A 6-year survey of resistance patterns of urinary tract pathogens in general practice

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Summary

A survey of resistance patterns of urinary pathogens causing infections in general practice over the period 1964-69, including 3100 cases of which 2718 were caused by *Bacterium coli*, *Proteus* species or coliform organisms has been made. The resistance patterns of the enterobacteria have been examined and reveal a rise in incidence of sulphonamide-resistant strains from 1964 to a peak of 61.3% in 1967 followed by a symmetrical fall to return to 24.9% in 1969. Ampicillin and nalidixic acid were the only two drugs of twelve to show a constant rise in incidence of resistant strains although the figures are much lower reaching peaks of 11.1% in 1969 for ampicillin and 3.2% in 1969 for nalidixic acid. The other drugs surveyed show less definite change; tetracycline constantly shows an incidence of about 30% resistance and nitrofurantoin varies between 2.7% and 8.7%. Low incidences of resistance against trimethoprim-sulphonamide mixture are recorded: 1.5% in 1968 and 2.0% in 1969. *Proteus* strains, treated separately, frequently show resistance to tetracycline, 90.3% in 1969, and to nitrofurantoin, 37.8% in 1969.

The incidence of multiple resistance is also increasing. Fifty-three percent of strains were resistant to at least one antibiotic and 6% to three or more in the period 1964-67 and 57.3% show resistance to at least one drug and 10.3% to three or more in the period 1967-69.

REALIZATION that enterobacteria possess the capacity to transfer antibiotic resistance among themselves has stimulated interest in the resistance patterns of normal bowel flora in human and animal populations (Maré, 1968; Datta, 1969; Gardner *et al.*, 1969; Moorhouse, 1969; Smith, 1969, 1970).

If it is accepted that urinary infections are caused by organisms usually present in the bowel (Grüneberg, 1969) any increase of resistance among the gut flora should be mirrored by an increase in urinary infections due to primarily resistant and multiply

resistant organisms. A survey of acute urinary pathogens isolated from general practice patients has been carried out in this area since 1964. In the first period of 40 months 6% of the coli, proteus, coliform organisms (CPC) were found to be resistant to three or more drugs and 53% to at least one (Robertson, 1968). A steep rise in the proportion of sulphonamide-resistant organisms was noted over this period and the present communication presents a continuation of this survey and an examination of resistance trends exhibited to individual drugs.

Materials and methods

All samples of urine received as normal practice from general practitioners during the period 1 January 1964 to 31 December 1969 were reviewed. Selection of cases for inclusion in the survey and all technical manipulations were similar to those previously described (Robertson, 1968) with the exception that from October 1968 'Oxoid' sensitivity test agar with 7% added horse blood was used for both isolation and sensitivity tests. The sensitivity test discs contained the following amounts of drugs, and organisms were recorded as resistant only if they grew right up to the edge of the disc: sulphafurazole 500 µg, streptomycin 25 µg, tetracycline 50 µg, nitrofurantoin 200 µg, ampicillin 25 µg, colistin 200 µg, nalidixic acid 30 µg, kanamycin 30 µg, chloramphenicol 10 µg, trimethoprim-sulphonamide mixture 25 µg, cephaloridine 25 µg and gentamicin 10 µg. The terminology used, e.g. *Bacterium coli* rather than *Escherichia coli*, was chosen as likely to be understood by clinicians in general and no serology or biochemical tests were carried out to prove strains were *Escherichiae*.

Results

Table 1 shows the numbers of each species isolated and their percentage of the total. 4.6% of infections are mixed and CPC organisms account for 87.5%. *Staphylococcus albus* causes only 4.3% and *Ps. pyocyanea* only very rarely is the cause of acute urinary infection outside hospital.

Table 2 shows the total number of infections in the series in each of the years studied and the percentages of infecting organisms resistant to up to eleven drugs.

Table 3 shows a similar breakdown of CPC infections. In both tables all the organisms were not necessarily tested against all eleven drugs. The removal of Gram-positive organisms and *Ps. pyocyanea* from the calculations significantly reduced the percentage of resistant strains only in the cases of kanamycin and nalidixic acid.

It is evident that the steep increase in incidence of CPC organisms resistant to sulphonamide reached

a peak in 1967 and since then has been progressively dropping, describing an almost symmetrical curve. This is not attributable to the change in culture medium instituted in late 1968 as the trend had set in beforehand and this factor could not, in any case, have affected the upswing between 1964 and 1967. The percentage of CPC organisms showing resistance to ampicillin slowly doubled from 1965 to 1968 and then again dramatically in 1969 to reach 11.1%. The only other drug to which a steady rise in resistant strains has been demonstrated is nalidixic acid, which shows a slower rise, doubling from 1.6% to 3.2% over 1966-68 but remaining steady in 1969. Nitrofurantoin, a drug of similar usage and which might be expected to show a similar trend has varied roughly between 3% and 8% resistance over the 6-year period and tetracycline between 22% and 33% after an initial fall. The other drugs studied are less often used in domiciliary urinary infections or have not been generally available for long enough for comment to be valid; apart from the fall in resistance to cephaloridine between 1967 and 1968 the figures are not remarkable. The numbers of organisms tested against cephaloridine and gentamicin were the smallest in the series, 205 and 188 respectively.

TABLE 1. Numbers of each species isolated

Species	Total isolated	% of total
<i>Bacterium coli</i>	1882	60.7
<i>Coliforms</i>	437	14.0
<i>Pseudomonas</i> species	399	12.8
<i>Staphylococcus albus</i>	135	4.3
<i>Enterococcus</i>	67	2.1
<i>Pseudomonas pyocyanea</i>	13	1.1
<i>Staphylococcus aureus</i>	20	
<i>Streptococcus pyogenes</i>	2	
Mixed	145	4.6
Total strains	3100	99.6

TABLE 2. Percentage of isolations resistant to various antibiotics (all organisms)

Year	Total Infections	Su	S	T	F	K	A	Col	NG	SU/TR	Ceph	C	G
1969	810	29.1	11.1	31.5	9.5	7.9	11.8	26.4	16.6	3.7	—	—	—
1968	618	42.7	9.5	23.9	6.0	3.3	7.0	18.7	15.7	3.3	8.9	—	—
1967	575	62.3	10.2	34.5	3.8	1.7	6.3	23.7	9.8	—	16.2	2.2	0
1966	522	42.7	10.3	32.1	5.9	0.9	4.2	19.9	8.6	—	—	0.9	1.0
1965	373	27.9	7.5	27.4	7.2	3.0	3.1	19.5	—	—	—	1.8	—
1964	202	17.8	2.9	43.5	4.4	2.5	—	—	—	—	—	0.9	—
Total	3100												

Su=Sulphonamide, S=Streptomycin, T=Tetracycline, F=Nitrofurantoin, K=Kanamycin, A=Ampicillin, C=Chloramphenicol, G=Gentamicin, Col=Colistin, NG=Nalidixic Acid, SU/TR=Sulphonamide/Trimethoprim, Ceph=Cephaloridine.

TABLE 3. Percentage of isolations resistant to various antibiotics (CPC organisms)

Year	CPC Infections	Su	S	T	F	K	A	Col	NG	SU/TR	Ceph	C	G
1969	694	24.9	7.9	30.0	8.7	1.5	11.1	22.3	3.2	1.5	—	—	—
1968	526	43.1	6.5	22.5	4.8	0.7	6.3	14.9	3.2	2.0	6.9	—	—
1967	510	61.3	7.3	33.7	3.5	0.8	5.3	18.3	2.0	—	15.7	2.5	0
1966	472	41.9	8.6	30.6	5.2	0.0	3.9	19.0	1.6	—	—	0.5	1.1
1965	331	25.9	5.7	26.6	7.8	1.2	3.1	18.1	—	—	—	1.8	—
1964	185	15.1	1.6	42.1	2.7	0.0	—	—	—	—	—	0.5	—
Total	2718												

Su=Sulphonamide, S=Streptomycin, T=Tetracycline, F=Nitrofurantoin, K=Kanamycin, A=Ampicillin, Col=Colistin, NG=Nalidixic acid, SU/TR=Sulphonamide/Trimethoprim, Ceph=Cephaloridine, C=Chloramphenicol, G=Gentamicin.

TABLE 4. Percentages of *Proteus* resistant

Year	Total isolated	% resistant to									
		Su	S	T	F	A	Col	NG	K	C	SU/TR
1969	104	23.0	4.6	90.3	37.8	3.8	89.0	3.8	0.0	—	0.9
1968	52	54.0	0.0	88.8	23.5	3.9	95.2	2.0	0.0	—	—
1967	73	64.3	4.7	88.7	13.6	0.0	91.7	3.3	1.3	—	—
1966	74	39.1	2.7	89.1	22.9	1.3	87.8	5.7	0.0	0.0	—
1965	65	30.7	3.0	84.3	32.3	0.0	89.4	—	0.0	1.5	—
1964	31	12.9	3.2	96.7	16.1	—	—	—	0.0	3.2	—

Su=Sulphonamide, S=Streptomycin, T=Tetracycline, F=Nitrofurantoin, A=Ampicillin, Col=Colistin, NG=Nalidixic acid, K=Kanamycin, C=Chloramphenicol, SU/TR=Sulphonamide/Trimethoprim.

Proteus species causing urinary infections in the Mansfield area have increased in resistance to nitrofurantoin over the period 1963–67 reaching a figure of 68% (Macis & Ward-McQuaid, 1968) but it is not clear whether all these organisms came from domiciliary sources. The figures for *Proteus* species in this area are shown in Table 4. The percentage showing resistance to nitrofurantoin fluctuates for the first 3 years and shows a steady rise in the second triennium to reach a maximum of 37.8%. The most outstanding feature of these figures is the high resistance to tetracycline, always over 84%, which has been maintained throughout. The sulphonamide resistance follows the trend for CPC organisms as a whole and the figures for nalidixic acid and ampicillin show little variation. *Proteus* strains are naturally resistant to colistin.

The number of CPC strains showing multiple resistance has increased in the second half of this study compared with the first. The figures are shown in Table 5. Strains resistant to at least one antibiotic have risen from 53% to 57.3% and to three or more drugs from 6% to 10.3%. This represents an increasing problem for the future. The commonly occurring patterns in the second half of the series are shown in Table 6; these are not unlike those found in pre-hospital admission stools (Datta, 1969) although multiple resistance is not commoner than resistance to a single drug as in the stool organisms. The

natural resistance of *Proteus* species to colistin has been excluded in compiling these figures. Table 7 shows the age and sex distribution of patients in the survey. Females predominate in all decades except 91–100 and the peak is in the child-bearing years. Both sexes have a high incidence in the first decade. The usual peaks in the older age groups are missing

TABLE 6. Multiple resistance patterns—April 1967 to December 1969

No. of resistances	Resistance pattern*	No. of strains
2	Su T	128
	Su S	29
	T F	29
	Su A	19
	Su Col	17
	T Col	13
	T A	11
	Su F	4
	19 other patterns	30
	Total	280
3	Su S T	21
	Su T Col	21
	Su T F	15
	Su T A	12
	Su S A	5
	T F Col	5
	T F NG	4
	19 other patterns	30
	Total	113
4	Su S T A	8
	Su T F Col	8
	Su T A Ceph	4
	Su T A Col	4
	15 other patterns	18
	Total	42
5	Four patterns	5
6	Two patterns	2
	Total	7
Grand total		442

* For abbreviations see Table 4.

TABLE 5. Numbers of CPC organisms showing multiple drug resistance

Number of drug resistances	January 1964 to April 1967		April 1967 to December 1969	
	No. of isolations	%	No. of isolations	%
None	551	47	667	42.6
1	383	33	454	29.0
2	164	14	280	17.9
3	54	4.6	113	7.2
4	13	1.1	42	2.6
5	4	0.3	5	0.31
6	Nil		2	0.12

due to the younger-than-average population of the area served and the exclusion of chronic cases.

Discussion

Little has been published on the resistance of urinary pathogens in general practice. Sulphonamides, the most commonly used drugs, have attracted most attention and reports of widely differing proportions of resistant organisms have emanated recently from scattered sources in Britain. These are shown in Table 8. In addition reports have come from Mansfield (Macis & Ward-McQuaid, 1968) of 42% resistance and from Adelaide, Australia (Anderson, 1969) of 35% but in neither of these is it clear that all the organisms included were from domiciliary practice. *Bacterium coli* from outpatients in Arkansas showed 92% resistance and *Proteus* species from the same series 94% resistance (Allen, 1968) but this series also contained a very high proportion of pseudomonas infections suggesting the cases studied were not very comparable to those seen in Britain.

It is apparent that the pattern of resistance to sulphonamide is not uniform throughout the country and indeed the figures here presented suggest it is varying from time to time in any one area. This geographical variation is not altogether unexpected as it has been shown that serological types of *Escherichia coli* causing domiciliary urinary

infections vary significantly between localities only a few miles apart (Grüneberg & Bettelheim, 1969). Each locality has its own predominant strains and as R factors are encouraged by antibiotics, resistance patterns could also be expected to vary from place to place and time to time with changing prescribing habits.

Less information is available about resistance to other drugs. Thirteen per cent of fifty isolates have been reported resistant to ampicillin (Grüneberg & Brumfitt, 1967), a figure comparable with the 11.1% here reported for 1969. Figures of 4% of *Esch. coli* and coliforms and 39.5% of *Proteus* species (Macis & Ward-McQuaid, 1968) have also been recorded. In Arkansas 24% of *Esch. coli* and 29% of *Proteus* were resistant (Allen, 1968). These figures for *Proteus* compare unfavourably with the present survey, seven resistant strains out of 331, 2.1% over 5 years. The overall finding of a very slow increase of resistance to ampicillin confirms the reported lack of significant increase in incidence of resistance of Gram-negative bacilli to ampicillin during 1961-67 (Slocombe & Sutherland, 1969). The sudden doubling in 1969 may, however, be cause for concern.

Nalidixic acid is the only other drug to show a steady rise in incidence of resistance in this series although the figures are very low. Two per cent of *Escherichia coli* and 20% of *Proteus* species are recorded elsewhere (Macis & Ward-McQuaid, 1968).

Nitrofurantoin, which might be expected to show a similar pattern to nalidixic acid has varied between 2.7% and 8.7%, showing a rise to the latter figure over the last 2 years. Elsewhere under 2% resistance is recorded (Milne *et al.*, 1969), 17% of *Escherichia coli* and 32% of *Proteus* (Allen, 1968) and 2% of *Escherichia coli* and 45% of *Proteus* (Macis & Ward-McQuaid, 1968). The last authors also quote 68% resistance for *Proteus* in autumn 1967. In the present series the CPC overall figure of 8.7% for 1969 compares very favourably with tetracycline and sulphonamide and is comparable with ampicillin but higher than either nalidixic acid or trimethoprim-sulphonamide mixture. *Proteus* species contribute very largely to this incidence of resistance.

The figures for other antibiotics excite little comment except to point out the high level of resistance to tetracycline, especially of *Proteus* species, the overall figure being roughly one third. Trimethoprim-sulphonamide appears to be a very promising mixture. It is to be hoped that sulphonamide and trimethoprim sensitive strains of organisms will develop resistance to both drugs only very slowly but development of resistance to trimethoprim by initially sulphonamide-resistant strains may occur more rapidly. This survey does not indicate that this is occurring to any great extent at present and indeed the fall in incidence of sulphonamide-

TABLE 7. Age and sex distribution

Decade	No. of cases		
	Male	Female	Total
0-10	153	378	531
11-20	23	204	227
21-30	53	702	755
31-40	101	510	611
41-50	98	298	396
51-60	60	154	214
61-70	43	92	135
71-80	36	59	95
81-90	8	18	26
91-100	1	—	1
	576	2415	2991
Insufficient data			109

TABLE 8. CPC organisms resistant to sulphonamide

Area	Author	% Resistant
Southampton	Sleet (1969)	80
Manchester	Brooks (1968)	82
East Lothian	Milne <i>et al.</i> (1969)	45
Middlesex	Grüneberg & Brumfitt (1967)	18
London	Hopkins, Boheimer & Henry (1968)	20
Stockport	Brown <i>et al.</i> (1968)	2

resistant strains may delay this happening in this locality. The future alone can decide this.

Oral cephaloridines are now on the market and although only a few organisms in this survey were tested against cephaloridine the figures for 1968 and further work in 1970 not included in this report suggest that the incidence of resistant strains will be very similar to that against ampicillin.

The variation of resistance percentages described from place to place in the literature, the known geographical variation in serological types of infecting organisms and the variation in resistance from time to time together with the increasing danger of multiple resistance, slowly increasing in this locality, emphasize the necessity for continual monitoring of the resistance patterns of pathogenic bacteria in their own districts by all clinical bacteriologists.

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