

cocci isolated in the UK have been between 2 and 4 mg/L, although these values are not predictive of clinical failure except in patients with meningitis.<sup>2-4</sup> MICs of 8 mg/L may represent a critical further increase. The pharmacokinetic parameter that is most important in terms of influencing the response to therapy with  $\beta$ -lactams is the period during which the serum concentration of the drug exceeds the MIC for the relevant pathogen. Studies in animals with pneumococcal infections have shown that the serum concentrations of  $\beta$ -lactams must exceed the MICs for the pathogen for 40–50% of the dosage interval in order to achieve maximum efficacy.<sup>5</sup> With commonly used regimens<sup>6</sup> of benzylpenicillin (600 mg twice to four times daily;  $C_{\max}$  = 12 mg/L;  $t$  = 0.8 h), amoxycillin (250 mg tds;  $C_{\max}$  = 5.4 mg/L;  $t$  = 1 h) and cefotaxime (1 g tds;  $C_{\max}$  = 20.5 mg/L;  $t$  = 1.3 h), it is unlikely that adequate serum concentrations will be maintained for this percentage of the dosage intervals. With meropenem (500 mg tds;  $C_{\max}$  = 25.6 mg/L;  $t$  = 1 h), adequate serum concentrations relative to MICs of 1–2 mg/L should be maintained, although the activity of this drug in the CSF of patients with meningitis is uncertain.

According to these data, it is likely that the markedly reduced susceptibility to  $\beta$ -lactams exhibited by the strains described here, as well as by others isolated in Hungary and Poland,<sup>7</sup> will be associated with therapeutic failures if the antibiotics are prescribed in standard dosages. While infections caused by highly  $\beta$ -lactam-resistant pneumococci may respond to high-dosage therapy, the initiation of such treatment will depend on the prompt recognition of high-level resistance. This condition is unlikely to be met in the community where treatment is usually empirical and microbiological investigations are undertaken infrequently or, at best, are qualitative rather than quantitative. The prospect of an increased incidence of infections caused by highly  $\beta$ -lactam-resistant pneumococci is therefore a cause for concern.

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## Antibiotic resistance amongst *Salmonella enterica* species isolated in the Republic of Ireland

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Sir,

Antibiotic resistance amongst isolates of *Salmonella enterica* in England and Wales is being recognized with increasing frequency.<sup>1-3</sup> Strains of *S. enterica* serovar *typhi* - *murium* DT 104, which are resistant to ampicillin, chloramphenicol, streptomycin, sulphonamides and tetracycline (ACSSuT phenotype), are particularly common isolates from both animals and humans.<sup>1-3</sup> In 1996, 24% and 14% of these strains were also resistant to trimethoprim and ciprofloxacin, respectively.<sup>4</sup> We report here the in-vitro susceptibilities of 181 strains of *S. enterica* isolated in 1996 in seven centres in the Republic of Ireland.

Clinical isolates were confirmed as belonging to the *S. enterica* group by the API20E system (bioMérieux, Marcy l'Etoile, France) and the serotypes were determined by an agglutination technique with standard antisera (Murex, Dublin, Ireland). The strains were maintained at  $-70^{\circ}\text{C}$  until studied. From the more commonly isolated serovars, 25–50% of non-replicate isolates were randomly selected; the composition of the 181 strains is summarized in the Table. Susceptibility testing was performed by a disc diffusion method according to recommendations of the National Committee for Clinical Laboratory Standards (NCCLS)<sup>5</sup> with *Escherichia coli* ATCC 25922 as a control. The antibiotics tested and the contents of the discs, which were obtained from Oxoid (Basingstoke, UK), were as follows: ampicillin (10  $\mu\text{g}$ ); chloramphenicol (30  $\mu\text{g}$ ); streptomycin (10  $\mu\text{g}$ ); a sulphonamide

## Correspondence

**Table.** Antibiotic susceptibilities of *S. enterica* serovars isolated in the Republic of Ireland

Serovar (no. of strains)	No. (%) of resistant strains					
	ampicillin	chloramphenicol	streptomycin	sulphonamide	tetracycline	trimethoprim
<i>S. enteritidis</i> (53)	0	0	0	0	2 (3.8)	0
<i>S. typhimurium</i> (51)	41 (80)	39 (76)	41 (80)	42 (82)	43 (84)	13 (25)
<i>S. derby</i> (15)	1 (7)	2 (13)	15 (100)	15 (100)	15 (100)	0
<i>S. virchow</i> (13)	4 (31)	1 (8)	1 (8)	4 (31)	4 (31)	3 (23)
<i>S. bredeney</i> (13)	1 (8)	0	1 (8)	3 (23)	1 (8)	2 (15)
<i>S. schwarzengrund</i> (11)	0	0	2 (18)	3 (27)	2 (18)	1 (9)
<i>S. agona</i> (6)	2	0	0	2	0	0
Others <sup>a</sup> (19)	1 (5)	1 (5)	4 (21)	5 (26)	6 (32)	1 (5)
All serovars (181)	50 (28)	43 (24)	64 (35)	74 (41)	73 (40)	20 (11)

<sup>a</sup>Including *Salmonella blockley* (one strain), *Salmonella brandenburg* (four), *S. hadar* (one), *Salmonella heidelberg* (one), *Salmonella indiana* (one), *Salmonella infantis* (two), *Salmonella kedougou* (one), *Salmonella kentucky* (three), *Salmonella mbandaka* (one), *Salmonella montevideo* (one), *Salmonella newport* (two), *Salmonella seegfeld* (one).

(300 µg); tetracycline (30 µg); trimethoprim (5 µg); ciprofloxacin (5 µg); and cefotaxime (30 µg). In addition, the MICs of ciprofloxacin for some strains were determined by the Etest method (AB Biodisk, Solna, Sweden) in accordance with the manufacturer's instructions.

The susceptibilities of the isolates to ampicillin, chloramphenicol, streptomycin, sulphonamides, tetracycline and trimethoprim are summarized in the Table; all of the strains were susceptible to cefotaxime and ciprofloxacin (data not shown). Rates of resistance to at least one of the six antibiotics mentioned above varied according to the serovar. For *Salmonella enteritidis*, only 4% of strains were resistant to one or more of these agents, compared with 94% for *S. typhimurium*. The corresponding values for the other serovars were as follows: *Salmonella derby*, 100%; *Salmonella virchow*, 31%; *Salmonella bredeney*, 38%; *Salmonella schwarzengrund*, 27%; and *Salmonella agona*, 33%. Thirty-seven (73%) of the *S. typhimurium* strains exhibited the ACSSuT phenotype and nine of these strains were resistant to trimethoprim as well. The ACSSuT phenotype was also observed in respect of one strain of *S. derby* and in the single isolate of *Salmonella hadar*.

The data reported here demonstrate high levels of antibiotic resistance amongst *S. enterica* serovars, other than *S. enteritidis*, in the Republic of Ireland. In particular, *S. typhimurium* strains exhibiting the ACSSuT phenotype, which is closely associated with DT 104,<sup>4</sup> now account for approximately three of every four clinical isolates of this serovar. In common with strains isolated in England and Wales, resistance to trimethoprim is also common,<sup>2,4</sup> but, in contrast to the data from England and Wales, resistance to ciprofloxacin was not observed. This discrepancy is almost certainly due to the fact that, in the former studies, a MIC resistance breakpoint for ciprofloxacin of >0.125

mg/L was used,<sup>2,4</sup> whereas we adopted the NCCLS interpretative criterion for the disc diffusion test which corresponds to a MIC breakpoint of >1 mg/L.<sup>5</sup> To test this theory, we determined the MICs of ciprofloxacin for 26 strains of *S. typhimurium* exhibiting the ACSSuT phenotype and for two *S. virchow* strains that were resistant to at least two antibiotics. While all of the *S. typhimurium* strains and one *S. virchow* strain were susceptible to ciprofloxacin, irrespective of the interpretative criterion, the second *S. virchow* strain was categorized as susceptible according to the NCCLS criterion and resistant according to the lower breakpoint adopted by some investigators in England and Wales.<sup>2,4</sup>

A further observation made in the course of this study in relation to streptomycin was that, for *S. enterica* serovars other than *S. enteritidis*, there was a marked clustering of the diameters of the zones of inhibition around the susceptibility breakpoint ( $\geq 15$  mm). This caused almost 8% of all strains to be placed in the intermediate susceptibility category. The tri-modal distribution of the zones of inhibition was also of interest because it suggests that resistance to streptomycin amongst *S. enterica* isolates develops as a two-step process.

The results of the present study have demonstrated high levels of antibiotic resistance amongst most serovars of *S. enterica*, particularly *S. typhimurium*, isolated in the Republic of Ireland. The patterns of resistance were similar to those for strains in England and Wales. There is, however, a need for continuing surveillance nationally of antimicrobial resistance in clinical isolates of *S. enterica*.

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### Clinical isolates of *Staphylococcus epidermidis* with reduced susceptibilities to teicoplanin in a paediatric hospital in Ireland

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Sir,

Coagulase-negative staphylococci (CNS) are important causes of infection in neonates and are often resistant to methicillin and other anti-staphylococcal antibiotics. The isolation of strains of *Staphylococcus epidermidis* exhibiting reduced susceptibility to teicoplanin (MICs  $\geq 4$  mg/L)<sup>1</sup> from blood cultures obtained from patients in a paediatric tertiary referral hospital was therefore of concern and prompted prospective surveillance in order to define the prevalence of these organisms. Isolates were also assessed for epidemiological relatedness by molecular techniques.

The susceptibilities of CNS isolated from blood cultures were initially determined by the disc diffusion method according to guidelines issued by a working party of the British Society for Antimicrobial Chemotherapy;<sup>1</sup> the medium used was IsoSensitest agar (Oxoid, Basingstoke, UK) and the discs contained 30  $\mu$ g of teicoplanin. Strains for which the inhibition zone diameters were  $< 17$  mm<sup>2</sup> were speciated with the ID 32 STAPH system (bio-Mérieux, Marcy l'Étoile, France) and MICs of teicoplanin and vancomycin for these isolates were determined by the Etest method (AB Biodisk, Solna, Sweden) on Iso-

Sensitest agar without additives; strains with teicoplanin MICs  $\geq 4$  mg/L were referred to the Antibiotic Reference Unit of the Central Public Health Laboratory for confirmation of MIC. The isolates were also compared by pulsed-field gel electrophoresis (PFGE) of *Sma*I chromosomal DNA digests. DNA was prepared as described previously<sup>3</sup> and digested with *Sma*I restriction endonuclease (Boehringer Mannheim, Mannheim, Germany) according to the manufacturer's instructions. The restriction fragments were separated by PFGE in 1.2% agarose gels in an electric field of 6 V/cm for 45 h with pulse times ranging from 1 to 45 s.

Between July 1996 and May 1997, CNS with reduced susceptibilities to teicoplanin, all of which were identified as *S. epidermidis*, were isolated from 34 blood cultures obtained from 15 patients. These represented 6.6% of all blood culture isolates and 11.4% of all CNS recovered from blood cultures during that period. The median age of the patients was 1 month (range, 1 week to 8 years). The median duration of hospital stay before isolation of a strain of *S. epidermidis* with reduced susceptibility to teicoplanin (TRSE) was 10 days (range, 0–20 days) and the median number of antibiotic days (total of the number of days during which each antibiotic was administered) was 13 (range, 0–61). No patient from whom one or more strains of TRSE were isolated had previously received teicoplanin, although five had been treated with vancomycin. In three patients, the isolates caused septicaemias. One of these, a 2 week old infant who had undergone surgical correction of gastroschisis, failed to respond to treatment with teicoplanin at a dosage of 7.6 mg/kg daily, but subsequently responded to a course of vancomycin. The isolates from the remaining 12 patients were regarded as skin contaminants ( $n = 11$ ) or as colonizing a central catheter ( $n = 1$ ).

The MICs of teicoplanin and vancomycin for the isolates ranged from 6 to 32 mg/L and 1.5 to 4 mg/L, respectively. Multiple isolates from individual patients, apart from one, exhibited identical antibiograms, although, even in the exception, PFGE confirmed that all of the isolates were variants of the same strain. For two pairs of patients, all of whom had been nursed on the intensive care unit (ICU), the isolates were clonally related and those from a further two patients appeared to be variants of one of these strains.

CNS have emerged as important nosocomial pathogens, although, in this study, TRSE strains were confirmed as pathogens in only three of 15 (20%) patients, all of whom had central lines. The presence of such lines is a significant risk factor for infection with *S. epidermidis*, owing to the ability of this organism to produce slime and to adhere to plastic catheters.<sup>4</sup> Neonatal and post-surgical intensive care patients are particularly susceptible to infections caused by CNS.<sup>5</sup> Ten (67%) of the patients in the present study were on the ICU at the time that strains of TRSE were isolated from them. The discovery of two pairs of