Hospital-acquired infection with methicillin-resistant and methicillin-sensitive staphylococci

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SUMMARY

In-patients at a London hospital over one year from whom the south-east England strain of 'epidemic' methicillin-resistant *Staphylococcus aureus* (MRSA) was isolated were compared with in-patients with strains of methicillin-sensitive *Staphylococcus aureus* (MSSA). MRSA were virtually entirely hospital-acquired; isolates before 10 days were uncommon and related to recent previous admission. Thereafter first isolates occurred at a fairly constant daily rate of about 1·9 per 1000 in-patients. Acquisition of MSSA after more than 4 days in hospital occurred at a similar constant rate. Such strains were less likely to be penicillin-sensitive than strains isolated in the first 4 days after admission (11 *vs.* 22%) and were considered to be hospital-acquired. The single MRSA strain caused 40 infections in a year, about half of all hospital-acquired staphylococcal infections. Patients prescribed anti-staphylococcal antibiotics and patients with indwelling cannulae both had about a ninefold increased risk of acquiring MRSA. There was no reciprocal increase in MSSA infections after control measures had substantially reduced the number of MRSA infections.

INTRODUCTION

A single 'epidemic' strain of methicillin-resistant *Staphylococcus aureus* (MRSA) has become widespread in hospitals in south-east England, having first been detected in 1981 (Marples & Cooke, 1985; Sanderson, 1986; Casewell, 1986). We have recently described an outbreak of this strain of MRSA in a district general hospital in London; prevalence of colonization was high (52% among in-patients 10 or more days in hospital) but rigorous measures succeeded in controlling the outbreak (Law *et al.* 1988). We now report a comparison of the patients with isolates of this single strain of MRSA with in-patients with isolates of hospital-acquired methicillin-sensitive *Staphylococcus aureus* (MSSA). This enabled us to examine the proportion of all nosocomial staphylococcal infections caused by the single MRSA strain in an extensive outbreak, risk factors for MRSA acquisition, and also the suggestion (Thompson *et al.* 1982; Linnemann *et al.* 1982) that successful reduction in the number of MRSA infections merely produces a reciprocal increase in nosocomial MSSA infections.

METHODS

The district general hospital contained 255 acute beds in 14 wards (5 general medicine, 4 general surgery, 3 orthopaedic, 1 gynaecological and the ICU). We recorded all laboratory isolates of *Staphylococcus aureus* from these acute wards over a period of one year (1985–6) before the instigation of control measures. The methods for the laboratory detection of methicillin resistance and for phage typing (at the Division of Hospital Infection, Central Public Health Laboratory, Colindale) to identify the strain of MRSA prevalent in south-east England have been previously described (Law *et al*. 1988). Age, sex and duration of admission of the patients with isolates of MRSA or MSSA were obtained from computerized admission data. Infections were diagnosed retrospectively from laboratory and hospital case records, and attributed to MRSA or MSSA, using criteria previously described (Law *et al*. 1988). Among the antibiotics that had been prescribed for these patients up to 4 weeks before isolation of MRSA or MSSA, documented from hospital case records, the following were considered 'anti-staphyloccal' in that hospital strains of MSSA are commonly susceptible to them: flucloxacillin, cephradine, cefuroxime, cefotaxime, erythromycin, tetracyclines, fusidic acid, co-trimoxazole and gentamicin. This classification was supported by a standard reference (Slack, 1987).

RESULTS

During the one year period before the introduction of control measures, the south-east England 'epidemic' MRSA strain was isolated from 74 in-patients on acute medical and surgical wards, other strains of MRSA (not further considered) from 5 patients and MSSA strains from 212. Fig. 1 shows the incidence of first isolation of 'epidemic' MRSA and of MSSA, according to duration of admission, among all in-patients (this denominator being obtained from Hospital Activity Analysis data). MRSA isolates were uncommon during the first 10 days, but thereafter occurred at a fairly constant daily rate of about 1·9 per 1000 in-patients. The daily rate of first isolation of MSSA was high during the first 4 days but fairly constant thereafter around a mean value of 1·7 per 1000 in-patients.

The south-east England strain of MRSA was isolated during the first 4 days of admission from 8 patients, and 5 of these had been admitted to hospital within the previous month and a seventh had twice attended out-patients. MRSA was isolated from a further 6 patients between the 5th and 10th days of admission; 3 of these also had had hospital admissions in the previous month and the other 3 were on the intensive care unit. There were 117 patients from whom MSSA was isolated during the first 4 days of admission, and of these only 7 (6%) had been admitted to hospital within the past month (for the comparison with 6 of 8 MRSA patients, $P < 0·001$, Fisher's exact test).

We took the association of MRSA isolates after 4 days or less in hospital with recent previous admission, and the observation (Law *et al*. 1988) of no isolates from out-patients or general practice, to indicate that the south-east England MRSA strain, like most MRSA strains, is virtually entirely hospital-acquired. To enable a comparison of MRSA with hospital-acquired MSSA, we took MSSA
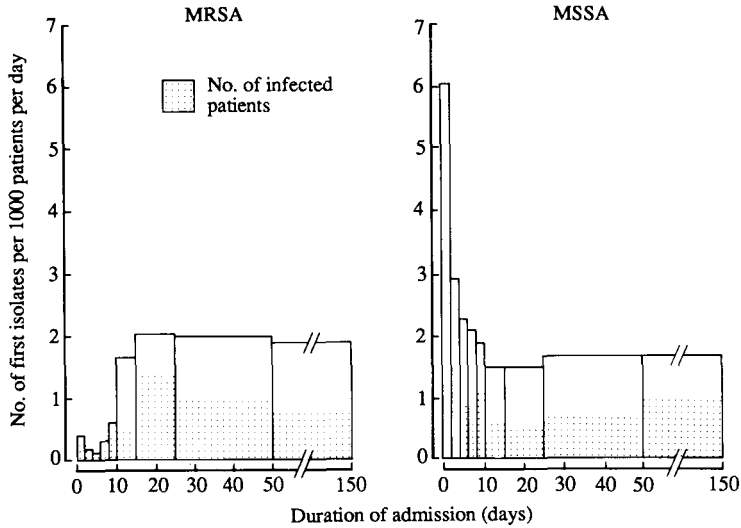
Fig. 1. Incidence of first isolates of methicillin-resistant (MRSA) and methicillin-sensitive (MSSA) *Staphylococcus aureus* and incidence of hospital-acquired infection, per 1000 patients per day, according to duration of admission.
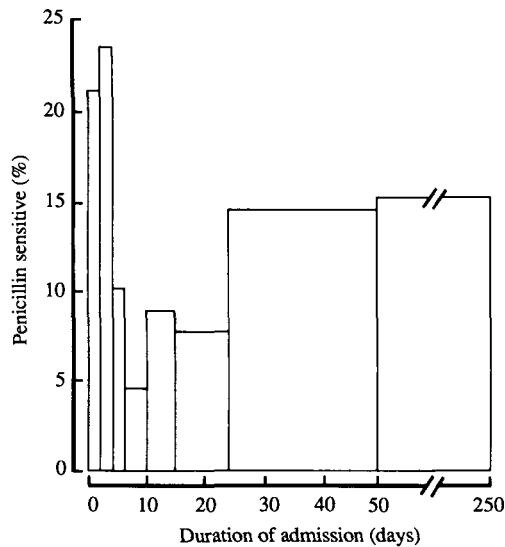

Fig. 2. Penicillin sensitivity of isolates of MSSA according to duration of admission.

isolated after more than 4 days in hospital as being likely to be hospital-acquired. A cut-off of about 4 days has been used by others (Boyce *et al*. 1983; Linnemann *et al*. 1982), and was confirmed in the present study by recording penicillin sensitivity, since community-acquired MSSA is more likely to be penicillin sensitive than hospital-acquired MSSA. As shown in Fig. 2, penicillin sensitivity was more common in MSSA isolated during the first 4 days of admission (26/

Table 1. *Comparison of in-patients with isolations of MRSA and hospital acquired MSSA over one year*

	MRSA		MSSA	
Number	74		95	
Age (y) – mean ($\pm$ s.d.)	68	($\pm$ 17)	65	($\pm$ 18)
Duration of admission before isolation of staphylococcus (days) – mean ($\pm$ s.d.)	34	($\pm$ 45)	30	($\pm$ 58)
Number (%) given anti-staphylococcal antibiotics	*60	(81 %)	31	(33 %)
Infections associated with in-dwelling cannulae:				
Urinary tract infection in catherized patients	12		3	
Pneumonia associated with endotracheal intubation	2		0	
Cellulitis around intravenous line	3		0	
Total	†17	(23 %)	3	(3 %)
Deaths				
Attributed to staphylococcal infection	3		2	
Unrelated to staphylococcal infection	15		13	

* Odds ratio = 9, $\chi_1^2 = 39$, $p < 0.001$.
† Odds ratio = 9, $\chi_1^2 = 16$, $p < 0.001$.

117 – 22 %) than on the fifth and subsequent days (10/95 – 11 %) – $\chi_1^2 = 6.2$, $P = 0.01$.

In Table 1, the 74 patients with isolates of MRSA and the 95 patients with isolates of MSSA after more than 4 days in hospital are compared. Age and sex ratio were similar. Taking MSSA patients as controls for the MRSA cases, antistaphylococcal antibiotics increased the risk of acquisition of MRSA by about ninefold ($P < 0.001$), and patients prescribed these antibiotics constituted 81 % of all patients with MRSA. Patients with indwelling cannulae (urinary catheters, endotracheal tubes, intravenous lines) also had about a ninefold greater risk of acquiring MRSA ($P < 0.001$). The two were associated in that patients with indwelling cannulae were also likely to have been prescribed anti-staphylococcol antibiotics. However both factors increased risk independently: among patients *without* cannulae, 45 of 57 (79 %) of patients with MRSA isolates but only 31 of 92 (34 %) with MSSA isolates had been prescribed anti-staphylococcal antibiotics ($\chi_1^2 = 29$, $P < 0.001$), while among patients prescribed anti-staphylococcal antibiotics, 15 of 60 (25 %) with MRSA isolates but only 1 of 31 (3 %) with MSSA had indwelling cannulae ($\chi_1^2 = 6.7$, $p = 0.01$).

Table 2 shows morbidity (as previously defined) from MRSA and MSSA infections according to duration of admission, and the incidence of infections is also shown in Fig. 1. About half of all isolates represented infections. Among patients in hospital more than 10 days, MRSA caused more infections than did MSSA. In all there were 40 infections (3 deaths) attributable to MRSA and 36 infections (2 deaths) attributable to MSSA isolated after more than 4 days in hospital.

Fig. 3 compares the combined number of urinary tract infections and

Table 2. *Morbidity from hospital-acquired MRSA and MSSA infections according to duration of admission*

	Duration of admission						
	1–4 days	5–10 days		11 + days		Total	
	MRSA*	MRSA	MSSA	MRSA	MSSA	MRSA	MSSA
Bacteraemia							
Alone	1	0	2	0	1	1	(3)
With pneumonia and/or septic shock	1	2	3	3	2	6	(5)
Deep surgical wound infection	0	0	0	5	2	5	(2)
Superficial surgical wound infection	1	2	5	5	7	8	(12)
Conjunctivitis	0	0	0	0	3	0	(3)
Skin infection	2	0	2	6	4	8	(6)
Urinary tract infection	1	2	3	9	2	12	(5)
Total episodes of infection	6	6	15	28	21	40	(36)
No. of patients with infection	5	5	14	27	21	37	(35)
No. of patients with isolates (with or without infection)	8	6	42	60	53	74	(95)

* No. of hospital-acquired MSSA infections after 1–4 days is uncertain.
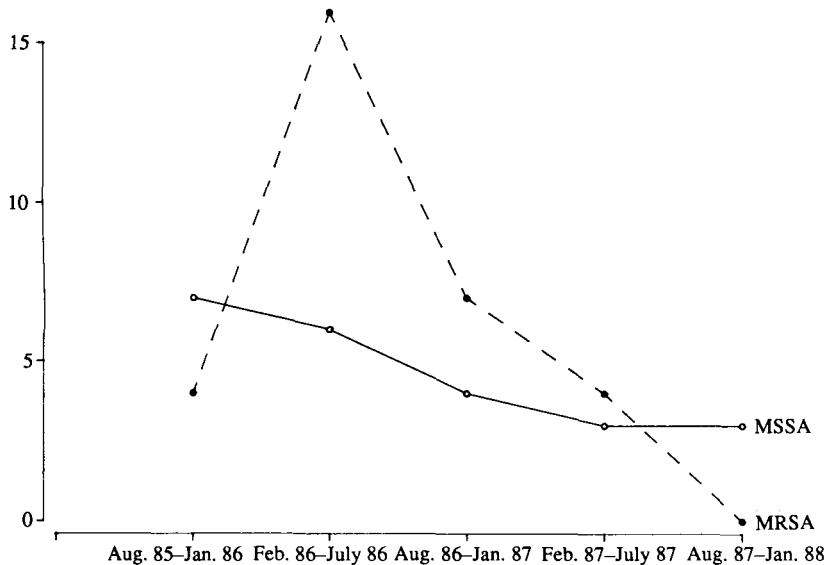

Fig. 3. Incidence of hospital acquired urinary tract infections and bacteraemias (combined) attributable to MRSA and MSSA before and after control measures for MRSA.

bacteraemias, as previously defined, attributable to MRSA, and to MSSA after more than 4 days in hospital, in 6-monthly periods over the one year before the instigation of control measures and 18 months subsequently. The incidence of MSSA infections remained fairly constant while MRSA infections declined. In testing the null hypothesis that there *is* a reciprocal association between the two,

i.e. that the total number of staphylococcal infections (MRSA and MSSA) in each 6-month period varied only randomly (about a Poisson average), χ_4^2 for heterogeneity was 18·6 ($P = 0·001$). The results indicate that the total number of staphylococcol infections did vary systematically with the number of MRSA infections, and that there was no reciprocal association between MRSA and MSSA.

DISCUSSION

As discussed above, the south-east England strain of MRSA appears virtually entirely hospital-acquired. Fig. 1 suggests a fairly uniform rate of first isolation after 10 days. MSSA isolated after more than 4 days in hospital is also likely to be hospital-acquired, as suggested by the fairly uniform rate of first isolation of MSSA (Fig. 1) and the lower rate of penicillin sensitivity (Fig. 2) after more than 4 days. We cannot estimate the proportion of MSSA isolates after 4 days or less that was hospital-acquired, but it is likely to be low. Thus, as shown in Table 2, the number of MRSA infections and the approximate number of hospital-acquired MSSA infections were similar. The single 'epidemic' strain of MRSA caused about half of all nosocomial staphylococcal infections.

Comparison with MSSA isolates likely to be hospital-acquired shows that risk factors for acquisition of MRSA included relatively long duration of admission (Fig. 1, Table 2) and anti-staphylococcal antibiotics (ninefold increased risk, Table 1), as previously shown for other strains (Boyce *et al.* 1981; Crossley *et al.* 1979). Indwelling cannulae (urinary catheters, endotracheal tubes and intravenous lines) were also a risk factor, independent of antibiotic therapy. The concentration of extensive antibiotic use, portals of entry (indwelling cannulae, surgical wounds) and the large numbers of medical and paramedical staff in intensive care units is likely to account for their high incidence of MRSA infections. Conversely, the relative absence of these factors on geriatric wards may account for our observation of only one MRSA infection in a year, and no colonized patients at the end of the year (Law *et al.* 1988).

The morbidity and mortality caused by this strain of MRSA would indicate a need for rigorous control measures. However two studies have suggested that reduction in the number of MRSA infections merely results in a reciprocal increase in the number of hospital-acquired MSSA infections, the total remaining fairly constant (Thompson *et al.* 1982; Linnemann *et al.* 1982). Boyce *et al.* (1983) observed no reciprocal association, the incidence of nosocomial MSSA infections remaining constant during a period of fluctuating incidence of MRSA infections. Our study supports the finding of Boyce *et al.* (1983) of no reciprocal association, and thereby supports our previous recommendation (Law *et al.* 1988) for the instigation of rigorous control measures in hospitals in which the south-east England MRSA strain is established.

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