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Control of Epidemic Methicillin-Resistant *Staphylococcus aureus* in a Dutch University Hospital

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Between 1986 and 1989 a single strain of a methicillin- and multiply-resistant *Staphylococcus aureus* caused three distinct outbreaks at Utrecht University Hospital, involving 11, 19 and 32 patients, respectively. In all three episodes, members of staff were screened for MRSA carriage, and 58 persons were found to have positive nose cultures. In each outbreak it became necessary to isolate colonized and infected patients on a separate isolation ward. Staff carriers were also treated. Over the 18 months since the last outbreak, no new acquisitions of this epidemic MRSA strain have occurred. Between 1986 and 1989, the strain which caused the three outbreaks was not the only MRSA strain which was introduced into the hospital. Six other strains, which differed from the epidemic strain as shown by phage typing and antimicrobial susceptibility pattern, were found in single patients. The experience at Utrecht University Hospital illustrates the need for strict measures to eradicate epidemic strains of MRSA as well as the differences in "epidemicity" among various strains of MRSA.

During the 1950s, *Staphylococcus aureus* was a major cause of nosocomial infections, especially of postoperative wound infections. With the introduction in the early 1960s of the β-lactamase-resistant penicillins and cephalosporins the problem of *Staphylococcus aureus* in hospitals seemed to be solved, and gram-negative microorganisms became the important nosocomial pathogens.

By the mid-1970s, however, *Staphylococcus aureus* strains appeared which were resistant not only to the β-lactamase-resistant penicillins and cephalosporins, but also to a wide range of other antimicrobial agents (1). These strains are commonly designated as methicillin-resistant *Staphylococcus aureus* or MRSA, although they are resistant to more antimicrobial agents. Recently, MARSA (methicillin-aminoglycoside-resistant *Staphylococcus aureus*) has been proposed as a more appropriate name (2). Several outbreaks of MRSA in hospitals have been described (3–5). The spread of these multiply-resistant *Staphylococcus aureus* strains may mean a return to the situation of the fifties with respect to nosocomial staphylococcal infections. This report describes the introduction of an epidemic MRSA into the Utrecht University Hospital, the ensuing three outbreaks and the measures taken which eventually resulted in elimination of the epidemic strain from the hospital. Besides the epidemic strain MRSA strains which caused only sporadic cases of colonization or infection were also isolated.

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The Three Outbreaks at Utrecht University Hospital

First Outbreak. A *Staphylococcus aureus* strain resistant to methicillin was first isolated from the urine of a catheterized male patient on a neurology ward at the end of July 1986. Before admission to our hospital, he had been treated for two months in an Italian hospital for a spinal injury after a car accident. The strain, which had never been isolated previously at Utrecht University Hospital, was resistant to several antimicrobial agents (Table 1). It was not typable with the international phages, but could be typed with an experimental set of phages specific for MRSA which has been developed at the Netherlands

Table 1: Antibiotic susceptibility pattern of the first MRSA strain isolated at Utrecht University Hospital.

Antimicrobial agent	MIC (mg/l)
Methicillin	> 64
Imipenem	> 16
Clindamycin	> 4
Erythromycin	> 4
Vancomycin	1
Teicoplanin	≤ 0.5
Fusidic acid	≤ 0.03
Rifampicin	> 2
Chloramphenicol	4
Tetracycline	> 16
Neomycin	≤ 0.25
Gentamicin	> 16
Amikacin	16
Cotrimoxazole	0.12
Ciprofloxacin	2

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The patient was immediately put under strict isolation in a side-room of the neurology ward and treated with vancomycin for his urinary tract infection. All other patients on the ward were screened for MRSA carriage by culture of nasal and throat swabs, and urine and wound exudate specimens. These screening cultures were performed once. All cultures remained negative. By mid-August, follow-up cultures of the first patient were negative and he was discharged to a nursing home.

A week later, the same MRSA strain was isolated from the sputum of a second patient on the neurology ward. Between September and November an outbreak occurred which involved nine other patients, two of whom developed an infection (one patient developed pneumonia and one a urinary tract infection). At the onset of this outbreak, patients were strictly isolated in side-rooms of the neurology ward. After further new cases occurred despite the isolation measures and after four new cases were identified in the first week of November, all patients were isolated on one ward which was closed for other patients. During the whole period, staff members attending the patients were screened three times a week for MRSA carriage by culture of nasal swabs. Ten nurses had positive nose cultures. After November 1986 no new cases of MRSA carriage or infection occurred on the neurology ward.

Second Outbreak. In April 1987, MRSA was isolated from the urine of a patient on a surgical ward. The resistance pattern and phage type of this strain were identical to that of the MRSA from the first outbreak. No relationship could be found between this patient and the first outbreak. The departments of surgery and neurology were located in different buildings, and no exchange of personnel had taken place between the two wards. This patient was nursed in strict isolation in a side-room of the surgical ward for a few weeks in April, and he was readmitted to the same ward in June. At the time he was still carrying MRSA, and was therefore nursed again in isolation in a side-room. At the end of June a patient from this surgical ward was transferred to the surgical intensive care unit (SICU) because of septic shock. Blood cultures grew MRSA. The patient died 72 hours after admission to the SICU.

During the next weeks 16 other patients in the SICU and surgery ward were found to be colonized with MRSA. All colonized surgery patients had been nursed for at least 24 hours in the SICU at the beginning of the outbreak. Of the 18 patients of this second outbreak, five developed infections with MRSA: one urinary tract infection, one pneumonia, one blood stream infection and two wound infections. After screening of staff members nine nurses were found to be carriers.

The SICU was closed for new admissions. The medical ICU in our hospital has the possibility of increasing its number of admissions by occupying a separate area with isolation facilities (for use in case of disasters). This provided the opportunity to create an isolation ICU with a separate team for patients carrying MRSA and needing intensive care. The patients who carried MRSA but did not need intensive care were isolated on a surgical ward, which was also closed for other patients. All patients who had possible contact with MRSA carriers were screened by three consecutive series of cultures of nose, throat, sputum, urine, perineum, and wound specimens. Members of the staff were screened by nose swabs. By the end of August the SICU could be opened again; the isolation wards remained in use until October when the last patient carrying MRSA was discharged.

Third Outbreak. In December 1988, more than a year after the last patient with MRSA had been discharged, MRSA was isolated from a perineal swab from a patient (hereafter referred to as the index patient) in the SICU. Again, the antibiotic resistance pattern and phage typing revealed that the strain was identical to the strain of the first two outbreaks. This patient had not been abroad and was being nursed in the SICU for four months for complications after operation of a ruptured aortic aneurysm. Surveillance cultures of throat, sputum, urine and perineum specimens twice weekly are routinely performed in the SICU as part of the

selective decontamination programme (6) which runs on this ward. These surveillance cultures had remained negative for MRSA for all patients during the previous months.

Since there was no possibility of isolating this patient on the SICU, he was transferred to the medical (ICU) were he was nursed in strict isolation in a side-room. The SICU was closed for new admissions and the patients and staff were screened. During the next two weeks six patients of the SICU and four staff members were found to be carriers. Since two of these staff members were attending to the patient on the ICU, all patients on the ICU were also screened, and six additional patients were found to be carrying MRSA. In January MRSA was isolated from patients in the ICU of the cardiosurgery ward and patients of a neurosurgery ward. The spread of the strain to these two wards was found to have occurred through staff members and through a computer tomography scanner. Indeed, the spread of the outbreak to the cardiosurgery ward most probably occurred through two technicians of the radiology department who made a CT scan of the abdomen of the index patient. A few days later they were found to be carriers, but in the meantime they had taken a chest X-ray of the first patient who developed a wound infection with the MRSA in the cardiosurgery ward. The first patient in the neurosurgery ward, who developed a shunt infection with meningitis with MRSA, had a CT scan of his brain taken in the afternoon after the index patient had his abdominal CT scan. Different technicians assisted in these two procedures.

By mid-December, the medical ICU was used as an isolation ICU, and all patients carrying MRSA and requiring intensive care were transferred to this unit. An isolation ward for patients who could be discharged from the ICU was also opened.

Altogether, 32 patients were involved in this third outbreak; 12 of them developed an infection, 20 were only colonized. Also, 39 staff members were found to have positive nose cultures. The extensive spread of the MRSA during this third outbreak was attributed to the probably extreme contagiousness of the index patient due to an allergic skin reaction with strong exfoliation of his skin. The contagiousness of this patient is well illustrated by the fact that 29 of the 39 carriers among the staff had taken care of him.

Control Measures

Screening of Patients and Staff. During the first outbreak, patients who had shared the room with affected patients were screened once. Specimens that were cultured included nose, throat, sputum, wound and skin lesion, urine and perineum specimens. Staff attending affected patients were screened three times a week by nose swabbing.

During the second and third outbreak screening of patients was repeated twice. During the screening period, transfer of patients was restricted.

Isolation of Patients. In the first outbreak, containment of MRSA was initially attempted by isolation of patients (both carriers and infected patients) in side-rooms of a neurology ward. After several weeks during which new cases occurred regularly an isolation ward was instituted by closure of the involved ward for new patients. Thereafter no new cases of MRSA colonization or infection of patients occurred.

At the start of the second outbreak, no attempt was made to isolate the patients in side-rooms, since there were no side-rooms in the SICU. It took several days before the decision was taken to close the SICU for new admissions and to create an isolation ICU. Several patients that had been nursed on the SICU during this period were found to be colonized or infected with the MRSA. A general ward was also used as an isolation ward for the patients who could be discharged from the ICU. Staff attending to the patients in the isolation units (nursing, medical and physiotherapy staff) were not allowed to attend to patients on other wards. Again, once the isolation unit was instituted no new cases occurred.

In the third outbreak, side-room isolation was attempted again, but proved insufficient. The quick spread of the MRSA in both the SICU and ICU prompted utilization of one of the two units as an isolation unit and the opening of a general ward as isolation ward, each with separate staff. Since in the meantime the MRSA had spread to cardiosurgery and neurosurgery, these wards were closed for new admissions for a few days to screen patients and staff, and all patients with positive cultures were transferred to the isolation ward.

Management of Staff Carriers. Screening of staff was done by nose culture. When a staff member was found to have a positive culture he or she was taken off duty. To determine whether the carrier was also a disperser, shedding of MRSA was determined. This was done by asking the person to undress and dress again in a cubicle of 2×2 m where five agar plates were placed on the floor. The extent of colonization was determined by swabbing the throat and perineum. If the person was not a disperser, he or she could return to work, otherwise he or she stayed off duty during treatment of carriage. Treatment consisted of a one week course of nasal application of a cream containing neomycin and bacitracin. During this week the person also had to use a disinfectant soap containing chlorhexidine. When this regimen

failed, nasal mupirocin was applied for one week, in combination with a disinfectant soap containing hexachlorophene. In the course of the three outbreaks, 58 staff members (53 nurses, 2 radiology technicians, 1 physiotherapist, 1 medical student and 1 cleaner) were found to be carriers. Carriage was eliminated by a one-week course of neomycin-bacitracin in 42 carriers, 16 were retreated by a one-week course of mupirocin. Four of them required a second course of mupirocin.

For two months after the last outbreak, all staff and patients from the affected wards were screened weekly for MRSA carriage. The epidemic strain was not isolated again.

Management of Patients. Patients were treated with vancomycin if they showed clear signs of infection with MRSA. Eradication of carriage was attempted by the same measures as for staff in patients free of any infection (with MRSA or other microorganisms). Patients were considered free of MRSA after four cultures of specimens from all sites taken over a two-week period were negative. Follow-up was not possible in all patients, since several patients died due to underlying disease or were discharged before follow-up cultures were done. The medical records of all affected patients were tagged and if readmission was necessary, the patients were nursed in isolation and screened for MRSA carriage.

Control of the Environment. During the second and third outbreak, environmental contamination was checked by settle plates. MRSA was found on the SICU near the patients' beds and at the desk of the nursing post. In the isolation ward it was cultured in the rooms and anterooms of the patients, in the corridor and in the recreational area of the staff. At the end of each outbreak, after discharge of the last patient, the isolation wards were closed and thoroughly cleaned and disinfected before new patients were admitted. This cleaning procedure was particularly thorough in the SICU and ICU.

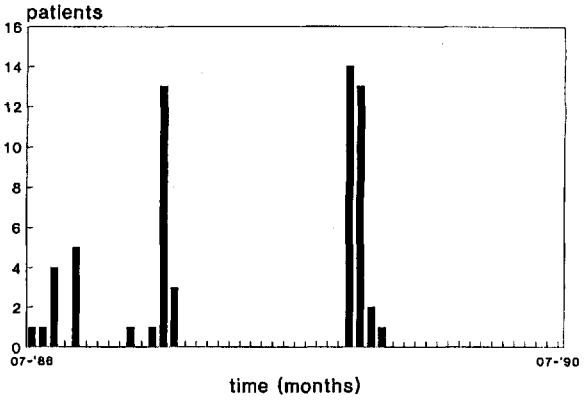

Figure 1: Number of patients with new acquisition of the epidemic MRSA strain at Utrecht University Hospital between July 1986 and July 1990.

MRSA Isolates at Utrecht University Hospital between August 1986 and June 1990

The last new acquisition of the epidemic MRSA occurred at the beginning of March 1989. In July 1989 the hospital moved from the old buildings located in the inner city to a new modern building at the outskirts of Utrecht. As of September 1990, the hospital on its new premises has been free of this strain for over a year.

The MRSA strain which caused the three outbreaks described above was not the only methicillin- and multiply resistant *Staphylococcus aureus* strain isolated at Utrecht University Hospital between August 1986 and September 1990. Six other strains were isolated from six different patients. All these strains were shown by phage typing and by their antibiotic resistance pattern to be different from the epidemic MRSA strain (Table 2). Four strains were imported from abroad (France, Portugal, Turkey and Yugoslavia respectively), one was cultured at the outpatient clinic from a dogbite wound in a veterinary surgery, and one was isolated from a patient who was transferred to Utrecht University Hospital from another Dutch hospital. This patient had never been abroad. Five of these six strains did not spread to other patients or to staff members, although for at least two of these five strains conditions for spread were favorable as the patients carrying the strains were shown to be dispersers, were severely ill with infected wounds, and were nursed in surgical wards. The sixth strain caused a limited outbreak which involved only three patients and one nurse. No infections were caused by this strain, and all carriers were free of the strain after one course of mupirocin treatment.

Discussion

Two lessons can be learned from the experience with MRSA at Utrecht University Hospital. Firstly, strict isolation of both carriers and infected patients on an isolation unit is essential to stop an outbreak. In 1984, Spicer in Australia described three possible strategies for the control of MRSA (7): the Scutari Strategy, the Search and Destroy Strategy, and the SALT (*Staphylococcus aureus* Limitation Technique) strategy. The Scutari Strategy is named after

Table 2: Origin, antibiotic susceptibility and phage type of MRSA strains isolated at Utrecht University Hospital between 1986 and 1990.

Origin	Phage type		Susceptibility
	International phages	Experimental phages	
Italy	NT	1/23/34/25/26	V, F, Ch, N, C
France	III (77)	1/22	V, F, N, C, R, Ci
Portugal	NT	6/16/23/25/27	V, F, Ch, N, C, R, A
Turkey	NT	27	V, F, N, C, Ci
Yugoslavia	NT	3/17/23/25/26	V, F, C, R
Dog bite	III (3/47/53/54/83A/84)	1/3/6/8/12/13/15/16/19/21/27	V, F, N, C, R, Ci, A
Unknown	III (6/47/42E/47/54/7/5)	–	V, F, Ch, C, R, Ci, E, T, Cl

V = vancomycin, F = fusidic acid, Ch = chloramphenicol, N = neomycin, C = cotrimoxazole, R = rifampicin, Ci = ciprofloxacin, A = amikacin, E = erythromycin, T = tetracycline, Cl = clindamycin. NT = not typable by the international phages.

the hospital in which Florence Nightingale worked during the Crimean war (1854–1856). It is based on simple hygienic measures and barrier nursing. The Search and Destroy Strategy is the most rigorous and apparently most expensive strategy. It involves strict isolation of all infected and colonized patients and a search for asymptomatic carriers. Its aim is to eliminate MRSA totally. The SALT strategy represents an intermediate way of dealing with MRSA: infected patients are strictly isolated, colonized patients are subject to precautions. According to Spicer (7), it is possible with this strategy to maintain the number of patients newly acquiring MRSA at acceptable levels, without spending too much time and money on strict measures.

The Utrecht experience casts doubts on both the Scutari and the SALT strategy. The Scutari strategy is in fact comparable to the side-room isolation measures attempted at Utrecht University Hospital at the beginning of each outbreak. This strategy did not prevent the spread of staphylococci, and to end each outbreak it was necessary to create an isolation ward. Clearly, staphylococci may have too many routes of transmission to be contained by simple measures. We did not try the SALT strategy because we do not believe that we should make a distinction between colonized and infected patients as sources of MRSA. A colonized patient today can be an infected patient tomorrow, and this was the case with the first patient in our third outbreak. MRSA was cultured only from his perineum at the start, and from his skin later. At this stage he was only colonized. Three weeks later he developed catheter-related septicemia. From the number of persons who acquired MRSA after contact with this patient, we know that he was a greater source of MRSA in the beginning than during his period of septicemia. In colonized patients, their rate of dispersal is probably the most important factor in determining their potential for spreading MRSA (8).

A drawback of the SALT strategy is the definition of an acceptable level of new acquisitions of MRSA. The SALT strategy also implicitly means accepting to move from an epidemic situation to the endemic presence of MRSA in a hospital. The endemic presence of MRSA will inevitably influence the antibiotic policy in the hospital, both in terms of initial therapy of *Staphylococcus aureus* infections (up to the moment when the antimicrobial susceptibility of the strain is known) and in terms of prophylaxis in surgical procedures where staphylococcal infections are feared.

The Search and Destroy strategy is what was eventually used at Utrecht University Hospital, and we apparently succeeded in totally eliminating the epidemic strain of MRSA. It is difficult to evaluate whether moving the hospital from the old buildings to the new played a role.

We feel that an isolation unit is essential to the Search and Destroy strategy, as is the search for asymptomatic carriers. The need for an isolation unit has also been advocated by others (3, 5). In Utrecht, Search and Destroy also means keeping track of known carriers by labelling the medical records, and isolation and screening of patients who come to our hospital from hospitals abroad or from other Dutch hospitals with a known MRSA problem.

The second important message from the Utrecht experience is a reinforcement of the notion of "epidemic *Staphylococcus aureus*". Not all strains seem to have equal epidemic potential. The existence of

specific epidemic strains of staphylococci was illustrated in the fifties by *Staphylococcus aureus* type 80 (9), which caused several outbreaks of nosocomial staphylococcal infections in various hospitals. Since 1982 a methicillin- and multiply-resistant strain has appeared in London and has caused several outbreaks. It has been termed "epidemic methicillin-resistant *Staphylococcus aureus*" (EMRSA) to distinguish it from other MRSA strains which do not cause epidemics (10).

The particular behaviour of the MRSA strain imported from Italy to Utrecht University Hospital in comparison to the several other strains introduced into the hospital in recent years, renders this strain worthy of the qualification "epidemic".

As stated by Williams in 1959, epidemic staphylococci "undoubtedly have something that many strains of staphylococci lack" (9), and this certainly applies to all epidemic staphylococci, whether methicillin-resistant or not. There is some evidence of a difference in coagulase and protein A content of epidemic and non-epidemic strains (11), and it has been shown that epidemic strains have several virulence factors (12). However, it is not possible to clearly distinguish epidemic from non-epidemic MRSA in the laboratory. The recognition of epidemic strains warrants further investigation, since this will make it possible to tailor the strategy (Scutari, SALT or Search and Destroy) for the control of MRSA to the peculiarities of the strain.

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