Short reports

Resistance to ciprofloxacin in pathogenic Enterobacteriaceae in England and Wales in 1996

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Abstract
In 1996, 6% of *Escherichia coli* from extraintestinal infections were resistant to ciprofloxacin with minimum inhibitory concentrations (MICs) $\geq$ 2 mg/l (high level resistance). Low level resistance (MIC 0.125–1 mg/l) was also identified in 7% of *Salmonella typhi*, 4% of *S paratyphi* A, and 4% of non-typhoidal salmonellas. However, resistance to ciprofloxacin was rarely identified in shigellas. For *E coli*, physicians should be aware that treatment failures may occur when patients with invasive illness are treated with ciprofloxacin before the results of laboratory sensitivity tests are available. For salmonellas an increasing number of treatment failures have been recorded for patients infected with strains with low level resistance. Because of the increasing incidence of Enterobacteriaceae with low level resistance to ciprofloxacin, it is recommended that for this group of organisms a breakpoint of 0.125 mg/l should be included in laboratory sensitivity tests.
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Keywords: ciprofloxacin; pathogenic Enterobacteriaceae; sensitivity testing

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Ciprofloxacin is the recommended antimicrobial agent for typhoid fever and has been recommended for the treatment of invasive infections with *Escherichia coli* and non-typhoidal salmonellas, and for acute shigellosis if clinically indicated. The emergence of resistance to this antimicrobial agent has been reported in several countries in a wide range of enterobacterial pathogens.[1-4] Should it be necessary to treat invasive disease before the results of laboratory sensitivity tests are known, a knowledge of the current incidence of resistance to ciprofloxacin in such organisms may be advantageous. In this communication we report the occurrence of resistance to ciprofloxacin in extraintestinal *E coli*, salmonella, and shigella isolated from patients in England and Wales in 1996.

Materials and methods
Strains of *E coli*, salmonella, and shigella isolated from patients in England and Wales in 1996 and referred to the Laboratory of Enteric Pathogens for identification and typing were investigated. None of the isolates had been preselected on the basis of antimicrobial susceptibility. All isolates were tested by an agar dilution method for resistance to ampicillin, chloramphenicol, gentamicin, kanamycin, streptomycin, sulphonamides, tetracyclines, trimethoprim, furazolidone, and ciprofloxacin.[5] For ciprofloxacin, the levels of antibiotic incorporated into the plates were 0.125 mg/l and 1 mg/l; isolates resistant at 1 mg/l were subjected to full minimum inhibitory concentration (MIC) determination.

Results
Table 1 summarises the incidence of resistance to ciprofloxacin in extraintestinal *E coli*, salmonella, and shigella from patients in England and Wales in 1996.

Twenty three of 368 (6%) isolates of *E coli* were resistant to ciprofloxacin with MICs ranging from 2–256 mg/l (high level resistance). All ciprofloxacin resistant isolates were also resistant to at least one additional antimicrobial agent and 21 were multiresistant (to four or more agents). Low level resistance to ciprofloxacin (MIC 0.25–1 mg/l) was not detected.

S typhi isolates from 14 of 210 patients (7%) were resistant to ciprofloxacin with MICs 0.25–1 mg/l. Six of 137 (4%) *S paratyphi* A isolates were ciprofloxacin resistant at similar levels. Nine of the 14 ciprofloxacin resistant *S typhi* were also resistant to chloramphenicol, ampicillin, trimethoprim, streptomycin, sulphonamides, and tetracyclines but none of the

Table 1 Resistance to ciprofloxacin in extraintestinal Escherichia coli, salmonella, and shigella from patients in England and Wales in 1996

Organism	Number of isolates studied	Number resistant to ciprofloxacin		
		Total	MIC (mg/l)	
			0.25–1.0	2–256
Extraintestinal *E coli*	368	23 (6%)	0	23 (6%)
Salmonella				
S typhi	210	14 (7%)	14 (7%)	0
S paratyphi A	137	6 (4%)	6 (4%)	0
Non-typhoidal	30075	1322 (4%)	1315 (4%)	7 (< 0.1%)
Shigella	1043	8 (0.8%)	8 (0.8%)	0

isolates of *S paratyphi* A were resistant to other agents. All patients with ciprofloxacin resistant *S typhi* and *S paratyphi* A had a history of recent return from countries in the Indian subcontinent. For non-typhoidal salmonellas 1322 of 30 075 (4%) isolates had ciprofloxacin MICs ranging from 0.25–1 mg/l (low level resistance) but only seven (< 0.1%) showed high level resistance. Ciprofloxacin resistance was identified in 31 non-typhoidal serotypes but was most common in the zoonotic serotypes *S typhimurium, S hadar,* and *S virchow.*[6] Of particular concern was an increase from 7% to 14% in the incidence of ciprofloxacin resistance in multiresistant *S typhimurium* definitive phage type (DT) 104, which has been the second most common salmonella strain in human infections in England and Wales since 1992 and is currently the most common strain in cattle and poultry in the UK. Of the seven non-typhoidal isolates with high level resistance, none were DT 104. Three patients from whom strains with high level resistance were isolated had a history of recent foreign travel.

Only eight of 1043 (0.8%) shigella isolates were resistant to ciprofloxacin (MICs 0.25–1 mg/l). The majority of ciprofloxacin resistant isolates were from patients who had recently returned from abroad.

Discussion

The expected serum concentration of ciprofloxacin during treatment at recommended doses is ≥ 2 mg/l. In 1996, 6% of *E coli* isolates from extraintestinal infections were ciprofloxacin resistant and in all cases the level of resistance was in the range of 2–256 mg/l. As *E coli* is the most common cause of bacteraemia in England and Wales,[7] physicians should be aware of the possibility of treatment failures if it is necessary to start treatment with ciprofloxacin before the results of laboratory sensitivity tests are available. It is also concerning that the majority of ciprofloxacin resistant isolates of *E coli* from extraintestinal infections were resistant to at least four other antimicrobial drugs.

Although 7% of isolates of *S typhi*, 4% of *S paratyphi* A, and 4% of non-typhoidal isolates were ciprofloxacin resistant, the level of resistance in all but seven non-typhoidal isolates was in the range of 0.25–1 mg/l. It is noteworthy that an increasing number of treatment failures have been recorded both for infections with *S typhi*,[8] and for invasive infections with non-typhoidal salmonellas[9]; in all cases the ciprofloxacin MICs of the strains have been in the range 0.25–1 mg/l.

A substantial increase in the incidence of ciprofloxacin resistance in non-typhoidal salmonellas has followed the licensing in 1993 for use in animal husbandry in the UK of the related fluoroquinolone antibiotic enrofloxacin. This agent has subsequently been extensively used for treatment and prophylaxis in both cattle and poultry.[6]

Resistance to ciprofloxacin is mediated either by chromosomal mutations in the gyrA gene, or by decreased cell wall permeability. Such mutations confer resistance not only to ciprofloxacin but also to the entire class of fluoroquinolone agents. As the majority of infections caused by non-typhoidal salmonellas in England and Wales are zoonotic in origin, it is possible that the use of fluoroquinolone antibiotics in animal husbandry has contributed to the upsurge of ciprofloxacin resistance in non-typhoidal salmonellas. In this respect it is regrettable that the effectiveness of ciprofloxacin in human medicine is being eroded by the use of related fluoroquinolone antibiotics in animal husbandry. Resistance to ciprofloxacin remains uncommon for shigella (< 1% of isolates) and should antimicrobial treatment for acute shigellosis be indicated, ciprofloxacin remains a useful option.

The breakpoints used by many laboratories in testing for ciprofloxacin sensitivity in Enterobacteriaceae are 1 mg/l (low level) and 4 mg/l (high level).[10] Using these levels the reduced susceptibility of the isolates with MICs in the range 0.25–1.0 mg/l would not be appreciated and treatment failures could follow. When testing for resistance to ciprofloxacin by breakpoint for enterobacteria, we recommend using 0.125 mg/l supported by full MICs for isolates resistant at this level. For disc testing, we endorse the recent recommendations of Murphy *et al* who considered that because borderline susceptibility in vitro may predict treatment failure, the full MICs of isolates resistant at ≥ 0.25 mg/l on disc testing should be determined.[2]

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