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Shigella species from Addis Ababa: frequency of isolation and *in vitro* drug sensitivity

By MESSELE GEDEBOU and ALEBACHEW TASSEW

Department of Medical Microbiology and Parasitology, Faculty of Medicine, Addis Ababa University, P.O. Box 1176, *Addis Ababa, Ethiopia*

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SUMMARY

One hundred and five shigella isolates from Addis Ababa were studied to determine serogroup frequency and *in vitro* antibacterial drug sensitivity.

About 70% of the isolates were *Shigella flexneri* followed by *Sh. dysenteriae* (15%), *Sh. boydii* (10%) and *Sh. sonnei* (5%). All or most of the strains were susceptible to cephalothin, gentamicin, kanamycin, polymyxin B and trimethoprimsulphamethoxazole. Frequencies of susceptibility to ampicillin, carbenicillin and chloramphenicol were, respectively, 79, 80 and 75%. Only 37, 23 and 58% were susceptible to streptomycin, sulphadiazine and tetracycline, respectively.

Resistance to one or more drugs was detected in 85% while 72% were multiply resistant. There were 24 different resistance patterns, varying from resistance to one drug to resistance to seven drugs.

The findings have been compared with reports from other countries. This study and several others cited support the view that trimethoprim-sulphamethoxazole is the best alternative drug for treatment of shigellosis particularly in regions with multiple drug-resistant strains.

INTRODUCTION

Reports from various areas suggest that one serogroup of shigella is prevalent in an area for a particular period of time, usually for a number of years (Aoki, 1968; Controni, Friedman & Ficke, 1978; Gillies, 1964; Ross, Controni & Khan, 1972).

Resistance to antibacterial drugs in shigella is being reported increasingly from various parts of the world. Shigella strains are particularly noted for their multiple drug resistance. Such strains have been the cause of several outbreaks and epidemics in both developing and developed countries (Aoki *et al.* 1969; Byers, Dupont & Goldschmidt, 1976; Chun & Seol, 1978; Davies, Farrant & Uttley, 1970; Farr & Dekle, 1967; Gangarosa *et al.* 1972; Gebre-Yohannes & Limenih, 1980; Martin *et al.* 1970; Mero, 1976; Olarte, Filloy & Galindo, 1976; Ross *et al.* 1972; Salzman, Scher & Moss, 1967; Urban, 1972).

Very little information is available on the antibacterial drug sensitivity and the frequency of isolation of *Shigella* species in Ethiopia. The drug sensitivity of a few shigella isolates from Addis Ababa was first presented at conferences of the Ethiopian Medical Association (Gedebou, Tassew & Akalu, 1977; Gedebou &

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Tassew, 1979). Later, Gebre-Yohannes & Limenih (1980) reported on multiple drug resistance in shigella and the frequency of serogroups isolated in their laboratory. The present study was initiated to determine the frequency of isolation of shigella serogroups in Addis Ababa and to assess the drug sensitivity patterns of the isolates.

MATERIALS AND METHODS

Sources of shigella strains

About 77 % of the strains in this study were isolated from stools or rectal swabs from adult diarrhoeal patients attending the Black Lion Teaching Hospital, the remaining strains were obtained from other hospital laboratories in Addis Ababa. These strains were collected mostly between 1975 and 1980.

Culture media

All culture media used in this work were prepared from Difco dehydrated powders. MacConkey agar, SS agar and Selenite F broth were used for primary isolation. Various other media were prepared as needed for biochemical characterization and identification of the non-lactose fermenting isolates.

Antisera

Shigella polyvalent and group antisera from Difco were employed to confirm the biochemical identification of shigella and speciate the strains.

Antibacterial drugs

The drugs for disk diffusion sensitivity testing were obtained from Pfizer in the following concentrations: ampicillin (Amp), 10 μg; carbenicillin (Car), 50 μg; cephalothin (Cep), 30 μg; chloramphenicol (Chl), 30 μg; gentamicin (Gen), 10 μg; kanamycin (Kan), 10 μg; polymyxin B (Pol), 300 units; streptomycin (Str), 30 μg; sulphadiazine (Sul), 150 units; tetracycline (Tet), 30 μg; trimethoprim-sulphamethoxazole (Tri-sul), 25 μg.

Isolation and identification of shigella

Stools or rectal swabs were inoculated onto MacConkey and SS agar and into a tube of Selenite F broth and incubated overnight at 35–37 °C. Non-lactose fermenting colonies were further subcultured and characterized biochemically following conventional procedures (Edwards & Ewing, 1972). Biochemically identified shigella were serogrouped by slide agglutination with shigella antisera. Strains obtained from other laboratories were also similarly characterized.

Antibacterial drug susceptibility testing

All strains identified as shigella were tested for drug sensitivity using the agar disk diffusion technique (Bauer *et al.* 1966). The standardized inoculum of each isolate was swabbed onto a Mueller–Hinton agar plate followed by the disks after drying for 3–5 min. A standard strain of *Escherichia coli* sensitive to all antibacterial drugs used in this study was routinely tested as a control. After appropriate incubation, the diameters of the zones of inhibition around the disks were measured in mm using slide calipers. Interpretations of the measurements as sensitive,

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Table 1. *Sensitivity of* 105 *strains of shigella to antibacterial drugs*

Shigella		Percent susceptible to										
Species	No. of strains	Amp	Car	Cep	Chl	Gen	Kan	Pol	Str	Sul	Tet	Tri-Sul
Sh. dysenteriae	16	75	69	100	63	100	100	100	19	25	44	100
Sh. flexneri	73	80	80	96	75	100	97	100	40	19	59	97
Sh. boydii	11	82	91	100	91	91	91	91	46	46	83	100
Sh. sonnei	5	80	100	100	80	100	100	100	40	0	60	100
All species	105	79	80	97	75	99	97	99	37	23	58	98

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Table 2. *Resistance to one or more drugs and multiple resistance in shigella*

Resistant to	Percent resistance				
	Sh. dysenteriae (16 strains)	*Sh. flexneri* (73 strains)	*Sh. boydii* (11 strains)	*Sh. sonnei* (5 strains)	All species (105 strains)
One drug only	6	12	18	20	12
Two drugs only	19	37	27	60	34
Three drugs only	6	11	18	0	11
Four drugs only	25	4	9	20	9
Five drugs only	6	3	9	0	4
Six drugs only	19	12	0	0	11
Seven drugs only	0	6	0	0	4
One or more drugs	81	85	82	100	85
Two or more drugs	75	73	64	80	72

intermediate or resistant were made according to the recommended interpretative table (Matsen & Barry, 1974). Since our strains were mostly either sensitive or resistant, the very few 'intermediate' readings were considered sensitive.

RESULTS

Frequency of isolation of shigella species

Sh. flexneri was the most commonly isolated species (70%) followed by *Sh. dysenteriae* (15%), *Sh. boydii* (10%) and *Sh. sonnei* (5%).

Sensitivity to antibacterial drugs

The sensitivity of all 105 shigella strains is shown in Table 1. Most of the strains were sensitive to cephalothin, gentamicin, kanamycin, polymyxin B and trimethoprim-sulphamethoxazole. Sensitivity to ampicillin, carbenicillin and chloramphenicol varied between 75 and 80%. Streptomycin and sulphadiazine were mostly ineffective while only 58% of the strains were sensitive to tetracycline. The frequency of sensitivity to carbenicillin, chloramphenicol, streptomycin, sulphadiazine and tetracycline varied for the four species, *Sh. dysenteriae* being the least sensitive. Only 16 strains (15%) were sensitive to all 11 drugs used in this study.

Resistance to antibacterial drugs

Resistance to one or more drugs in shigella is shown in Table 2. Resistance to one or more drugs was detected in 81% *Sh. dysenteriae*, 85% *Sh. flexneri*, 82% *Sh. boydii* and 100% *Sh. sonnei*. About 85% of all the shigella strains, were resistant to one or more drugs. The most frequent resistance was to two drugs only (34%) followed by resistance to one drug (12%), six drugs (11%) and to three drugs (11%). Resistance to four drugs, five drugs and seven drugs respectively, was about 9, 4 and 4%.

Multiple drug resistance, i.e. resistance to two or more drugs, was detected in *Sh. dysenteriae* (75%), *Sh. flexneri* (73%), *Sh. boydii* (64%) and in *Sh. sonnei* (80%) (Table 2). About 72% of the 105 strains of shigella were multiply resistant.

There were seven different resistance patterns in *Sh. dysenteriae*, 16 in *Sh.*

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Table 3. *Shigella patterns of resistance to antibacterial drugs*

Species	Resistance pattern	No. of strains
Sh. dysenteriae	Str	1
	Str/Sul	3
	Str/Sul/Tet	1
	Car/Str/Sul/Tet	1
	Chl/Str/Sul/Tet	3
	Amp/Car/Str/Sul/Tet	1
	Amp/Car/Chl/Str/Sul/Tet	3
Sh. flexneri	Sul	8
	Tet	1
	Chl/Tet	1
	Str/Sul	17
	Sul/Tet	9
	Str/Sul/Tet	6
	Str/Sul/Tri-sul	1
	Chl/Str/Sul	1
	Chl/Str/Sul/Tet	1
	Kan/Str/Sul/Tet	2
	Amp/Car/Chl/Str/Sul	2
	Amp/Car/Chl/Str/Sul/Tet	8
	Amp/Car/Chl/Kan/Str/Sul	1
	Amp/Car/Cep/Chl/Kan/Str/Sul	1
	Amp/Car/Chl/Str/Sul/Tet/Tri-Sul	1
	Amp/Car/Cep/Chl/Str/Sul/Tet	2
Sh. boydii	Str	1
	Sul	1
	Sul/Tet	1
	Str/Sul	2
	Amp/Str/Tet	1
	Amp/Car/Chl/Tet	1
	Cep/Str/Sul	1
	Gen/Kan/Pol/Str/Sul	1
Sh. sonnei	Sul	1
	Str/Sul	2
	Amp/Tet	1
	Chl/Str/Sul/Tet	1

flexneri, eight in *Sh. boydii* and four in *Sh. sonnei* (Table 3). In all, 24 different patterns of resistance were observed.

DISCUSSION

Our finding of *Sh. flexneri* as the most frequent isolate (70%) revealed this species as predominant in the aetiology of shigellosis in Addis Ababa during the particular period of study. This was in agreement with the report of Gebre-Yohannes & Limenih (1980) on shigella isolated in their laboratory in Addis Ababa at about the same period. It is not known, however, whether all their isolates were from patients in Addis Ababa, since their laboratory is the National Laboratory called upon to study epidemics anywhere in the country. They isolated *Sh. flexneri* most frequently (49%) but at a lower percentage than ours (70%); *Sh. dysenteriae* was

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second in frequency of isolation (29 %) followed by *Sh. boydii* (12 %) and *Sh. sonnei* (10 %). This order of frequency was exactly similar to ours. Since there was no earlier study in Addis Ababa this order of frequency cannot be compared to that of an earlier period.

In contrast, *Sh. sonnei* was the predominant serogroup in the United States in the period of 1966 to 1974 (Neu *et al.* 1975; Byers *et al.* 1976; Controni *et al.* 1978). The same trend was reported from Sweden in 1970 (Urban, 1972), from United Kingdom (Gillies, 1964) and from the Far East (Aoki, 1968). The position of *Sh. dysenteriae* as the second most frequent isolate (15 % in our study) and *Sh. sonnei* as the least frequent isolate (5 %) in Addis Ababa is in remarkable contrast to reports from the United States (Controni *et al.* 1978), Sweden (Urban, 1972) and the Far East (Aoki, 1968), where *Sh. dysenteriae* was rarely if ever isolated while *Sh. sonnei* was predominant. In Somalia, however, *Sh. dysenteriae* was the most frequently isolated species (over 60 %) (Mero, 1976).

The predominant *Shigella* species is apparently alternating between *Sh. flexneri* and *Sh. sonnei* dependent upon time and geographical region. In the years prior to about 1964, *Sh. flexneri* was the most commonly isolated serogroup in the United States (Reller, Gangarosa & Brachman, 1970), the Far East (Aoki, 1968) and Europe (cited by Ross *et al.* 1972). Since 1974, *Sh. flexneri* has been isolated with increasing frequency in some regions of the United States while the incidence of *Sh. sonnei* is decreasing (Controni *et al.* 1978).

Shigella strains are generally sensitive to cephalothin, gentamicin, kanamycin, polymyxin B and trimethoprim-sulphamethoxazole as found in our study and reported by several other workers (Neu *et al.* 1975; Farrar & Eidson, 1971; Ross *et al.* 1972; Gebre-Yohannes & Limenih, 1980; Controni *et al.* 1978). The frequency of sensitivity to all the drugs in this study (15 %) was much lower than that (30 %) of Gebre-Yohannes & Limenih (1980).

The frequency of resistance of our shigella strains to one or more antibacterial drugs, 85 %, is higher than that of strains from Sweden, 60 % (Urban, 1972), United States (New York), 66 % (Neu *et al.* 1975), Soviet Union, 66 % (cited by Urban, 1972) and Korea, 80 % (Chun & Seol, 1978). It should be noted, however, that our study comprised all four serogroups of shigella while the studies cited were either on *Sh. sonnei* only or on both *Sh. flexneri* and *Sh. sonnei*. The number of drugs used in those studies was also less than ours. Our finding was also in significant contrast to that of Gebre-Yohannes & Limenih (1980) who reported 70 % of resistance to one or more drugs of strains from the same country but perhaps from different cities.

It is of particular note that of the 11 drugs tested, single resistance was found only against streptomycin, sulphadiazine and tetracycline (Table 3) similar to the finding from Japan (Mitsuhashi, 1969). Resistance to sulphadiazine was the most frequent (10 %). Single resistance only to ampicillin was found in *Sh. sonnei* by Smith, Bremner & Datta (1974) and to ampicillin, tetracycline or sulphisoxazole by Neu *et al.* (1975). Single resistance was reported only to tetracycline or sulphonamide by Chun & Seol (1978) from Korea.

The resistance patterns of our strains were generally different from those of other reports (Neu *et al.* 1975; Byers *et al.* 1976; Mitsuhashi, 1969; Chun & Seol, 1978). The most common resistance pattern was that of streptomycin/sulphadiazine

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(23%) followed by ampicillin/carbenicillin/chloramphenicol/streptomycin/sulphadiazine/tetracycline resistance (11%). The streptomycin/sulphadiazine resistance was found in all four species of shigella. The two patterns accounted for 33% of the multiply drug resistant shigella. The latter pattern of resistance to six drugs detected in *Sh. dysenteriae* and *Sh. flexneri* (Table 3) was similar (except for the additional resistance to carbenicillin) to that of one of the strains of *Sh. dysenteriae* type 1 involved in the 1972 dysentery outbreak in Mexico City (Olarte *et al.* 1976).

The resistance pattern of the *Sh. dysenteriae* type 1 pandemic strain of Central America (Mata *et al.* 1970) and Mexico (Datta & Olarte, 1974), i.e. resistance to chloramphenicol, tetracycline, streptomycin and sulphadiazine, was also found among our strains of *Sh. dysenteriae*, *Sh. flexneri* and *Sh. sonnei* (Table 3). This pattern in shigella was also reported among strains from United States (Controni *et al.* 1978), Japan (Mitsuhashi, 1969), Korea (Chun & Seol, 1978) and Sweden (Urban, 1972).

Because of lack of published information on previous frequency of resistance, we cannot determine whether the incidence of ampicillin resistance in our study, i.e. 21%, indicates an increase. This frequency of ampicillin resistance is very similar to that reported by Gebre-Yohannes & Limenih (1980) on strains isolated at about the same period. From the trend of increasing frequency of resistance to ampicillin reported by various investigators (Byers *et al.* 1976; Controni *et al.* 1978; Davies *et al.* 1970; Gordon *et al.* 1975; Lexomboon *et al.* 1972; Nelson *et al.* 1976; Ross *et al.* 1972; Urban, 1972), it is not unreasonable to consider our 21% of ampicillin resistance a reflexion of the same trend. Twenty-one of the 22 ampicillin resistant strains were also resistant to two or more other drugs. The majority were resistant to four, five or six other drugs including carbenicillin, chloramphenicol, streptomycin, tetracycline, sulphadiazine and cephalothin (Table 3).

Shigella resistance to the commonly used drugs including ampicillin is increasingly being reported from various institutions and regions of the world, indicating the need for a newer and more effective drug. Although our strains were highly susceptible *in vitro* to cephalothin, gentamicin, kanamycin and polymyxin B, none of these drugs can replace ampicillin as the drug of choice in shigellosis because of their known clinical ineffectiveness (Controni *et al.* 1978).

Nearly all our shigella strains (98%) were sensitive to trimethoprim-sulphamethoxazole. This is in agreement with the findings from Thailand (Lexomboon *et al.* 1972), United States (Byers *et al.* 1976), Sweden (Frazen, Lidin-Janson & Nygren, 1972), England (Jarvis & Scrimgeour, 1970) and from Ethiopia (Gebre-Yohannes & Limenih, 1980). Evaluation of ampicillin and trimethoprim-sulphamethoxazole in the treatment of shigellosis has demonstrated the greater effectiveness of trimethoprim-sulphamethoxazole in producing bacteriological cure as well as better clinical response (Chang *et al.* 1977; Nelson *et al.* 1976; Rodriguez *et al.* 1978). Our finding, with shigella strains, of the high frequency of *in vitro* multiple drug resistance but nearly uniform sensitivity to trimethoprim-sulphamethoxazole and similar reports by others cited strongly support the current view that this drug should be the choice for treatment of shigellosis particularly in regions with strains of high frequency of multiple drug resistance.

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