ANTIMICROBIAL RESISTANCE IN COAGULASE-NEGATIVE STAPHYLOCOCCI

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SUMMARY. Patterns of resistance to antimicrobial agents were studied in 193 strains of coagulase-negative staphylococci isolated from hospital patients. Strains isolated from patients with malignant disease were significantly more often resistant to sulphonamide, trimethoprim, gentamicin and methicillin than were strains from other sources. Susceptibility to various β -lactam antibiotics and aminoglycosides was investigated in members of the two most frequent species: *Staphylococcus epidermidis* and *S. haemolyticus*. *S. haemolyticus* strains were not only more often resistant to methicillin than *S. epidermidis* strains (respectively 81% and 17%) but they were more highly resistant (mean MICs respectively 85 and 19 mg/L). Methicillin-resistant *S. haemolyticus* strains were highly resistant to nine other β -lactam antibiotics, whereas methicillin-resistant *S. epidermidis* strains showed both lower levels and a narrower spectrum of cross-resistance. Resistance to methicillin in members of both species was “heterogeneous”, i.e., only a minority of cells in a culture showed significant resistance. Almost all gentamicin-resistant strains were sensitive to netilmicin and amikacin; rifampicin, vancomycin and teicoplanin were also highly active *in vitro*.

INTRODUCTION

Recent changes in therapeutic practice, especially those that have led to the longer survival of patients with defective immunity and the increased use of intravenous catheters, have given a new importance to coagulase-negative staphylococci (CNS) as pathogens (Lowy and Hammer, 1983). If the presence of CNS in a specimen is judged to be clinically significant, it may be difficult to decide upon appropriate antibiotic therapy because the use of two important groups of antibiotics—the β -lactams and the aminoglycosides—may be ruled out by the presence of resistance to them (Archer and Tenenbaum, 1980; Richardson and Marples, 1982; Karchmer, Archer and Dismukes, 1983).

To clarify several outstanding questions in relation to drug resistance among CNS, we surveyed resistance patterns in organisms isolated from a highly “at risk” population—patients undergoing cytotoxic treatment for various leukaemias—and compared these with strains isolated from other types of patients.

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MATERIALS AND METHODS

Antibiotics

The following compounds were obtained from the manufacturers: methicillin, flucloxacillin, cloxacillin (Beecham Research Laboratories); streptomycin, cephalixin, ceftazidime (Glaxo Laboratories Ltd); tobramycin, cephalothin, cefamandole, vancomycin (Eli Lilly and Co. Ltd); gentamicin, cefotaxime (Roussel Laboratories Ltd); teicoplanin, rifampicin (Merrell Pharmaceuticals Ltd); netilmicin (Schering Pharmaceuticals); kanamycin (Bristol-Myers Pharmaceuticals); neomycin (Biorex); ceftoxitin (Merck Sharp and Dohme Ltd); and cephradine (E.R. Squibb and Sons Ltd).

Bacterial strains

Strains of CNS (193 in number), isolated between November 1982 and November 1983, were investigated; 132 of them were from surveillance cultures (mostly nose and throat swabs) from patients being treated for a haematological malignancy (most commonly acute myeloid leukaemia); 61 strains were from patients without malignant disease, most of whom had in-dwelling intravascular lines of one kind or another.

The methods of Marples (1981) and Marples and Richardson (1982) were applied to identify 182 of these strains; 126 (69%) were allocated to biotype SII and 32 (18%) to biotype SVIh. These correspond to *Staphylococcus epidermidis* and *S. haemolyticus* (Kloos and Schleifer, 1975) respectively (Marples, 1981). Of the remaining strains, 11 (6%) belonged to biotype SIII, two to biotype SV, and 11 were not identifiable. Full details of these strains are given in a separate paper (Hamilton-Miller and Iliffe, in press).

Sensitivity testing

Disk test. IsoSensitest Agar (Oxoid) was inoculated with *c.* 10^4 cfu of staphylococci per plate, and set with disks containing the following antibiotics (μ g): clindamycin (2), erythromycin (5), fusidic acid (10), gentamicin (10), rifampicin (5), Sulphatriad (200), tetracycline (10), trimethoprim (2.5). Plates were incubated at 37°C overnight. Some of the gentamicin-resistant strains were further tested against seven other aminoglycosides: amikacin (10), kanamycin (30), neomycin (10), netilmicin (10), sisomicin (10), streptomycin (10) and tobramycin (10). Interpretation of "resistance" in terms of zone diameters was as laid down in the manufacturer's specifications (Oxoid, 1980; and package inserts).

Strip test. Six strains were tested on each 85-mm-diameter plate of Oxoid Nutrient Agar. They were streaked in equidistant parallel lines by means of a wool swab that had been dipped in a bacterial suspension containing *c.* 10^6 cfu/ml. A paper strip (57 $\times$ 6 mm) containing 25 μ g of methicillin (Mast Laboratories, Liverpool) was laid at right angles to the streaks. The plates were incubated at 30°C overnight. The Oxford staphylococcus (NCTC 6571), which was included on every plate, consistently gave a zone of between 10 and 11 mm on each side of the strip. Most of the resistant strains grew right up to the strip, but any strain showing a markedly decreased zone (i.e. 5 mm or less) was also recorded as resistant. The majority of strains were also tested in parallel at 37°C.

Determination of MIC. A large inoculum was used, in order to detect heterogeneous resistance (Jones *et al.*, 1983). Each strain was shaken (100 rpm) at 37°C overnight in 10 ml of IsoSensitest Broth (Oxoid) in a 100-ml conical flask in an orbital incubator (Gallenkamp); 0.7 μ l (*c.* 2×10^7 cfu) was inoculated on to plates of IsoSensitest Agar containing doubling dilutions of 19 antibiotics. Plates were examined after overnight incubation at 37°C, the MIC being taken as the lowest concentration that allowed the growth of 10 colonies or fewer.

Population structure in respect of methicillin resistance. Organisms were grown overnight in Digest Broth (Southern Group Laboratories) and 0.1-ml volumes of decimal dilutions (to 10^{-7}) were spread on to a series of plates of IsoSensitest Agar containing doubling dilutions of methicillin (0.5 to 1024 mg/L). Plates were incubated at 37°C and the proportion of the population able to grow at each antibiotic concentration was calculated. For one strain (*S. haemolyticus* no. 640) two extra series of plates were prepared and were incubated at 40°C and 28°C respectively.

Statistical analysis

Differences in the occurrence of resistant strains from different sources were checked for significance by the χ^2 test, with Yates's correction applied when necessary. For analysis of MICs for organisms of various sensitivity classes (viz. tables II and III), Student's *t* test was applied to logarithms of the individual MIC results.

RESULTS

Antibiotic resistance in strains isolated from patients with malignant disease and from other patients

The results of disk tests with nine antibiotics are shown in table I. There was no significant difference in the frequency of resistance to clindamycin, rifampicin or tetracycline between the two groups of organisms. However, resistance to sulphonamide, trimethoprim, gentamicin and methicillin was significantly more common in patients with malignancy ($p < 0.05$). An unexpected finding was that organisms from patients with a non-malignant condition were more likely to be resistant to erythromycin and to fusidic acid than were organisms from patients with a malignancy ($p < 0.01$).

Most of the gentamicin-resistant strains (90/101) were tested further against a wider range of aminoglycosides. Netilmicin was active against all but one strain, and only five were resistant to amikacin. There was complete cross-resistance between gentamicin and kanamycin, while tobramycin and sisomicin were each active against six strains only (93% resistance). Thirty-one strains (34.5%) were sensitive to neomycin and 52 (58%) to streptomycin.

There was no difference in the frequency of resistance to individual aminoglycosides in gentamicin-resistant strains isolated from patients with a malignancy in comparison with strains from other patients, except in the case of streptomycin; 64% of the former (47/73) but only 29% of the latter (5/17) were sensitive to this antibiotic ($p < 0.05$).

Variation in resistance between staphylococcal species. *S. haemolyticus* strains were more often resistant ($p < 0.01$) than *S. epidermidis* strains to gentamicin (respectively 22/32 and 52/125), to methicillin (26/32 and 21/125) and to both antibiotics (21/32 and 10/125).

Methicillin- and gentamicin-resistant strains of S. epidermidis and S. haemolyticus

Nine strains of each of these two species were selected for further tests of susceptibility to antibiotics.

MICs of β -lactam antibiotics. The 18 strains, and nine strains of methicillin-sensitive *S. epidermidis*, were tested against 10 β -lactam antibiotics (table II). Two points emerged from the results. First, methicillin-resistant strains of *S. haemolyticus* were more resistant to all of these agents than were methicillin-resistant strains of *S. epidermidis*; geometric mean MIC values were significantly higher ($p < 0.05$) in the former than the latter. Second, geometric mean MICs of other β -lactam antibiotics for methicillin-resistant *S. epidermidis* were in several cases not greatly in excess of the values found for methicillin-sensitive strains of the same species. The difference

TABLE I
Resistance to nine antibiotics in coagulase-negative staphylococci isolated from different groups of patients

Source of bacteria	Number of strains	Percentage resistant to								
		clindamycin	erythromycin	fusidic acid	rifampicin	sulphonamide	trimethoprim	gentamicin	tetracycline	methicillin*
Patients with a malignancy	132	2.3	11.4 (<0.001)	4.5 (<0.01)	2.3 (NS)	70.5 (<0.01)	76.5 (<0.01)	62.1 (<0.001)	34.8 (NS)	30.3 (<0.05)
Patients with non-malignant disease	61	4.9	39.3	18	4.9	37.7	57.4	31.1	32.8	16.4
Both groups	193	3.1	20.2	8.8	3.1	60.1	70.5	52.3	34.2	25.9

* Tested at 30°C.

† Significance (p) of difference between the groups; NS = not significant.

TABLE II

MICs of β -lactam antibiotics for nine strains each of methicillin-sensitive *S. epidermidis*, methicillin-resistant *S. epidermidis* and methicillin-resistant *S. haemolyticus*

Antibiotic	Geometric mean MIC (mg/L) (and range) for		
	methicillin-sensitive <i>S. epidermidis</i>	methicillin-resistant <i>S. epidermidis</i> *	methicillin-resistant <i>S. haemolyticus</i> *
Methicillin	3.4 (2-4)	19.1 (1-128)	85 (16-1024)
Flucloxacillin	0.8 (0.25-2)	3.2 (1-128)	20 (2-512)
Cloxacillin	0.9 (0.25-2)	3.2 (1-128)	40 (4-512)
Cefamandole	2.3 (0.5-4)	4.6 (2-16)	20 (16-32)
Ceftazidime	11.7 (8-16)	17 (8-128)	130 (32-256)
Cefotaxime	4 (0.5-8)	7.3 (2-512)	190 (32-1024)
Cephalexin	8.6 (0.5-32)	29.5 (8-256)	305 (128-512)
Cephadrine	8.6 (2-32)	15.9 (4-64)	200 (128-256)
Cephalothin	0.8 (0.25-1)	2.1 (0.5-16)	45 (4-256)
Cefoxitin	5.4 (2-16)	17 (8-128)	70 (32-256)

* The strains were also gentamicin resistant (see table III).

TABLE III

MICs of aminoglycosides for nine strains each of gentamicin-resistant *S. epidermidis* and *S. haemolyticus*, and for the Oxford staphylococcus

Antibiotic	Geometric mean MIC (mg/L) for		
	<i>S. epidermidis</i> *	<i>S. haemolyticus</i> *	Oxford staphylococcus
Neomycin	31.6	7.2	1
Streptomycin	17	> 512	8
Tobramycin	25.1	46.8	0.5
Netilmicin	3	2.3	< 1
Gentamicin	23.4	33.9	< 1
Kanamycin	> 512	> 512	2

* These strains were also methicillin resistant (see table II).

reached the formal level of statistical significance ($p < 0.05$) in respect of flucloxacillin, cloxacillin, cephalexin, cephalothin and cefoxitin but not of cefamandole, ceftazidime, cefotaxime and cephradine. With the latter four antibiotics, however, a small minority of strains showed a degree of resistance exceeding that of any of the methicillin-sensitive strains of *S. epidermidis*.

MICs of aminoglycosides. There were few clinically important differences between the geometric-mean MICs of individual aminoglycosides for members of the two species (table III). Their susceptibility to tobramycin, netilmicin, gentamicin and kanamycin was similar, though *S. epidermidis* strains were on average significantly more resistant to neomycin and less to streptomycin than *S. haemolyticus* strains.

MICs of other antibiotics. All the strains tested were sensitive to rifampicin, vancomycin and teicoplanin (MIC < 1 mg/L).

TABLE IV
Analysis of population structure in terms of sensitivity to methicillin at 37°C; two sensitive, two moderately resistant and two highly resistant strains were tested

Bacterial strain	MIC of methicillin*	Percentage of inoculum capable of growing in the presence of methicillin (mg/L)													
		0.25	0.5	1	2	4	8	16	32	64	128	256	512	1024	
<i>S. epidermidis</i> no. 55836	4	...	100	100	0.0014	0	...	...	...	...	...	...	...	...	
<i>S. haemolyticus</i> no. 46405	†	100	3.3	3.3	0	...	...	...	...	...	...	...	...	...	
<i>S. epidermidis</i> no. 57841	32	...	...	...	100	100	0.097	0.005	0.0003	0.0002	0.0001	0.0001	0	...	
<i>S. epidermidis</i> no. 345	16	...	...	...	100	3.8	0.012	0.005	0.00008	0	...	...	...	...	
<i>S. haemolyticus</i> no. 57839	> 512	...	...	...	...	100	0.013	0.013	0.013	0.013	0.013	0.013	0.013	0.0001	
<i>S. epidermidis</i> no. 57839	256	...	...	...	...	100	75	3.1	0.24	0.14	0.097	0.042	0.02	...	
<i>S. haemolyticus</i> no. 640		...	...	...	...	100								...	

* Determined with a large inoculum, as described in the text.

† MIC not determined, but this strain was fully sensitive in the methicillin-strip test.

Character of methicillin resistance in CNS

Effect of temperature on the methicillin-sensitivity test. Of the 173 strains tested against methicillin at 30° and at 37°C, 116 (67%) were sensitive at both temperatures and 46 (26·5%) were resistant at both temperatures; six were sensitive at 30° but resistant at 37°C and five were resistant at 30° but sensitive at 37°C. It thus appears that methicillin resistance in CNS can be detected equally well at either temperature, in contrast to *S. aureus*, in which testing must be carried out at 30°C (Annear, 1968).

Heterogeneity of methicillin resistance. Six strains of CNS were submitted to population-structure analysis—one sensitive, one moderately resistant and one highly resistant representative each of *S. epidermidis* (nos. 55836, 57841 and 57839 respectively) and *S. haemolyticus* (nos. 46405, 345 and 640 respectively). The results of this experiment (table IV) demonstrated that methicillin-resistant strains of CNS contained only a minority of cells capable of growing in the presence of high concentrations of the antibiotic at 37°C. The test was repeated with *S. haemolyticus* strain 640 at 40° and 28°C (table V). Resistance was expressed most strongly at the lowest temperature and least at the highest.

TABLE V
Heterogeneity of resistance to methicillin in S. haemolyticus strain 640 at various growth temperatures

Growth temperature (°C)	Percentage of inoculum capable of growing at the indicated temperature in the presence of methicillin (mg/L)		
	4	32	256
40	1·9	0·008	0·00006
37	100	0·25	0·042
28	95	39	0·28

DISCUSSION

Study of the literature shows that there is still marked disagreement as to whether or not methicillin-resistant CNS show cross-resistance to the cephalosporins. On the one hand some workers (e.g., Lowy and Hammer, 1983; Karchmer *et al.*, 1983) state that for clinical purposes methicillin-resistant CNS should be regarded as resistant to all cephalosporins irrespective of results of laboratory tests: this is also the case with methicillin-resistant *S. aureus* (Jones *et al.*, 1983). On the other hand, there have been several reports that methicillin-resistant CNS are sensitive to certain cephalosporins *in vitro* (Marsik and Brake, 1982; Price and Flournoy, 1982; Gill *et al.*, 1983; Winston *et al.*, 1983), and cephalosporins have actually been recommended for treatment of infections with methicillin-resistant CNS (Archer, 1978; Winston *et al.*, 1983). These differences may in part be attributed to the methods used by some of the investigators; for example, Lowy *et al.* (1983) showed that the broth-dilution method may fail to detect some resistant strains. However, many previous workers (e.g., Lowy and Hammer, 1983; Winston *et al.*, 1983) did not speciate the CNS strains they tested, and our results show clearly that differences in the "mix" of *S. epidermidis* (*sensu stricto*) and *S. haemolyticus* would greatly affect the results obtained. We found that

methicillin-resistant strains of *S. haemolyticus* showed markedly increased resistance to all seven cephalosporins tested with a large inoculum. On the other hand, methicillin-resistant strains of *S. epidermidis* (Marples biotype SII) had significantly raised mean levels of resistance to only some β -lactam antibiotics. Cephradine, cefamandole, ceftazidime and cefotaxime were almost as active against the majority of methicillin-resistant strains as against methicillin-sensitive strains.

Methicillin resistance in CNS, unlike that in *S. aureus*, can be detected as well at 37° as at 30°C if a large inoculum is employed. Wilkinson *et al.* (1980) reported this for *S. epidermidis*, and our findings confirm their observations and extend them to *S. haemolyticus*. Analysis of population structure showed that methicillin resistance in *S. epidermidis* and *S. haemolyticus* was heterogeneous. In *S. epidermidis* it has been shown to be temperature-dependent (see, for example, Sabath, 1977, and Hansen, 1983); this was also so in our *S. haemolyticus* strain 640. In these respects, therefore, methicillin resistance in the two species of CNS resembles that in *S. aureus* (Annear, 1968; Dyke, 1969).

In all, we found that 26% of the CNS we isolated were resistant to methicillin and 52% to gentamicin. These frequencies were greater in strains isolated from patients with malignant disease than in other patients. This is of potential importance, because patients under treatment for malignant diseases may well need antibiotics for generalised infections caused by CNS. Many of them have already received several antibiotics, including gentamicin and β -lactams, which tend to select resistant organisms. The increased resistance to trimethoprim and sulphonamide in our patients with malignant disease may be explained by the frequent use of prophylactic co-trimoxazole.

The pattern of resistance to aminoglycosides strongly suggested the presence in resistant strains of the inactivating enzyme aminoglycoside phosphotransferase (APT) 2'', which is not active against netilmicin. Aminoglycoside acetylase 6' always accompanies APT 2'' in staphylococci (Shannon and Phillips, 1982) and if present in large amount causes resistance to amikacin. This probably explains the 5% of gentamicin-resistant strains which were found to be resistant to amikacin. Aminoglycoside resistance is plasmid-mediated in CNS; it has been reported recently that the plasmids can be passed from CNS to *S. aureus*, probably by conjugation as well as by transduction (Cohen *et al.*, 1982; Jaffe *et al.*, 1982; Forbes and Schaberg, 1983; McDonnell *et al.*, 1983). Weinstein *et al.* (1982) consider that multi-resistant CNS strains may thus act as a reservoir of resistance for *S. aureus*.

Besides netilmicin and amikacin, the only antibiotics tested to which resistance was infrequent or not detected were rifampicin, vancomycin and teicoplanin. Brumfitt *et al.* (1983) found that the combinations rifampicin plus novobiocin and rifampicin plus teicoplanin had promising in-vitro action against multi-resistant staphylococci. We feel that future strategies for the treatment of infections caused by such organisms will depend upon the use of antibiotics at present considered to be in the "reserve" category.

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