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# Resistance of *Escherichia coli* in faeces and the use of antimicrobial agents in the treatment of hospital patients

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## SUMMARY

Resistance of faecal *Escherichia coli* to ampicillin, tetracycline, sulphamethoxazole and gentamicin was studied in patients admitted to seven different departments in two hospitals. The resistance to ampicillin, tetracycline and sulphamethoxazole in the seven patient groups was 27–57%, 26–56% and 35–63%, respectively. Resistance to gentamicin was found in only one department. An *E. coli* flora predominantly resistant to ampicillin, tetracycline or sulphamethoxazole (> 50% of the *E. coli* strains in a faecal sample resistant) was found in 10–38%, 4–30% and 21–35% of the samples. A cross-sectional study focusing on the influence of the use of antimicrobial agents on the occurrence of resistant strains revealed a positive correlation between the annual turnover of broad-spectrum penicillins in various departments and the occurrence of predominantly ampicillin-resistant *E. coli* strains in these departments.

## INTRODUCTION

Studies relating the use of antimicrobial agents to the problem of resistance of the bacterial flora are nearly always follow-up studies (Bauer, Perry & Kirby, 1960; Bulger, Larson & Sherris, 1970; Price & Sleigh, 1970; Søgaard, Zimmerman-Nielsen & Siboni, 1974; Mouton, Glerum & van Loenen, 1976; Weinstein *et al.* 1980). Studies of this design are evidently well suited to detect trends in the development of antimicrobial resistance. Studies of the occurrence of resistant bacterial strains in a hospital should take into account the prevalence of such strains in the normal extramural population. This resistance as a rule pertains to antimicrobial agents routinely used in general practice (Guinée, Ugueto & van Leeuwen, 1970; Datta *et al.* 1971; Linton *et al.* 1972; Degener *et al.* 1983). The use of antimicrobial agents in hospital patients may affect the prevalence of resistant strains. In a cross-sectional study we have tried to quantify this increase. For this purpose patients admitted to departments which varied in their turnover of antimicrobial agents were divided into users and non-users of these agents. The density of *E. coli* strains resistant

to ampicillin, tetracycline, sulphamethoxazole or gentamicin was determined in faecal samples from these patients. The samples were collected on the tenth day after admission. As a rule a hospital stay of more than one week will be sufficient to determine the prevalence of resistant strains (Datta, 1969; Salzman & Klemm, 1966). The annual turnover of antimicrobial agents per department was then compared with the resistance rates observed in these departments.

## MATERIALS AND METHODS

### *Patients*

This study was performed in 1980 and 1981 in seven different departments in two hospitals: the departments of paediatrics, internal medicine and surgery of a community hospital, and the departments of paediatrics, internal medicine, surgery and urology of a university hospital. Efforts were made to collect a faecal sample from each of 50 patients consecutively admitted to each department, on the tenth day after admission.

### *Use of antimicrobial agents*

For each patient entered into the study the use of antimicrobial agents during the hospital stay was determined. The term 'treated patients' pertains to patients being given an antimicrobial agent in at least three doses during 24 hours. The hospital apothecary supplied the data with which the use of the main categories of antimicrobial agents per department could be calculated. These main categories are: narrow-spectrum penicillins, broad-spectrum penicillins, cephalosporins, aminoglycosides, sulphonamides and cotrimoxazole. For this study the data on the annual turnover (in grams) per department in the year of the study were used. The turnover per bed was calculated on the basis of the percentage occupation.

### *Faecal samples*

Faecal samples were collected in Amies transport medium. Within 24 h, dilutions were prepared which yielded a countable number of colonies on McConkey agar without antibiotics and on McConkey agar with 30 $\mu$g/ml tetracycline and with 40 $\mu$g/ml ampicillin, respectively, on IsoSensitestagar (Oxoid) with 10 $\mu$g/ml gentamicin and on DST agar (Oxoid) with 0·5% haemolysed horse blood and 100 $\mu$g/ml sulphamethoxazole. After incubation the colonies were counted. The percentage of resistant strains per faecal sample could thus be calculated. Morphologically different colonies were differentiated with the aid of a biochemical series, as described by Cowan (1975).

### *Statistical analysis*

The relative risk of acquisition of resistant strains by users of antimicrobial agents versus non-users was calculated in the various patient groups. The $P$-value for the relative risk was also calculated (Rothman & Boice, 1979). The correlation between the turnover of antimicrobial agents in the year of the study in the various departments and the percentages of resistance found in the various patient groups was determined with the aid of regression analysis.

Table 1. *Ampicillin-resistant* E. coli *in faecal samples of patients who did or did not receive antimicrobial agents (by department)*

| | Antimicrobial agents | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | With | | Without | | Total | | | | |
| Department | Samples | Resistant | Samples | Resistant | Samples | Resistant | Relative risk | $\chi$ | $P$ |
| Paediatrics, UH | 19 | 12 (63) | 29 | 10 (34) | 48 | 22 (46) | 2·0 | 1·9 | 0·02 |
| Paediatrics, CH | 11 | 5 (45) | 12 | 8 (67) | 23 | 13 (57) | 0·7 | — | — |
| Medicine, UH | 14 | 9 (64) | 26 | 11 (42) | 40 | 20 (40) | 1·5 | 1·3 | 0·09 |
| Medicine, CH | 10 | 6 (60) | 37 | 11 (30) | 47 | 17 (36) | 2·0 | 1·8 | 0·04 |
| Surgery, UH | 13 | 5 (49) | 19 | 6 (32) | 32 | 11 (34) | 1·3 | 0·4 | 0·4 |
| Surgery, CH | 17 | 9 (53) | 31 | 4 (13) | 48 | 13 (27) | 5·0 | 2·9 | 0·001 |
| Urology, UH | 15 | 7 (47) | 33 | 13 (39) | 48 | 17 (35) | 1·2 | 0·5 | 0·4 |

UH, university hospital; CH, community hospital. Figures in parentheses are percentages.

Table 2. *Predominance of ampicillin-resistant* E. coli *in faecal samples of patients who did or did not receive antimicrobial agents (by department)*

| | Antimicrobial agents | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | With | | Without | | Total | | | | |
| Department | Samples | Resistant | Samples | Resistant | Samples | Resistant | Relative risk | $\chi$ | $P$ |
| Paediatrics, UH | 19 | 11 (58) | 29 | 6 (21) | 48 | 17 (35) | 2·8 | 3·3 | <0·001 |
| Paediatrics, CH | 11 | 5 (46) | 12 | 2 (17) | 23 | 7 (30) | 2·7 | 1·5 | 0·06 |
| Medicine, UH | 14 | 8 (57) | 26 | 7 (27) | 40 | 15 (38) | 2·1 | 1·9 | 0·03 |
| Medicine, CH | 10 | 5 (50) | 37 | 3 (8) | 47 | 8 (17) | 6·2 | 2·8 | 0·002 |
| Surgery, UH | 13 | 4 (31) | 19 | 2 (11) | 32 | 6 (19) | 2·8 | 1·5 | 0·06 |
| Surgery, CH | 17 | 7 (41) | 31 | 3 (10) | 48 | 10 (21) | 4·6 | 2·5 | 0·006 |
| Urology, UH | 15 | 4 (27) | 33 | 1 (3) | 48 | 5 (10) | 9·0 | 2·4 | 0·008 |

See footnote to Table 1.

Table 3. *Tetracycline-resistant* E. coli *and predominance of tetracycline-resistant* E. coli *in faecal samples of patients who did or did not receive antimicrobial agents (by department)*

| | | Resistant | | | Predominantly resistant | | |
|---|---|---|---|---|---|---|---|
| Department | Samples | Total | Relative risk | *P* | Total | Relative risk | *P* |
| Paediatrics, UH | 48 | 21 (44) | 1·4 | 0·16 | 8 (17) | 1·5 | 0·27 |
| Paediatrics, CH | 23 | 6 (26) | 2·1 | 0·16 | 1 (4) | 0 | — |
| Medicine, UH | 40 | 20 (50) | 1·0 | — | 12 (30) | 1·9 | 0·10 |
| Medicine, CH | 47 | 16 (34) | 1·7 | 0·11 | 8 (17) | 2·1 | 0·11 |
| Surgery, UH | 32 | 18 (56) | 0·7 | — | 6 (19) | 1·4 | 0·31 |
| Surgery, CH | 48 | 18 (38) | 2·8 | 0·002 | 9 (19) | 6·8 | 0·002 |
| Urology, UH | 48 | 17 (35) | 0·7 | — | 9 (19) | 1·1 | 0·42 |

See footnote to Table 1.

Table 4. *Sulphamethoxazole-resistant* E. coli *and predominance of sulphamethoxazole-resistant* E. coli *in faecal samples of patients who did or did not receive antimicrobial agents (by department)*

| | | Resistant | | | Predominantly resistant | | |
|---|---|---|---|---|---|---|---|
| Department | Samples | Total | Relative risk | *P* | Total | Relative risk | P |
| Paediatrics, UH | 48 | 20 (42) | 1·6 | 0·1 | 12 (25) | 2·2 | 0·07 |
| Paediatrics, CH | 23 | 11 (48) | 1·9 | 0·08 | 8 (35) | 3·2 | 0·04 |
| Medicine, UH | 40 | 14 (35) | 0·8 | — | 10 (25) | 0·8 | — |
| Medicine, CH | 47 | 23 (49) | 2·0 | 0·01 | 13 (28) | 2·3 | 0·04 |
| Surgery, UH | 32 | 20 (63) | 0·8 | — | 8 (25) | 1·3 | 0·34 |
| Surgery, CH | 48 | 20 (42) | 1·8 | 0·04 | 10 (21) | 2·6 | 0·04 |
| Urology, UH | 48 | 26 (54) | 0·8 | — | 15 (31) | 0·8 | — |

See footnote to Table 1.

Table 5. *Annual turnover of antimicrobial agents in g/bed with percentage of total used in a department in brackets*

| | Departments | | | | |
|---|---|---|---|---|---|
| Antimicrobial agents | Medicine, UH | Medicine, CH | Surgery, UH | Surgery, CH | Urology, UH |
| Narrow-spectrum penicillins | 16·1 (11) | 31·4 (20) | 9·1 (9) | 45·4 (26) | 2·7 (2) |
| Broad-spectrum penicillins | 100 (69) | 76·6 (48) | 49·7 (50) | 80·2 (47) | 50·5 (34) |
| Tetracyclines | 0·4 (0) | 1·1 (1) | 0·1 (0) | 1·9 (1) | 0·2 (0) |
| Sulphonamides and cotrimoxazole | 9·8 (7) | 28·2 (18) | 19·9 (20) | 27·1 (16) | 71·4 (48) |
| Aminoglycosides | 2·2 (2) | 2·9 (2) | 2·6 (3) | 3·5 (2) | 2·7 (2) |
| Cephalosporins | 17 (12) | 20·3 (13) | 18·6 (19) | 13·3 (8) | 22·3 (15) |
| Total | 145·5 (100) | 160·5 (100) | 100·0 (100) | 171·5 (100) | 149·9 (100) |

See footnote to Table 1.

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Table 6. *Annual turnover of antimicrobial agents (by weight per bed) and the prevalence of a predominantly ampicillin-resistant* E. coli *in faecal samples of patients (by department)*

| | Department | | | | | Resistance and turnover | |
|---|---|---|---|---|---|---|---|
| | Medicine, UH | Medicine, CH | Surgery, UH | Surgery, CH | Urology, UH | Linear regression | |
| Prevalence of resistance in patients receiving antimicrobial agents* | 57% | 50% | 31% | 41% | 27% | | |
| Annual turnover of broad-spectrum pencillins | | | | | | | |
| Percentage of total antibiotics | 69% | 48% | 50% | 47% | 34% | $Y = 0{\cdot}81X - 0{\cdot}97$ | 0·81 |
| Amount (g) per bed | 100·0 | 76·6 | 49·7 | 80·2 | 50·5 | $Y = 0{\cdot}55X - 1{\cdot}64$ | 0·94 |
| Prevalence of resistin patients *not* receiving antimicrobial agents* | 27% | 8% | 11% | 10% | 3% | | |
| Annual turnover of broad-spectrum pencillins | | | | | | | |
| Percentage of total antibiotics | 69% | 48% | 50% | 47% | 34% | $Y = 0{\cdot}70X - 23{\cdot}1$ | 0·98 |
| Amount per bed (g) | 100·0 | 76·6 | 49·7 | 80·2 | 50·5 | $Y = 0{\cdot}33 - 11{\cdot}6$ | 0·78 |

See footnote to Table 1.
* See Table 2.

## RESULTS

### *Faecal samples*

In six departments, 43–63 samples were collected. In one department only 29 samples were collected because the average hospital stay was < 10 days and the number of beds was small. *E. coli* was the species of the Enterobacteriaceae most frequently found (82% of all samples). All further data on resistance pertain exclusively to samples containing *E. coli*.

### *Resistance of* E. coli *in patients who did or did not receive antimicrobial agents*

The prevalence of resistance to ampicillin occurring in treated and untreated patients admitted to different departments is shown in Table 1. In all departments except the department of paediatrics of the community hospital ampicillin-resistant *E. coli* strains were more prevalent in treated than in untreated patients. In three departments treated patients showed a significantly increased risk of carrying ampicillin-resistant *E. coli*. The data concerning carriage of a predominantly resistant *E. coli* flora (> 50% of the *E. coli* flora resistant) are presented in a similar way in Table 2. The data show that a significantly increased risk of resistance prevailed in five departments and that in addition the significance had increased. Tables 3 and 4 summarize the results regarding the resistance and the predominant



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resistance to tetracycline and sulphamethoxazole in the departments. Significant differences were less frequently observed than with ampicillin. In one department only, gentamicin-resistant *E. coli* strains were found in two samples.

*Resistance of* E. coli *and turnover of antimicrobial agents*

In all departments except the department of urology the annual turnover of broad-spectrum penicillin exceeded the turnover of the other antimicrobial agents. This is shown in Table 5. A positive correlation was found between the annual turnover of broad-spectrum penicillins expressed as the percentage of the total turnover of antimicrobial agents and the occurrence of a predominantly ampicillin-resistant *E. coli* flora in the patient groups examined (Table 6). In the different departments the correlation was found in patients who did or did not receive antimicrobial agents. This positive correlation persisted when the turnover of the broad-spectrum pencillins (in grams) was related to the number of beds present in each department.

## DISCUSSION

Resistance of Enterobacteriaceae to antimicrobial agents is a widespread phenomenon. Several epidemiological studies have attempted to define the resistance problem outside hospitals (Guinée, Ugueto & Leeuwen, 1970; Datta *et al.* 1971; Linton *et al.* 1972; Degener *et al.* 1983). The extramural prevalence of carriage of resistant Enterobacteriaceae is high and ranges from 30 to 74%.

The influence of the use of antimicrobial agents on the development of resistance is more easily studied in hospitals than in general practice. Intramural studies, however, are impeded by the fact that the majority of patients admitted are already carriers of resistant strains. A hospital stay is known to influence in particular the density of resistant *E. coli* in the intestine (Salzman & Klemm, 1966; Datta, 1969). Our cross-sectional study also shows that quantitative examination of faeces is important in resistance studies. Differences between users and non-users of antimicrobial agents are found especially in patients with a predominantly (> 50%) resistant faecal *E. coli* flora.

Of the patients studied, 35% were using an antimicrobial agent. This percentage is comparable to the percentages reported in other studies of the use of antimicrobial agents in hospitals (Simmons & Stolley, 1974; Townsend *et al.* 1979*a*, *b*; Cooke, Salter & Phillips, 1980; Moss *et al.* 1981). In these studies, as in ours, broad-spectrum penicillins were the drugs most frequently used. The positive correlation between the annual turnover of broad-spectrum penicillins and the prevalence of a predominantly ampicillin-resistant *E. coli* flora was found in patients, whether they were using antimicrobial drugs or not. This suggests that the use of broad-spectrum penicillins in the hospital environment has consequences for the susceptibility of the *E. coli* flora in all patients. The relationship between antibiotic turnover and resistance was found exclusively in adults, not children. This is probably explained by the difference in dosage; dosages can vary widely, both between individual children and between children and adults (Townsend *et al.* 1979*a*, *b*).

Follow-up studies usually cover a period of many years, and have revealed increasing frequency of resistant bacterial strains with the increasing use of

antimicrobial agents (Mouton, Glerum & van Loenen, 1976; Weinstein *et al.* 1979). Inversely, follow-up studies can also show that with a diminishing use of a particular agent the frequency of strains resistant to this agent also diminishes (Price & Sleigh, 1979; Søgaard, Zimmerman-Nielsen & Siboni, 1974; Bulger, Larson & Sherris, 1979).

We have demonstrated that a cross-sectional study performed in several clinical departments can provide short-term insight into the development of resistance to broad-spectrum penicillins. In a different clinical situation this has proved possible in a similar way for gentamicin (Block, 1978). Little gentamicin resistance was found in the course of our study.

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