Methicillin-resistant *Staphylococcus aureus*: associated morbidity and effectiveness of control measures

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SUMMARY

The strain of methicillin-resistant *Staphylococcus aureus* (MRSA) prevalent in south-east England produced in one acute hospital in a year 40 infections (bacteraemia, pneumonia and surgical wound, skin and urinary tract infections) with three attributable deaths. Rigorous measures succeeded in controlling the outbreak despite its extent, but our results suggest that less stringent measures could fail to control outbreaks of this scale. Several subsequent localized outbreaks within the hospital, probably caused by separate re-introductions of MRSA from other hospitals, were controlled by re-institution of control measures on individual wards. The overall success of the intervention was shown by the decline in the incidence of MRSA infections from 27 in the 6 months beforehand to 2 in the most recent 6 months, and by the decline in the prevalence of colonization among patients 10 or more days in hospital from 52% immediately before the intervention to 3% 7 months after it. The incidence of attributable morbidity and death without control measures warrants a concerted effort to tackle the epidemic in all affected hospitals in Britain.

INTRODUCTION

Hospital outbreaks of infection with so-called 'epidemic' strains of methicillin-resistant *Staphylococcus aureus* (MRSA) have in recent years been reported from several countries including the USA, Australia, Ireland and Saudi Arabia (Casewell, 1986; Marples & Cooke, 1985; Cooke & Marples, 1985). Such strains spread easily within and between hospitals, and are resistant to many antibiotics besides methicillin (although the acronym MRSA has persisted). An 'epidemic' strain of MRSA, the same as the Saudi strain but different from strains prevalent in other countries, was first isolated in Britain in the North East Thames Region in 1981 and has now become widespread in hospitals in south-east England (Marples & Cooke, 1985; Cooke & Marples, 1985). There has been debate about the pathogenicity of MRSA, and whether it causes sufficient morbidity to justify control measures (Lacey *et al.* 1986; Cristino *et al.* 1986; Sanderson, 1986). There has also been uncertainty as to the effectiveness of control measures. A review by

Thompson *et al.* (1982) of 18 reported attempts to control MRSA in US hospitals between 1976 and 1982 found that eradication was complete in only two of the outbreaks, both small and localized. Similarly, in other reported outbreaks, control measures have generally succeeded only where outbreaks were localized to one or two wards with fewer than 20 colonized or infected patients (Dacre *et al.* 1986; Shanson *et al.* 1985; Locksley *et al.* 1982; Dunkle *et al.* 1981), or where the MRSA was not of the present 'epidemic' strain (Selkon *et al.* 1980; Shanson *et al.* 1976) but otherwise have not succeeded (Bacon *et al.* 1985; Cristino *et al.* 1986; Linnemann *et al.* 1982; Crossley *et al.* 1979).

We report the success of rigorous control measures in an extensive outbreak of the south-east England strain of 'epidemic' MRSA in a London hospital. We also assessed the pathogenicity of the organism by retrospectively documenting morbidity for one year before the introduction of control measures.

METHODS

Microbiological techniques

Methicillin resistance was detected in clinical isolates of *Staphylococcus aureus* by incubation with a 10 unit methicillin disk at 30 °C for 24 h. For screening for MRSA colonization, moist swabs were inoculated directly onto mannitol salt agar plates with a 10 unit methicillin disk at 37 °C for 48 h; colonies suspected to be MRSA were incubated on blood agar with a 10 unit methicillin disk at 30 °C for 24 h. The national reference laboratory (Division of Hospital Infection, Central Public Health Laboratory, Colindale) confirmed methicillin resistance and carried out phage typing to identify the strain of MRSA prevalent in south-east England. This strain fails to react with the international set of phages but types with experimental phages 88A and 932; it also has a characteristic pattern of antibiotic resistance (Marples *et al.* 1986).

Assessment of morbidity

We retrospectively examined the hospital case records of all patients from whom MRSA had been isolated during the year before the introduction of the control measures. Morbidity was defined as follows: (a) septic shock – bacteraemia and documented hypotension (systolic blood pressure < 90 mmHg) and oliguria; (b) pneumonia – chest X-ray showing infiltration or consolidation in the absence of another documented cause and either fever (> 38 °C) or purulent sputum in the presence of positive blood cultures; (c) superficial surgical wound infection – documentation of purulent discharge or erythema of wound edges; (d) deep surgical wound infection and (e) infected skin lesion – documented clinical diagnosis; (f) urinary tract infection – > 10⁵ bacteria per ml and 10 or more leucocytes per high power field on urine microscopy. These conditions were attributed to MRSA if the staphylococcus was cultured in moderate or heavy growth within 48 h and if no other organism was cultured from a specimen relevant to the condition.

Outbreak description

The district general hospital contained 14 acute wards (5 general medical, 4 general surgical, 3 orthopaedic, 1 gynaecology and the intensive care unit), 4

Table 1. *The numbers of patients from whom clinical specimens cultured MRSA, as a proportion of all patients with Staphylococcus aureus, during the year before the instigation of control measures*

	All <i>S. aureus</i>	MRSA 'epidemic' strain	MRSA other strains
In-patients			
Intensive care units (5 beds)	24	11 (46%)	0
13 other acute medical and surgical wards (250 beds)	266	63 (24%)*	4 (6%)
4 geriatric wards (105 beds)	48	3 (6%)	1 (2%)
4 psychiatric wards	7	0	0
Total	345	77 (22%)	5 (2%)
Out-patients			
Accident and emergency	149	0	0
Hospital outpatients	96	3 (3%)	0
General practice	106	1 (1%)	0
Total	351	4 (1%)	0

* $\chi^2_1 = 5.6$, $P = 0.02$.

† $\chi^2_1 = 7.5$, $P = 0.006$.

geriatric wards and 4 psychiatric wards. During the year before the intervention, epidemic MRSA was isolated from clinically-indicated specimens from 77 in-patients (Table 1), with at least one isolate from each of the acute wards. The intervention followed the transfer of all the acute beds to an adjacent new hospital building. Two weeks before this transfer, admissions to the acute wards were curtailed, allowing six to be closed and their patients transferred to the remaining eight. Immediately before the transfer, patients on these eight wards were screened for colonization with MRSA by culturing swabs from the nose, hairline and groin, any skin lesions, wounds or I-V sites, and also urine in catheterized patients. The results of this survey are shown in Fig. 1. In all, 49 of 95 (52%)

Fig. 1. Prevalence of MRSA colonization among all in-patients on acute wards before and 7 months after instigation of control measures.

patients who had been in hospital for more than 10 days were colonized. Each of the eight acute wards contained at least one colonized patient; the prevalence of colonization on individual wards varied between 1/13 (8%) and 15/17 (88%).

Control measures

These were based on published guidelines (Combined Working Party, 1986) and begun immediately after the transfer to the new hospital. Patients who were found to be infected or colonized with MRSA in the above survey at the old hospital were admitted in the new hospital to one of two designated isolation wards or, on the intensive care unit, to isolation cubicles. Patients who were negative on the survey were admitted in the new hospital to wards designated as 'contaminated' (since staff and patients had mixed with MRSA patients). New patients were not admitted to any 'contaminated' ward until it was 'cleared' (i.e. declared free of MRSA). Staff movement between wards was strictly limited. Clearance was done in one of two ways. When two 'contaminated' wards had discharged sufficient patients to amalgamate, the empty ward was extensively cleaned and all staff screened. In wards that could not be emptied, staff and patients were repeatedly screened 3 or more days apart (with patients found to be colonized being transferred to an isolation ward), until two successive screens were entirely negative, then the ward was extensively cleaned, and a final screen of staff and remaining patients conducted after this cleaning. Wards cleared by either method were called 'clean' and were opened to new admissions but not to patients from 'contaminated' wards. Colonized staff and patients were treated in a standard manner (Combined Working Party, 1986). Nasal carriage was treated with 'Naseptin' cream (ICI) or, when available, the nasal preparation of Mupirocin (Bactroban, Beecham Laboratories Limited); infected skin lesions were treated with topical Mupirocin, and povidone-iodine preparations were substituted for ordinary soap and shampoo.

Staff continued working and patients left the isolation wards either on discharge home or when three successive negative screens after completion of treatment allowed them to transfer to a 'clean' ward. One of the two isolation wards was cleared after its patients could all be transferred to the second; this ward was cleared when the number of remaining colonized patients became small enough for them all to be nursed in side rooms used as isolation cubicles.

To avoid re-introduction of MRSA, all new patients who had been discharged within the previous 3 months from a hospital known to harbour MRSA were admitted to side rooms until screening for MRSA was known to be negative. When MRSA did re-appear, staff and patients on the ward were screened, and side rooms were used as isolation cubicles for infected and colonized patients.

RESULTS

Morbidity and prevalence of MRSA before control measures

During the year before the instigation of control measures the south-east England strain of 'epidemic' MRSA was cultured from clinical specimens from 77 in-patients and other strains of MRSA (not further considered) from five (Table 1). 'Epidemic' MRSA constituted 46% of all staphylococcal isolates from the

Table 2. *Morbidity attributable to MRSA in patients on acute wards during the year before the instigation of control measures*

Bacteraemia	
Alone	1
With septic shock	3 (2 deaths)
With pneumonia and septic shock	3 (1 death)
Deep surgical wound infection	
Empyema	1
Pelvic abscess	1
Perianal abscess	1
Infected joint prosthesis	2
Superficial surgical wound infection	8
Skin infection	
Cellulitis related to skin lesion or intravenous lines	6
Abscess	2
Urinary tract infection	12
Number of episodes of infection	40
Number of patients with infection	37
Deaths attributable to MRSA	3
MRSA isolated from clinical specimen, but no infection	37

intensive care unit, 24% of isolates from other acute medical and surgical wards and 6% of isolates from geriatric wards (the differences being statistically significant) (Table 1).

Table 2 shows the morbidity attributed to 'epidemic' MRSA in in-patients on the 14 acute wards during the year. A total of 40 infections occurred in 37 patients. Three patients died from MRSA bacteraemia, only one of whom had serious underlying chronic illness. On the geriatric wards by contrast, the only morbidity attributable to MRSA was one infected leg ulcer.

Of the 77 in-patients with 'epidemic' MRSA, the organism was isolated during the first 4 days of admission in only eight. Six of these eight had been admitted to hospital within the previous month and a seventh had twice attended out-patients. The four MRSA isolates from out-patients and general practice were also from patients recently hospitalized.

In the survey of in-patients on acute wards in the old hospital immediately before the transfer and intervention, the prevalence of MRSA colonization (Fig. 1) increased with duration of admission (X^2_1 for linear trend = 14.5, $P < 0.001$), and, as stated above, among 95 patients in acute wards for more than 10 days, 49 (52%) were found to be colonized. In two geriatric wards by contrast, average duration of admission was longer but only 1 of 42 patients was colonized, and MRSA had previously been isolated from that 1 patient while on an acute ward.

Outcome of control measures

There were 99 patients who were negative on the initial survey and were transferred to 'contaminated' wards at the new site; 11 (11%) of these were found to be positive on subsequent screening (Table 3). This tended to occur on wards

Table 3. Results of screening in-patients for MRSA colonization during the clearance procedure. (Positives at each stage were isolated, repeat screening done only on those previously negative.)

	Number screened	Number (%) positive
Initial screen	163	52 (40)
Clearance screens		
1	99	7 (7.1)
2	73	1 (1.4)
3	36	2 (5.6)
4-5	27	0
Final screen (after two negative clearance screens and cleaning of ward)	67	1 (1.5)

where the initial survey had shown a high prevalence of colonization. All patients were ultimately screen-negative on three successive occasions (unless discharged before-hand). Of the staff in contact with MRSA patients, 20 (5%) were colonized, a similar prevalence to values of 2%, 6% and 8% reported by others (Linnemann *et al.* 1982; Boyce *et al.* 1981; Crossley *et al.* 1979).

Fig. 2 shows the number of patients developing MRSA infections before and after the instigation of control measures. During the 6 months immediately before the control measures were introduced 27 patients developed MRSA infections and during the most recent 6 months only 2 patients ($X^2_1 = 22, P < 0.001$). Morbidity associated with infection also declined; since completion of control measures there

Fig. 2. The number of patients developing infection attributable to MRSA, before and after the instigation of control measures.

have been no bacteraemias, only one deep surgical wound infection, and no deaths attributable to MRSA.

Seven months after the completion of the control measures, a second prevalence survey of MRSA colonization among all acute in-patients was conducted – the result is contrasted with the initial prevalence survey in Fig. 1. Among patients in hospital for more than 10 days the prevalence declined from 49/95 (52 %) to 4/124 (3 %) ($X^2_1 = 68$, $P < 0.001$). Not included in the second prevalence survey were four patients already known to be colonized who were isolated and undergoing treatment.

DISCUSSION

In one year the south-east England 'epidemic' strain of MRSA caused 40 infections and 3 deaths on acute wards. The estimate of 40 infections is likely to be low because we used conservative criteria for diagnosing infections and attributing them to MRSA so as to exclude cases where MRSA was merely a contaminant. We found no evidence for community acquisition; 69 (90 %) of the 77 in-patients from whom MRSA was isolated had been in hospital for more than 4 days, and both in-patients admitted for 4 days or less and out-patients with MRSA had recently been discharged from hospital. The 40 infections were therefore probably all nosocomial. This evidence of nosocomial infection with associated mortality, together with other reports of deaths caused by the strain (Marples & Cooke, 1985; Bradley *et al.* 1985) is sufficient to justify rigorous control measures.

The long-term success of the rigorous control measures we used can be judged by the substantial reduction both in the prevalence of colonization (Fig. 1) and in the incidence of infection attributable to MRSA (Fig. 2) after the intervention. As stated above there are few reported instances of control of outbreaks as extensive as this. Factors which favoured the success of our intervention despite the high prevalence of colonization at the outset included not only the availability of temporary designated isolation wards but also the fact that we were able simultaneously to tackle all the hospital reservoirs of MRSA – infected and colonized patients, colonized staff and contaminated hospital furnishings. Determining the extent of the reservoirs of MRSA among patients and staff required extensive and repeated screening. However our experience suggests that a less rigorous approach may have failed to control the outbreak; Table 3 shows that of 99 patients who were negative on the initial screen, 11 were subsequently found to be colonized when re-screened after the transfer to the new site. Had these 11 not been identified they may have been sufficient to maintain the outbreak. It is noteworthy that they tended to have been on wards at the old hospital where the prevalence of colonization was particularly high. The extent to which they represent limited sensitivity of the original screen or colonization after this screen, perhaps from contaminated ward furniture, is not clear, but MRSA can frequently be isolated from the inanimate hospital environment (Thompson *et al.* 1982; Crossley *et al.* 1979). In an extensive MRSA outbreak, patients negative on a single screening for colonization need to be nursed in 'contaminated' wards and be submitted to repeated screening procedures in order to establish the true extent of colonization.

The main cost of our control measures was closure of the hospital to all waiting list cases and many emergency admissions for 5 weeks because of the limited number of 'clean' wards. However the need for our policy of not admitting new patients to empty beds on 'contaminated' wards is unproven. Also, on geriatric and other chronic wards we found neither clinical illness or colonization with MRSA, suggesting that control measures may not be necessary on such wards, and also suggesting that it is reasonable to discharge colonized patients to old people's homes, although in our experience the homes were reluctant to receive them.

Surveillance after completion of the control measures detected several subsequent minor outbreaks on individual wards. The infections that have occurred in the 15 months after completion of control measures (Fig. 2) resulted from such outbreaks, and they were contained by reinstigating control measures on the wards in question, using side rooms as isolation cubicles. These minor outbreaks appeared unrelated to each other, and probably represented separate reintroductions of MRSA into the hospital after its initial elimination. We continued to screen new patients recently discharged from hospitals known to harbour MRSA, but other means of transmitting MRSA between hospitals are more difficult to control, such as staff who work at more than one hospital (agency nurses, certain medical staff), and patients briefly transferred to other hospitals for investigations.

A concerted effort to tackle the 'epidemic' MRSA outbreak in all affected hospitals in south-east England is needed. In the absence of control measures in individual hospitals it is clear that the organism can become ubiquitous and cause deaths. Moreover vancomycin, the treatment of choice for serious MRSA infections, is expensive and toxic, and a high prevalence of MRSA in a hospital would necessitate the incorporation of vancomycin into any treatment regime for serious infections until microbiological culture and sensitivities were available. It is more difficult for hospitals which have tackled an outbreak to remain reasonably free of MRSA if neighbouring hospitals are not. Unless many hospitals adopt rigorous control measures it is likely that the organism will in time establish itself in hospitals throughout Britain.

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