

Ciprofloxacin-resistant *Escherichia coli* from bacteraemias in England; increasingly prevalent and mostly from men

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Objectives: To assess ciprofloxacin resistance among *Escherichia coli* isolates from bacteraemia patients in England in relation to age, sex and Region.

Methods: Routine susceptibility data for bacteraemia isolates were collected from over 90% of hospitals in England.

Results: During 1995–2001, the prevalence of ciprofloxacin resistance trebled, from 2.1% to 6.5%. Isolates from men were more frequently resistant than those from women, possibly because infections in men more often involve nosocomial strains. Resistance was rare (<1.5%) in isolates from patients aged <1 year; among older patients, resistance was unrelated to age in isolates from women, but peaked in the 15–44 age group for men.

Conclusions: The prevalence of ciprofloxacin resistance in *E. coli* from bacteraemia is strongly associated with sex and, to a lesser extent, age.

Keywords: *E. coli*, bacteraemia, gender, ciprofloxacin resistance

Introduction

Fluoroquinolones are valuable and potent antimicrobials, but are increasingly compromised by mutational resistances that reduce target sensitivity, restrict permeability or increase efflux.¹ We reported previously a steady year-on-year rise in the prevalence of ciprofloxacin resistance in *Escherichia coli* isolates from bacteraemias in England, from 0.8% in 1990 to 3.7% in 1999.² Although low compared with the prevalence rates in many developing countries,² these data indicate a disturbing trend. Here, we extended the analysis to 2001, and investigated relationships between resistance and patient demographics.

Materials and methods

Data collection

Voluntary reporting to the Health Protection Agency's LabBase/CoSurveillance system captures routine microbiological information on

bacteraemias from over 90% of the clinical diagnostic laboratories in England and Wales.³ Analysis for *Staphylococcus aureus*, where there is a parallel mandatory reporting scheme, suggests that about two-thirds of bacteraemias are reported.⁴

Data analysis

All reports of *E. coli* bacteraemia in England, received under the routine reporting scheme during 1995–2001, were extracted for analysis. Overall trends were described either as a ratio of the proportions resistant in two specific years (a risk ratio, RR), or as an average percentage increase between successive years, estimated by a generalized linear model of the binomial family and a log link function. Significance tests were based on logistic regression, and so compared odds ratios. The overall trend was estimated by controlling for Region, sex and age; sex-specific trends were estimated controlling for Region and age; differences between age groups were tested controlling for Region and year; Region-specific trends were estimated controlling for sex and age group.

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Ciprofloxacin resistance in bloodstream *E. coli*

Table 1. Ciprofloxacin resistance among bloodstream *E. coli* isolates from England in relation to year and sex

	1995	1996	1997	1998	1999	2000	2001
Men							
% resistant isolates	2.2	2.6	4.9	5.0	4.5	6.0	8.0
[95% CI]	[1.7, 2.9]	[1.9, 3.4]	[3.9, 6.0]	[4.1, 5.9]	[3.7, 5.3]	[5.1, 7.0]	[7.0, 9.0]
Number of isolates	2285	1957	1685	2498	2694	2606	2700
Women							
% resistant isolates	2.0	2.9	2.8	3.1	3.2	4.3	5.5
[95% CI]	[1.5, 2.5]	[2.3, 3.6]	[2.2, 3.6]	[2.5, 3.7]	[2.7, 3.8]	[3.6, 5.0]	[4.8, 6.2]
Number of isolates	3025	2611	2246	3449	3612	3397	3929
Overall							
% resistant isolates	2.1	2.7	3.7	3.9	3.8	5.0	6.5
[95% CI]	[1.7, 2.5]	[2.3, 3.3]	[3.2, 4.4]	[3.4, 4.4]	[3.3, 4.3]	[4.5, 5.6]	[5.9, 7.1]
Number of isolates ^a	5342	4601	3952	5952	6370	6054	6674
Total <i>E. coli</i> reported ^b	8575	8835	10 056	10 477	10 761	10 602	11 297

^aIncludes isolates from patients whose sex was not recorded.

^bIncludes isolates with no ciprofloxacin susceptibility data reported.

Results

During 1995–2001, 8575–11 297 *E. coli* bacteraemias per annum were reported, with 39.3%–62.3% of the reports including data on ciprofloxacin susceptibility (Table 1). The proportion of isolates reported to be ciprofloxacin resistant rose from 2.1% in 1995 to 6.5% in 2001, (RR 3.3; 95% CI: 2.6–4.1), an average annual increase of 19% (95% CI: 16–22). Average percentage annual increases for Regions were estimated as: London 22%, Eastern 30%, Northern & Yorkshire 23%, West Midlands 22%, South East 17%, South West 19%, North West 9% and Trent 7%. These trends were highly significant ($P \leq 0.0001$) except in the North West ($P = 0.02$) and Trent ($P = 0.26$). By 2001, resistance rates were: London 9.2%, Eastern 8.3%, Northern & Yorkshire 7.3%, West Midlands 6.8%, South East 5.6%, South West 5.4%, North West 5.2% and Trent 2.2%.

Women accounted for 57% of all the *E. coli* bacteraemia patients reported, but there was a stronger trend of rising resistance among isolates from men (average annual increase 22%; 95% CI: 18–27) than from women (16%; 95% CI: 12–21). By 2001, 8.0% of the *E. coli* isolates from men were reported to be resistant, compared with 5.5% of those from women (Table 1). The prevalence of resistance also varied with the patient's age (Table 2), being lowest (<1.5%) in isolates from those aged under 1 year ($P \leq 0.002$ for men and $P \leq 0.02$ for women compared with all other ages). Resistance among isolates from females peaked in the 1–14 age group (5.1%), but its prevalence was not significantly reduced for older age groups. Among isolates from males, however, resistance clearly peaked in the 15–44 age group, where it was significantly more prevalent than in 45–64-year-olds ($P = 0.02$) and those aged ≥ 65 ($P < 0.0005$).

Discussion

E. coli remains the second most common agent of bacteraemia in England and Wales, after *Staphylococcus aureus*. Thus, changes in its susceptibility pattern are important, and it is disturbing that ciprofloxacin resistance continues to accumulate in the species.

It was striking also, from this analysis, that although more *E. coli* bacteraemias occur in women, ciprofloxacin resistance is more prevalent in those from men. We are unaware of any such strong association between resistance and gender having been found previously. A likely factor is that women are anatomically more prone than men to ascending urinary tract infections by the resident gut microflora, with some of these infections leading to bacteraemias. Because such infections are rarer in men (at least until later life, when prostatitis has an impact), relatively more of the fewer *E. coli* bacteraemias in men are likely to be caused by hospital strains, which may tend to be more resistant than *E. coli* from the normal gut flora.

This hypothesis is supported by the observations, using the same database, that resistance was more prevalent in *E. coli* isolates from men to gentamicin (RR, 1.30; 95% CI: 1.14–1.50) and ceftazidime (RR, 1.64; 95% CI: 1.34–2.02), both of which are used almost exclusively in hospitals. Conversely, the pattern was reversed for ampicillin (RR, 0.95; 95% CI: 0.93–0.97) and trimethoprim (RR, 0.88; 95% CI: 0.85–0.92), which are oral drugs widely used in the community. Selection in women may also be mitigated by a disinclination to use quinolones in those of child-bearing age.

Routine laboratory data received by the Health Protection Agency offer few insights into the origins of the reported bacteraemias. The British Society for Antimicrobial Chemotherapy's Bacteraemia Surveillance (<http://www.bsacsurv.org>) does have such data, based on 10 consecutive *E. coli* bacteraemias and isolates per annum from each of 25 UK and Irish hospitals. Among 482 *E. coli* isolates in 2001 and 2002, 279 (58%) were from women; and 67% of those from women were community-acquired (<48 h hospitalization) compared with 60% of those from men ($P = 0.14$). Ciprofloxacin resistance was seen in 7.4% (22/296) of the community-acquired isolates compared with 8.4% (14/166) of those from hospital-acquired infections ($P = 0.72$). These differences failed to achieve statistical significance but are consistent with the hypothesis that *E. coli* bacteraemias in men are more likely to be nosocomial, and to be caused by ciprofloxacin-resistant organisms. This hypothesis is further supported by an analysis of 861 *E. coli* bacteraemia episodes treated at a London hospital during 1969–1987.⁵ Among hospital-acquired bacteraemias, the

Table 2. Ciprofloxacin resistance among bloodstream *E. coli* isolates from England, related to age and sex, based on pooled data for 1995–2001

Age group	From men			From women		
	<i>n</i>	resistant (%)	95% CI	<i>n</i>	resistant (%)	95% CI
<1	505	1.4	[0.6, 2.8]	343	1.2	[0.3, 3.0]
1–14	198	6.1	[3.2, 10.3]	216	5.1	[2.6, 8.9]
15–44	1057	9.0	[7.3, 10.9]	2470	3.9	[3.2, 4.8]
45–64	3144	6.6	[5.8, 7.5]	3414	3.7	[3.1, 4.4]
≥65	10992	4.0	[3.6, 4.4]	15 171	3.3	[3.0, 3.6]

Data were omitted where patients' ages were not recorded; hence the totals are lower than those in Table 1.

male:female ratio was 1.2:1, compared with 0.46:1 among community-acquired cases. Resistances to gentamicin and (in that earlier period) ampicillin were more frequent among the nosocomial cases. The study pre-dated ciprofloxacin, and the resistance rates were not analysed in relation to gender.

The relationship between the patient's age and the prevalence of resistance also was notable (Table 2). Very low resistance rates in those aged <1 year might reflect the lack of fluoroquinolone use in these infants. Since, however, quinolone use should also be limited in the 1–14 year group (where these drugs are only used if their benefits are thought to exceed the arthropathy risks) the relationship is more likely to reflect the fact that neonatal units develop a particular flora that contributes to patient colonization.⁶

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References

1. Hooper, D. C. (2001). Emerging mechanisms of fluoroquinolone resistance. *Emerging Infectious Diseases* **7**, 337–41.
2. Livermore, D. M., James, D., Reacher, M. H. *et al.* (2002). Trends in fluoroquinolone (ciprofloxacin) resistance in *Enterobacteriaceae* from bacteremias in England and Wales, 1990–1999. *Emerging Infectious Diseases* **8**, 473–8.
3. Reacher, M. H., Shah, A., Livermore, D. M. *et al.* (2000). Bacteraemia and antibiotic resistance of its pathogens reported in England and Wales between 1990 and 1998: trend analysis. *British Medical Journal* **320**, 213–6.
4. Public Health Laboratory Service. (2003). *Staphylococcus aureus* bacteraemia: England, Wales and Northern Ireland. *Communicable Disease Report CDR Weekly* **13**, 5–10.
5. Gransden, W. R., Eykyn, S. J., Phillips, I. *et al.* (1990). Bacteremia due to *Escherichia coli*: a study of 861 episodes. *Reviews of Infectious Diseases* **12**, 1008–18.
6. Fryklund, B., Tullus, K., Berglund, B. *et al.* (1992). Importance of the environment and the faecal flora of infants, nursing staff and parents as sources of gram-negative bacteria colonizing newborns in three neonatal wards. *Infection* **20**, 253–7.