Communicable Diseases

Drug resistance in *Shigella dysenteriae*, *S flexneri* and *S boydii* in England and Wales: increasing incidence of resistance to trimethoprim

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Abstract

A total of 2753 strains of shigella belonging to subgroups A, B, and C that were isolated from patients in England and Wales during the period from 1979 to mid-1983 were studied. Of these, 1690 (61%) were from patients recently returned from abroad or in contact with recent travellers, and 760 (45%) of these affected travellers from the Indian subcontinent. The number of strains resistant to sulphonamides and streptomycin remained at a high level throughout (average 76% and 72% respectively). Resistance to tetracyclines, ampicillin, and chloramphenicol rose, reaching 63%, 51%, and 48%, respectively, in 1982. Strains resistant to trimethoprim were seen in substantial numbers for the first time and increased from 1.3% of all strains in 1979 to 9.9% in 1982 and 16.8% in the first half of 1983.

The proportion of patients with recent foreign contact was notably smaller among those with strains resistant to trimethoprim than among those with strains sensitive to trimethoprim. The increase in resistance to trimethoprim might partly result from the use in Britain of compounds containing trimethoprim for the treatment of shigellosis.

Introduction

Infections caused by *Shigella dysenteriae*, *S flexneri*, and *S boydii*—that is subgroups A, B, and C—in patients in England and Wales are often acquired abroad, and the incidence of such infections has not decreased in recent years. In contrast, *S sonnei*—that is subgroup D—is indigenous but its incidence has decreased considerably since the 1960s when it accounted for more than 90% of all shigella infections. As a result infections caused by subgroups A, B, and C accounted for one quarter of all shigella infections reported to the Communicable Disease Surveillance Centre in England and Wales during the period 1979–82.

We have previously reported that the incidence of drug resistance in members of shigella subgroups A, B, and C

increased rapidly during the period 1974–78 while that in *S sonnei* decreased.¹ In particular, the incidence of resistance to sulphonamides, streptomycin, tetracyclines, ampicillin, and chloramphenicol increased. We report the incidence of drug resistance in these organisms during the period 1979 to mid-1983 and note in particular the appearance of appreciable numbers of strains resistant to trimethoprim.

Methods

Bacterial strains—During the period 1979 to mid-1983 2753 strains of *S dysenteriae*, *S flexneri*, and *S boydii* isolated in England and Wales from human faeces were examined in the Division of Enteric Pathogens, Central Public Health Laboratory, London. *S sonnei* strains are not referred to this laboratory. All the strains were identified as members of the genus shigella by the methods of Edwards and Ewing² and were serotyped according to the internationally accepted scheme.³

Drug resistance tests—Initial screening for resistance to ampicillin, chloramphenicol, gentamicin, neomycin or kanamycin, streptomycin, and tetracyclines was performed by a strip diffusion method.⁴ Strains found to be resistant by this method were further tested by an agar dilution method.⁵ Resistance to sulphonamides, trimethoprim, furazolidone, and nalidixic acid was also tested by the agar dilution method. Table I shows the drug concentrations used in the agar dilution tests.

TABLE I—Drug resistance of 2753 shigella strains belonging to subgroups A, B, and C; England and Wales from 1979–mid 1983

	Concentration (mg/l)	No resistant	%
Ampicillin	8	1164	42.3
Cephaloridine	4	172	6.2
Cephalexin	4	23	0.8
Chloramphenicol	8	1141	41.4
Furazolidone	20	1	0.04
Gentamicin	4	15	0.5
Mecillinam	2	196	7.1
Nalidixic acid	20	4	0.1
Neomycin	8	51	1.9
Streptomycin	16	1981	72.0
Sulphonamides	100	2087	75.8
Tetracycline	16	1675	60.8
Trimethoprim	0.5	161	5.8
No fully sensitive		428	15.5
No tested		2753	100

Transfer and mobilisation of trimethoprim resistance—Fifty five strains resistant to trimethoprim were tested for the ability to transfer trimethoprim resistance to a strain of *Escherichia coli* K12, F⁺-lac⁺ (strain No 14R525) resistant to nalidixic acid.⁶ If no direct transfer was detected, mobilisation of trimethoprim resistance was attempted using autotransferring plasmids of several different compatibility groups as the mobilising vectors.⁷

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Results

Of the 2753 strains of shigella examined, 256 (9.3%) were *S. dysenteriae*, 2101 (76.3%) were *S. flexneri*, and 396 (14.4%) were *S. boydii*. One thousand six hundred and ninety strains (61.4%) were isolated from patients recently returned from abroad or in contact with recent travellers, and 760 (45%) of these were in travellers from the Indian subcontinent.

Two thousand three hundred and twenty five (84.5%) of the strains were resistant to one or more drugs. Table I shows the incidence of resistance to each drug. Table II summarises the changing incidence of resistance to some important drugs during the period of study and during our previous study. In particular, between 1979 and mid-1983 the proportion of strains resistant to ampicillin rose from 30% to 47.6% and to chloramphenicol from 27% to 52.1%. Furthermore, though table II shows the lower concentrations of these drugs used, most isolates were also resistant to concentrations of at least 256 mg/l.

TABLE II—Drug resistance among strains of shigella subgroups A, B, and C isolated in England and Wales, 1974–83. Figures are percentage resistant

	1974	1975	1976	1977	1978	1979	1980	1981	1982	1983*
Ampicillin	2	3	10.5	15.5	24	30	37.9	49	51	47.6
Chloramphenicol	2.6	5.4	10.2	15.2	18.5	27	38.2	49	48	52.1
Sulphonamide	68	75	75	79	78	78	72.6	77	77	72.7
Streptomycin	43	49	56	64	66	70	69.1	74	76	71.7
Tetracycline	15	26	35	42	51	53.3	58.3	66	63	69.2
Trimethoprim	0.3	0.2	0.2	0.0	0.5	1.3	2.2	5.3	9.9	16.8
No tested	343	464	469	500	594	627	638	617	505	286

*First half only.

TABLE III—Foreign contact among patients with infections due to shigella subgroups A, B, and C in England and Wales from 1981 to mid 1983

	Foreign contact		Total
	No*	Yes (%)	
Trimethoprim sensitive	480	869 (64.4)	1349
Trimethoprim resistant	79	60 (43.2)	139
Total	559	929	1488

($\chi^2 = 24.1$, $p < 0.001$).

*Either no foreign contact or no information received.

Strains resistant to trimethoprim comprised only 1.3% of strains isolated in 1979, but by 1983 16.8% of strains were resistant to this drug.

Trimethoprim resistance was transferable in 29 of 55 strains tested (52.7%), directly in 28 strains (50.9%) and by mobilisation in one strain (1.8%). In 15 of 28 strains with transferable trimethoprim resistance (53.6%), the plasmids that conferred resistance to trimethoprim did not specify resistance to other antibiotics; in 13 strains (46.4%) trimethoprim resistance was cotransferred with resistance to other antibiotics. In the strain with resistance able to be mobilised, the trimethoprim resistance plasmid also conferred resistance to sulphonamides. An account of these plasmids will be presented elsewhere.

We have previously suggested that the increase in resistance to ampicillin, chloramphenicol, streptomycin, sulphonamides, and tetracyclines might be due to the use of the respective antimicrobial drugs in countries other than Britain.¹ With this in mind, the incidence of foreign travel, or contact with recent travellers, among patients with strains resistant to trimethoprim was compared with that among patients with strains sensitive to trimethoprim (table III). Significantly fewer patients with strains resistant to trimethoprim had recently travelled abroad or had been in contact with recent travellers ($\chi^2 = 24.1$, $p < 0.001$).

Discussion

Epidemics of bacillary dysentery, especially those caused by *S. dysenteriae* 1 (Shiga's bacillus), continue to occur in tropical

areas and may be accompanied by a high level of mortality. For example, a widespread epidemic in 1969 and 1970 originated in Guatemala and spread to most other Central American countries: 120 000 cases and 13 000 deaths were reported.⁸ Returning travellers imported the infection into the United States, giving rise to 140 cases in the years 1970–2 in comparison with only 11 cases in the years 1965–8.⁹ A similar epidemic occurred in Bangladesh in 1972,¹⁰ and another began in Central Africa in 1979.¹¹ In all these epidemics the causative organisms possessed plasmid mediated, multiple drug resistance.

Infections due to members of shigella subgroups A, B, and C occur in Britain but are often acquired abroad, especially in the Indian subcontinent and in North Africa. We have previously reported that the incidence of drug resistance in these strains rose rapidly during the period 1974–8.¹ In particular, we drew

attention to the sudden increase in the incidence of ampicillin resistance. Ampicillin is widely regarded as the drug of choice for the treatment of severe bacillary dysentery and is used routinely in many countries. We have suggested that the rapid increase in drug resistance observed in strains isolated in Britain might be the result of the uncontrolled use of antibiotics in certain developing countries. In the present study we have seen a continuing rise in the incidence of resistance to ampicillin, chloramphenicol, and tetracycline among strains of shigella subgroups A, B, and C isolated in Britain during the period 1979 to mid-1983. In addition, a sudden increase in the incidence of trimethoprim resistance occurred—an important finding as trimethoprim is regarded as the drug of choice for the treatment of bacillary dysentery caused by strains resistant to ampicillin. In this case, however, the statistical evidence does not support the suggestion that trimethoprim resistance has arisen entirely as a result of the use of antibiotics in other countries. Notably fewer patients with strains resistant to trimethoprim had a history of foreign travel or contact with travellers than did patients with strains sensitive to trimethoprim. Furthermore, the increase in trimethoprim resistance coincided with products containing trimethoprim but not sulphonamides becoming available in Britain. In this respect it may be important that more than half of the trimethoprim resistance plasmids identified conferred resistance to trimethoprim but not to sulphonamides. Co-trimoxazole resistance, however, has recently been observed in family outbreaks of *S. dysenteriae* 1 in rural Bangladesh, and the overuse of antibiotics by local practitioners in that country has been suggested as a contributory factor.¹² Thus it must be considered that the use of products containing trimethoprim in both Britain and developing countries has led to the increased incidence of trimethoprim resistance in shigella strains isolated in Britain.

Although bacillary dysentery is often a mild, self limiting disease in otherwise healthy subjects, the severe symptoms and high mortality seen in epidemics in the tropics indicate that prompt antibiotic treatment may be life saving, particularly in the very young, the very old, and the malnourished. In such circumstances it may be necessary to begin treatment without the benefit of the results of in vitro sensitivity tests. In the central African epidemic the causative organisms were resistant

to ampicillin, and treatment with co-trimoxazole was consequently adopted and found to be effective in reducing mortality. Nevertheless, resistance to trimethoprim was rapidly acquired as the epidemic progressed, presumably in response to selective pressures imposed by the use of co-trimoxazole.¹³ Treatment with nalidixic acid was subsequently introduced, but the impact of this on fatality has not yet been evaluated.

The need for antibiotic treatment of patients in Britain can only be assessed individually on clinical grounds. The rapidly increasing range of drug resistance among the shigella strains studied underlines the value of performing in vitro sensitivity tests before starting antibiotic treatment whenever possible. The choice of antibiotic for initial treatment without benefit of such tests is becoming increasingly restricted.

References

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- ² Edwards PR, Ewing WH. *Identification of enterobacteriaceae*. Minneapolis: Burgess Publishing Company, 1972.
- ³ Subcommittee on Taxonomy of the Enterobacteriaceae. Report. *International Journal of Systematic Bacteriology* 1958;**8**:93-5.

In a patient with a family history of malignant hyperthermia does a normal muscle biopsy specimen give 100% assurance that that patient will not have a hyperthermic reaction?

Muscle biopsy followed by pharmacological testing of living muscle tissue in vitro has become the preferred method of screening members of families with malignant hyperpyrexia for susceptibility. Until recently each laboratory used its own test regimen and applied its own criteria before making the diagnosis; most investigators admitted to nominating an equivocal result to be susceptible and thereby increasing the incidence of false positives. Standardisation of the test protocol has been urged by Rosenberg¹ and by members of the newly established European Malignant Hyperpyrexia Group,² so that diagnostic criteria may be agreed. The early suggestions of both variable penetrance and expressivity emerged from the practice of screening families with serum creatine phosphokinase estimations, but this is now generally accepted to be unreliable. Muscle testing seems not to have the same variability, there being no published account of generation skipping. It is doubtful whether any diagnostic test can provide 100% assurance, though muscle testing for malignant hyperpyrexia has yet to be shown to be fallible.—F R ELLIS, reader in anaesthetics, Leeds.

¹ Rosenberg H, Reed S. In vitro contracture tests for susceptibility to malignant hyperthermia. *Anaesth Analg* 1983;**62**:415-20.

² Ellis FR, Fletcher R, Halsall PJ, et al. A protocol for the investigation of patients for malignant hyperpyrexia. *Br J Anaesth* (in press).

How reliable are the findings obtained from (a) open lung biopsy and (b) closed lung biopsy in the diagnosis of mesothelioma of the pleura?

The histological appearance of a mesothelioma is characterised by the presence of two neoplastic components—one of epithelial type and the other of connective tissue type.¹ In different patients either type may be dominant. In addition, a wide variation in the distribution of epithelial and connective tissue neoplastic components may be seen in different parts of the same tumour. Thus if a needle biopsy specimen of the pleura is taken from one site only it may contain only one of the two components of a mesothelioma. If only epithelial tumour is seen an absence of mucin secretion by special stains will be consistent with—but not diagnostic of—a mesothelioma. On the other hand, the presence of epithelial mucin will positively indicate a diagnosis of adenocarcinoma. If the biopsy specimen shows only connective tissue tumour the differential diagnosis between a mesothelioma and a sarcoma may remain unresolved. The chance of obtaining a definite diagnosis of mesothelioma from a single, limited needle biopsy is small.² Since the histological diagnosis of mesothelioma

- ⁴ Anderson ES, Threlfall EJ. The characterisation of plasmids in the enterobacteria. *J Hyg (Lond)* 1974;**72**:471-87.
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- ⁹ Weissman JB, Morton KI, Lewis JN, Friedmann CTH, Gangarosa EJ. Impact in the United States of the *Shiga dysentery* pandemic in Central America and Mexico. Review of surveillance data through 1972. *J Infect Dis* 1974;**129**:218-23.
- ¹⁰ Rahaman MM, Huq I, Dey CR, Kibriya AKMG, Curlin G. Ampicillin-resistant *Shiga bacillus* in Bangladesh. *Lancet* 1974;ii:406-7.
- ¹¹ Frost JA, Rowe B, Vandepitte J, Threlfall EJ. Plasmid characterisation in the investigation of an epidemic caused by multiply resistant *Shigella dysenteriae* type 1 in Central Africa. *Lancet* 1981;iii:1074-6.
- ¹² Zaman K, Yunus MD, Baqui AH, Hossain KMB, Khan MU. Co-trimoxazole-resistant *Shigella dysenteriae* type 1 outbreak in a family in rural Bangladesh. *Lancet* 1983;iii:796-7.
- ¹³ Frost JA, Rowe B, Vandepitte J. Acquisition of trimethoprim resistance in epidemic strain of *Shigella dysenteriae* type 1 from Zaire. *Lancet* 1982;ii:963.

is so dependent on adequate sampling of the tumour, a thoracotomy with multiple larger samples will clearly give a greater chance of success. The disadvantage of open thoracotomy is the tendency for mesothelioma subsequently to spread through the incision site and form a mass in the subcutaneous tissue.³ Because of this potential complication thoracotomy has been avoided as much as possible, but recent clinical comment has affirmed that in most cases no additional pain or distress has been caused to patients by this procedure, and only rarely does the tumour ulcerate through the skin. A useful compromise may be obtained by using thoracoscopy techniques whereby a relatively small incision in the chest wall enables the pleural cavity to be inspected and multiple biopsy specimens taken. In all investigative procedures if pleural fluid is present this should be examined by cytological methods.—STEPHEN JONES, consultant pathologist, Nottingham.

¹ McCaughey WTE. Criteria for diagnosis of diffuse mesothelial tumours. *Ann NY Acad Sci* 1965;**132**:603-13.

² Elmes PC. Therapeutic openings in the treatment of mesothelioma. In: *Biological effects of asbestos*. (IARC Scientific Publications No 8.) Lyon: International Agency for Research on Cancer, 1973:277-80.

³ Jones JSP, Lund C, Planteydt HT. *Mesothelioma atlas*. Lancaster: MTP Press Ltd (in press).

What legal powers, if any, does a doctor have to arrange for compulsory admission of a patient who has attempted suicide?

A suicidal attempt does not in itself necessarily justify compulsory admission to hospital. Nevertheless, if the patient's known history, together with the circumstances at the time of the attempt, lead the doctor to suspect that the patient is suffering from mental disorder then compulsory admission will be indicated. It is not necessary at this stage to decide which legal category of mental disorder is present (mental illness, psychopathic disorder, mental impairment, or severe mental impairment). A potentially lethal overdose and a declared determination to die would raise sufficient concern about the patient's safety to justify admission to hospital compulsorily. It is sufficient to suspect that the patient may be suffering from mental disorder. In an urgent situation the patient may be admitted under section 4 of the new Mental Health Act 1983¹ necessitating an application from the patient's nearest relative (not any relative as previously) or from a mental welfare officer (approved social worker from 28 October 1984), together with a recommendation from one medical practitioner that the patient is believed to be suffering from mental disorder and requires urgent admission for assessment.—R BLUGLASS, professor of forensic psychiatry, Birmingham.

¹ Mental Health Act 1983. London: HMSO, 1983.

² Bluglass R. *A guide to the Mental Health Act 1983*. London and Edinburgh: Churchill Livingstone, 1983.