, lack of appropriate transport media,

and treatment with antibiotics before stool specimens were obtained. Even with direct inoculation of stool specimens in pediatric wards, HUS resulted in a low yield of *S. dysenteriae* type 1 (8,9).

Treatment of BD due to *S. dysenteriae* type 1 with ampicillin may precipitate HUS. It would be valuable to retrospectively examine this association in other countries where both dysentery due to *S. dysenteriae* type 1 and HUS are reported.

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