

Sulfaguanidine in the Treatment of Dysentery in Children¹

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DIARRHEAL DISEASES have always been a primary problem in the tropics. It was early realized, however, that most of the diarrhea was of infectious origin, and the development of chemotherapy opened, therefore, a new prospect for the control of such infections. The original work of Marshall and his associates² indicated striking benefit from the use of sulfaguanidine in the treatment of bacillary dysentery, if used early in the disease, in a series that included both children and adults but no controls. Similarly favorable results in a controlled series, but including both children and adults, were reported by Lyon *et al.*³ Anderson, Cruickshank, and Walker⁴ observed considerable benefit in seven cases of adults in a mental hospital and, in Puerto Rico, the studies of Suárez and Hernández Morales⁵ also indicated the value of the drug.

Since all forms of diarrhea, particularly bacillary dysentery, cause the greatest mortality and the severest illness in children, the present study was undertaken to evaluate the use of the drug in the younger age groups.

MATERIAL USED

The original plans called for studying children under three years of age, who were suffering from diarrhea of less than four days' duration, the severity of which was manifested by the presence of fever and bloody stools. Although persistent and continuous attempts were made to encourage referral of such patients, it was soon apparent that very few would be available. This was not surprising in view of the general inadequacy of medical facilities on the Island and the concomitant apathy among patients in seeking such

1. Received for publication July 11, 1944.
2. E. K. Marshall, Jr., A. C. Bratton, L. B. Edwards, and E. Walker, Sulfanilylguanidine in treatment of acute bacillary dysentery. *Bull. Johns Hopkins Hosp.*, 68:94-111, 1941.
3. G. M. Lyon, T. G. Folsom, W. J. Parsons, and I. Sprouse, Sulfaguanidine in "bloody flux." *West Virginia M.J.*, 38:19-27, 1942.
4. D. E. W. Anderson, R. Cruickshank, and J. Walker, Treatment of bacillary (Flexner) dysentery with sulfanilylguanidine. *Brit. M.J.*, 2:497-501, 1941.
5. R. M. Suárez and F. Hernández Morales, Bacillary dysentery. Preliminary report on use of sulfaguanidine. *Bol. Asoc. méd. de Puerto Rico*, 33:347-358, 1941.

care as is available. The requirements were therefore relaxed to include children up to four years of age with diarrhea of any duration, as long as the child appeared at least moderately ill. In all, the records of seventy-seven children were sufficiently complete for analysis. They form the basis of the present report.

The cases were studied at two hospitals in Puerto Rico—the University Hospital of the School of Tropical Medicine, in San Juan, and the District Hospital, at Bayamón. Cultures from the latter institution were made at the Enteric Research Division of the Biological Laboratory of the Insular Health Department.

METHODS USED

On admission to the hospital with a diagnosis of diarrhea, not associated with other diseases likely to cause loose stools, the cases were assigned alternately to the treated or control groups. Routinely, physical examination, complete blood count, urine analysis, serologic test for syphilis, and microscopic examination of the stool for parasites were made. As might have been expected, some children subsequently turned out to be suffering from some other condition of which the diarrhea was only one manifestation. These were dropped from the study.

Immediately after admission, a rectal swab culture was made in each case, using the technique described by Hardy, Watt, and DeCapito,⁶ and the swab later inoculated on a plate of SS agar, which had been shown by these same investigators to offer the greatest promise of detecting the presence of *Shigella* or *Salmonella*. This medium was used in all cultures made on admission and subsequently. The admission cultures at the University Hospital were also put on MacConkey's and Wilson-Blair media, but these failed to detect any cases not positive on the SS agar. Suspicious colonies were picked and seeded on Russell's double sugar tubes; those showing acid in the butt were set up directly for presumptive agglutination with *Shigella* antisera. Later, confirmation was made with fermentation reactions and specific typing sera. It was planned to make daily cultures of all cases in the study but, in some instances, there were gaps of as long as four days. The number of cultures missed, however, was essentially similar in the treated and the control cases.

6. A. V. Hardy, J. Watt, and T. M. DeCapito, Studies of acute diarrheal diseases; new procedures in bacteriological diagnosis. *Pub. Health Rep.*, 57:521-524, 1942.

A. V. Hardy, J. Watt, J. Peterson, and E. Schlosser, Studies of acute diarrheal diseases; sulfaguanidine in control of *Shigella dysenteriae* infections. *Pub. Health Rep.*, 57:529-535, 1942.

After the rectal swab was taken, another culture was made of the first stool passed after admission to the hospital. In the cases to be treated, administration of sulfaguanidine was then begun with a daily dose of 0.1 gm. per kilo of body weight. Half of this daily dose was given on admission, followed by one quarter of the daily dose every six hours. The dosage was reduced to half the amount when diarrhea had been absent for two days and discontinued entirely after four days without diarrhea. In those cases in which the diarrhea persisted, the drug was stopped after fourteen days. All cases received the same type of general therapy consisting of preliminary starvation, adequate parenteral fluids, transfusion when indicated, and gradual resumption of feedings.

All stools were recorded on a sheet, separate from the general chart, which called for their description as to size, character, color, and presence or absence of blood or mucus.

RESULTS

After accumulation of the records, it was found that a total of seventy-seven cases were sufficiently complete to be available for analysis. Of these, forty had had at least one culture positive for *Shigella*, Flexner V, W, Z, or Sonn . Other varieties of *Shigella* were not encountered. Of the culturally positive cases, twenty-three were treated and seventeen were untreated controls. To assess the comparability of these two groups, they were analyzed with regard to age, severity of the disease as measured by the presence or absence of bloody stools on admission, and the duration of the disease on admission. The data are given below.

	Number of Cases	Mean Age	Percentage with Bloody Stools	Percentage Sick Less Than 8 Days
Treated	23	14.7 months	63	57
Untreated	17	12.8 months	59	44

The similarity of the two groups indicates that the method of alternate selection had resulted in comparable samples within the age limits.

DURATION OF THE DIARRHEA

Evaluation of the effectiveness of the drug was made on the basis of two criteria—duration of the diarrhea and duration of the infection. In determining the former, it was necessary to set up stand-

TABLE 1
Days of Diarrhea—Continuous Diarrhea

	Duration Disease in Days Before Admission	Duration of Diarrhea in Days								Total
		0-2	3-4	5-6	7-8	9-10	11-12	13-14	>14	
T R E A T E D	<5	4	3							7
	5-8	1	3	1	1					6
	9-30	1	2	2						5
	>30	1	2	1			1			5
	Total	7	10	4	1		1			23
U N T R E A T E D	<5		3				1		1	5
	5-8		1						1	2
	9-30		1	2					2D	5
	>30		2	1				1		4
	Unknown		1							1
Total		8	3			1	1	4		17
T R E A T E D	<5	3		Total Diarrhea			2	1		7
	5-8		2	3	1					6
	9-30		1	3			1			5
	>50	1	2			1			1	5
	Total	4	5	7	1	1	3	1	1	23
U N T R E A T E D	<5		3				1	1		5
	5-8								2	2
	9-30		1	1		1			2D	5
	>30		1	1	1				1	4
	Unknown								1	1
Total		5	2	1	1	1	1	6		17

D=Death.

ards as to what would be called diarrhea. Existence of one or more of the following conditions in a twenty-four hour period was considered diagnostic of this condition: (a) any bloody stool; (b) any liquid stool; (c) more than five stools of any type; (d) more than three stools, if any contained mucus. While there may be disagreement as to the absolute nature of these standards, their equal application to all cases should make them adequate for the purposes of this study.

The duration of the diarrhea, as related to the duration of the disease at admission, is presented in Table 1 for both the treated and control cases. To compensate further for possible error in the choice of these criteria and, because of the difficulty in deciding when a given attack of diarrhea had ceased, two arbitrary categories were set up—continuous and total diarrhea. The former term—continuous—referred to the number of days of uninterrupted diarrhea, as defined above, after admission. The term total referred to the period from admission until the patient had been free of the condition for seven consecutive days and might, therefore, include days on which no diarrhea occurred. For instance, a child who had six days of diarrhea after admission followed in order by three days of no diarrhea, four days of diarrhea, five days of no diarrhea, three days of diarrhea, and seven days of no diarrhea, would be classified as continuous—six days and total, twenty-one days.

It will be noted that the general pattern is similar for both continuous and total diarrhea. The treated cases, regardless of the duration of the disease before treatment was begun, tended to terminate within a few days' time, while a good proportion of the control cases lasted two weeks, or more. In both instances the mean number of days of diarrhea was significantly smaller in the treated group than in the controls. On the other hand, the apparently striking efficacy of sulfaguanidine reported in previous studies was absent in the present series. This may be related to generally poorer health in ward patients in Puerto Rico or to the younger age group involved. The number of untreated cases that did recover in a few days' time illustrates the tendency of bacillary dysentery to be a self-limited disease in many instances, and emphasizes the necessity of observing an adequate series of controls in any study dealing with the therapy of this disease.

While the number of cases is obviously too small for generalization, it was surprising to observe no great difference in course, as measured by the diarrhea, between disease of short duration contrasted with long duration, prior to admission. This observation

seems to hold as much for the untreated controls on general therapy alone as for those treated with the specific drug—an apparent disagreement both with the original findings of Marshall *et al*⁷ and with general experience with effective therapeutic procedures, which may be due to a sampling error or may be connected with the absence in this series of any number of cases of less than 48 hours' duration. Of course, the effects of the disease must be measured in broader terms

TABLE 2
Negative Cultures—Days of Continuous Diarrhea

Duration Disease Before Admission	Days of Continuous Diarrhea								Total	
	0-2	3-4	5-6	7-8	9-10	11-12	13-14	>14		
TREATED	<5		3		2					5
	5-8	2	1		1	1				5
	9-30	2	2	4						8
	>30	1	1							2
	Total	5	7	4	3	1				20
UNTREATED	<5	3	1	2						6
	5-8	3	1	1						5
	9-30	1			2	1	1			5
	>30	1								1
	Total	8	2	3	2	1	1			17
Duration Disease Before Admission	Days of Total Diarrhea								Total	
	0-2	3-4	5-6	7-8	9-10	11-12	13-14	>14		
TREATED	<5		1	1		1	1		1	5
	5-8		1	1	1		1	1		5
	9-30	1	1	4				2		8
	>30		1			1				2
	Total	1	4	6	1	2	2	3	1	20
UNTREATED	<5		1	3		1	1			6
	5-8		3	1			1			5
	9-30					1	1	3		5
	>30								1	1
	Total		4	4		1	3	1	4	17

7. E. K. Marshall, Jr., A. C. Bratton, L. B. Edwards, and E. Walker, *op. cit.*

than merely number and character of the stools. General debility and malnutrition are serious and frequent accompaniments of a prolonged dysentery.

In contrast to the cases diagnosed as bacillary dysentery because of the isolation of Shigella, Table 2 shows the observations on the thirty-seven cases originally included in the study but whose cultures were never positive. Analysis of the treated and control groups showed them also to be entirely comparable in age, severity, and duration of the disease. This picture is quite different from the positive cases, for there is clearly very little difference between the treated and control cases. Here, too, the observations are at variance with several reports in the literature, which have indicated value for sulfaguanidine even in the absence of positive cultures. The contrast in this study, however, adds to the evidence that sulfaguanidine must have a specific effect on Shigella in the body.

DURATION OF THE INFECTION

Table 3 indicates the results with regard to the last day of observation in the hospital in which a positive culture was obtained.

The advantage of the treated cases is obvious and striking and the difference between the two groups of a high order of statistical significance. Four-fifths of the treated cases were culturally nega-

TABLE 3
Duration of Infection

Duration Disease in Days Before Admission	Duration of Infection (Day of Last Positive Culture)									Total	
	0-2	3-4	5-6	7-8	9-10	11-14	15-18	19-22	23†		
TREATED	<5	4			2					1	7
	5-8	2		3				1			6
	9-30	2	2		1						5
	>30	2					2			1	5
	Total	10	2	3	3		2	1		2	23
UNTREATED	<5		1	1				1	1	1	5
	5-8								1	1	2
	9-30						1	1		3	5
	>30	1							2	1	4
	Unknown									1	1
	Total	1	1	1			1	2	4	7	17

tive by the second week, while four-fifths of the untreated cases continued positive past this period. As in the case of the diarrhea, there is no apparent relation, in the treated group, between duration of the infection and duration of the disease at the time of admission.

RECURRENCES

Since it was unfortunately impossible to follow cases after discharge as carefully as was desirable, the incidence of recurrences cannot be stated with any accuracy. Known recurrences did occur in three of the cases treated specifically, although in only one was it possible again to recover the organism. In two of the three cases the patients had been discharged from the hospital sooner than planned through a misunderstanding, and the drug was stopped two or three days earlier than usual.

COMMENT

More recent studies⁸ published since the completion of these observations indicate that other drugs of the sulfonamide series, notably sulfadiazine, have greater efficacy in *Shigella* infections than sulfaguanidine. There were no evidences of reactions in any of the cases in this series, hence the apparent absence of toxicity of the latter drug indicates a certain usefulness that may find a definite place in the planned treatment and prophylaxis of the disease.

The evidence here presented, while not as striking nor as unequivocal as in other studies, nevertheless is quite definite in indicating the value of the drug. It seems clear that further observations on a larger series are essential to elucidate such problems as dosage, recurrences, optimum time of administration, and possible differences in the therapeutic value of the various drugs for various strains. Differences between strains were not observed in this series but, of course, the number of cases was too small to warrant conclusions.

The high case fatality rate for diarrheal diseases in young infants, the general prevalence of *Shigella* in Puerto Rico, and the excessive infant mortality on the Island, all point up the obvious need for extension of control measures. Chemotherapy offers promise as one of the measures to lower morbidity and mortality from *Shigella*

8. A. V. Hardy, W. Burns, and T. DeCapito, Studies of acute diarrheal diseases; cultural observations on relative efficacy of sulfonamides in *Shigella dysenteriae* infections. Pub. Health Rep., 58:689-693, 1943.

A. V. Hardy and S. D. Cummins, Studies of acute diarrheal diseases; a preliminary note on clinical response to sulfadiazine therapy. Pub. Health Rep., 58:693-696, 1943.

infections, but it is important to view it in the proper perspective. More general availability and use of sanitary facilities are of basic importance. Furthermore, it should be remembered that adequate feeding, medical, or at least nursing, supervision, and instruction of mothers is essential to any long-range program for the reduction of infant mortality. In the treatment of the disease itself, proper management, with particular emphasis on combatting dehydration and supervision of feeding, is basic.

SUMMARY

In a series of forty cases of bacillary dysentery, observed in Puerto Rican children under four years of age, definite benefit was observed following the use of sulfaguanidine. Improvement was manifest both in terms of the duration of the diarrhea and the duration of the infection.