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REVIEW ARTICLE

Spread of Staphylococcus aureus in Hospitals: Causes and Prevention

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Methicillin-resistant Staphylococcus aureus (MRSA) has become a major nosocomial pathogen in many hospitals worldwide. Even more alarming, MRSA strains that are vancomycin intermediate-susceptible are isolated with increasing frequency, making therapy for staphylococcal infections even more difficult and prevention more important than ever. Spread of S. aureus in hospitals and infection control measures are reviewed. The major sources of S. aureus in hospitals are septic lesions and carriage sites of patients and personnel. Carriage often precedes infection. The anterior nares are the most consistent carriage site, followed by the perineal area. Skin contamination and aerial dissemination vary markedly between carriers and are most pronounced for combined nasal and perineal carriers. The principal mode of transmission is via transiently contaminated hands of hospital personnel. Airborne transmission seems important in the acquisition of nasal carriage. Infection control strategies include screening and isolation of newly admitted patients suspected of carrying MRSA or S. aureus with intermediate resistance to vancomycin, implementation of an infection control program to prevent transmission of resistant strains between patients and hospital personnel, and institution of a proper antibiotic policy to minimize antibiotic resistance development. MRSA carriers should be treated with intranasal antibiotics, e.g. mupirocin, and skin disinfectants to eliminate carriage. Education of hospital personnel is essential. Improved knowledge about the best ways to ensure favourable infection control practices is needed. Active intervention against the spread of MRSA is important.

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INTRODUCTION

The problem of penicillin-resistant Staphylococcus aureus infections in hospitals in the 1950s and early 1960s was a major stimulus for research into staphylococcal epidemiology. Extensive studies were carried out in a number of hospitals to evaluate important issues such as common sources of S. aureus infection, routes of transmission of the microorganisms and measures to prevent infection (1, 2). Based on the results of these studies, strict infection control measures were introduced, including proper isolation facilities and measures to prevent infection from hospital staff, and over the subsequent several years the frequency of S. aureus infections was reduced.

Fourty years later the spread of methicillin-resistant S. aureus (MRSA) strains has become a major problem in many hospitals worldwide. MRSA strains now commonly cause 20–40% of all S. aureus infections in hospitals where these strains are endemic (3–5). Furthermore, many MRSA strains are also resistant to other antibiotics, including erythromycin, aminoglycosides, tetracyclines, rifampicin, clindamycin, trimethoprim-sulfamethoxazole and fluoroquinolones (5, 6), and in many hospitals vancomycin and teicoplanin are the only antimicrobial agents available for the treatment of patients with serious MRSA infections. Even more alarming, MRSA strains that are vancomycin intermediate-susceptible are being isolated with increasing frequency, making therapy of staphylococcal infections even more difficult and prevention more important than ever (7, 8). In this situation, however, it seems that we have forgotten how vitally the infection control measures were needed to reduce staphylococcal infection in the 1950s, and how important they still are. This holds particularly true for isolation procedures, identification of the source of an outbreak and screening and treatment of carriers among hospital patients.

This review discusses the spread of S. aureus in hospitals and measures to prevent this spread. There is no reason to believe that the epidemiology of MRSA is different from that of methicillin-susceptible S. aureus (MSSA).

SPREAD OF S. AUREUS IN HOSPITALS

For practical purposes the only true sources of S. aureus in hospitals are septic lesions and carriage sites of patients and personnel. These are the places where the microorganisms multiply, and from these places they are transmitted to other patients and personnel and to vehicles for infection, i.e. blankets, clothes, ward dust, etc. The anterior nares are regarded as the principle site of S. aureus carriage (2, 9, 10). The perineum is the main carriage site on normal skin (11–14), and in some perineal carriers the staphylococci are not found on repeated cultures of the anterior nares (11, 12, 14). Other carrier sites, e.g. throat and axillae, are less frequent (12, 15).

Nasal carriers

The nasal vestibule is the most consistent carrier site (9, 11, 16). If repeated samples are obtained over time from the anterior nares, S. aureus is isolated from up to 80% of adults. Approximately 20% are persistent carriers, i.e. almost always carry 1 type of strain, 60% are intermittent carriers and 20% are non-carriers, i.e. they almost never carry S. aureus (16). Persistent carriage is more common in children than in adults (17). Increased carriage rates have been demonstrated in several patient groups, including

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patients with insulin-dependent diabetes mellitus (18), S. aureus skin infection (19), human immunodeficiency virus (HIV) infection or AIDS (20) and intravenous drug abuse (18), and those on hemodialysis (18) or continuous ambulatory peritoneal dialysis (CAPD) (21). Why some individuals remain non-carriers while others are persistent or transient carriers is not well understood and remains one of the key problems in staphylococcal epidemiology to be further elucidated. However, persistent carriage seems to have a protective effect on the acquisition of other strains (22).

In nasal carriers, the hands, fingers and area adjacent to the nose are regularly colonized by the nasal strain (13, 15, 23). This holds particularly true for persistent carriers who commonly yield more S. aureus colonies in nasal cultures than intermittent carriers (15, 24). In most carriers, the S. aureus isolated from the fingers and hands seems to represent transfer from the anterior nares (13, 15). This is supported by the findings that the numbers of S. aureus isolated from the fingers and hands increase with increasing numbers in nasal cultures.(15, 25, 26) and that elimination of nasal carriage by topical antibiotics also eliminates hand carriage (15, 25–27).

Nasal carriage of S. aureus has been identified as a major risk factor for the development of S. aureus infections in various patient groups, including patients undergoing surgery (28, 29), hemodialysis (10, 30) and CAPD (10, 21) and patients with intravascular devices (31) and HIV infection (32). Furthermore, the infection rate seems to increase with increasing numbers of S. aureus in nasal cultures (28, 29). Elimination of nasal carriage by topical antibiotic treatment markedly reduces the infection rate in patients undergoing surgery (28), hemodialysis (33) and CAPD (10). Accordingly, S. aureus nasal carriage plays an important role in the development of infections with these microorganisms.

Perineal carriers

Hare and Ridley (13) were the first to point to the perineum as an area where S. aureus can multiply. In a careful study of 50 male medical students, Ridley (14) showed that 11 (22%) had sufficiently large numbers of S. aureus isolated from the perineal area to class them as perineal carriers. Six of these were also nasal carriers. Perineal carriage persisted for months in 7 individuals. Later, perineal carriage of S. aureus was demonstrated in most patient groups, including 30–50% of 2–10-d-old neonates (34), 13% of patients admitted to a medical department (11) and 60–65% of patients with chronic furunculosis (35). About 50–70% of perineal carriers are also nasal carriers, often of the identical strain (11, 15).

Why S. aureus colonizes and multiplies in the skin of the perineum is not well understood. However, both the nasal vestibule and the perineum are areas with large apocrine glands. It may be that these glands offer a suitable environment for survival and multiplication of S. aureus (14).

Characteristic for perineal carriers is the heavy contamination with the perineal strain of the areas adjacent to the perineum, including the groin and the upper part of the thighs (14, 15). Large numbers of S. aureus are also isolated from the bedclothes and trousers. Particularly, this holds for persistent carriers who have more S. aureus cultured from the perineal area than transient carriers (14, 15). Patients who develop S. aureus lesions on the buttocks and lower half of the abdomen and back while in hospital often have identical strains isolated from the perineum on admission to those later demonstrated in the lesions (15). It is most likely that S. aureus lesions on the lower half of the body are caused by microorganisms from the perineum (15, 35).

Patients with S. aureus lesions

Patients with widespread, staphylococcal-infected skin lesions are often heavily contaminated with S. aureus (15, 36). This also holds for normal skin areas, including the fingers and hands. In patients with minor skin lesions such as boils, however, S. aureus skin contamination compares well with that of nasal and perineal carriers (15). Covering of the lesions with bandages markedly reduces S. aureus skin contamination. Strong evidence has been presented that individuals with lesions have been the source of infections in maternity units (37) as well as in medical and surgical wards (38). Whether this is due to more virulent strains, increased numbers and infective doses or both, is not known.

Dissemination of S. aureus

In their classical studies, Hare and Thomas (23) demonstrated that very few S. aureus are expelled into the air directly from the nose and mouth of carriers during breathing, talking or even more vigorous activities, such as coughing and snoring. A more indirect route of dissemination was suggested involving egress of S. aureus in nasal secretions, contamination of the hands, clothing and bedding, release of the microorganisms by friction or movement and finally transportation to others by air currents (13, 14, 39). A most important observation was made by Davies and Noble (40), who demonstrated that large numbers of skin fragments (scales) were dispersed into the air during activities known to liberate bacteria, such as bedmaking, and that S. aureus could be cultivated from the epithelial fragments, provided the disperser was a carrier. They suggested that most bacteria dispersed by carriers into the air of hospital wards are carried on desquamated skin scales. A marked variation was observed in the dispersal of S. aureus by the patients (41). White (42) found that the extent to which patients contaminated their bedding was correlated with the numbers of S. aureus in their nasal cultures.

Solberg (15, 26) extended these studies and examined 157 persistent S. aureus carriers and 18 patients with S. aureus lesions drawn from 2614 patients admitted to a medical

department in a 15-month period. The amount of S. aureus on various skin areas, including the hands, anterior nares and perineum, was measured by standardized washing techniques, and the patients were isolated in special test chambers for 2 h while S. aureus air contamination was measured by slit-samplers and sedimentation plates. While in the test chamber the patients were allowed to behave as usual, and the bed was made by a nurse using a sterile gown, sterile gloves, haircover and face mask. The dissemination of S. aureus into the air during the 2 h varied from less than 20 colony-forming units (lowest count to be measured) to about 1,000,000 units (Fig. 1), and there was an even distribution (log-normal) between patients dispersing small amounts of staphylococci and those dispersing large numbers, indicating that the so-called 'heavy dispersers' (1, 2) represent the top end of a continuous distribution.

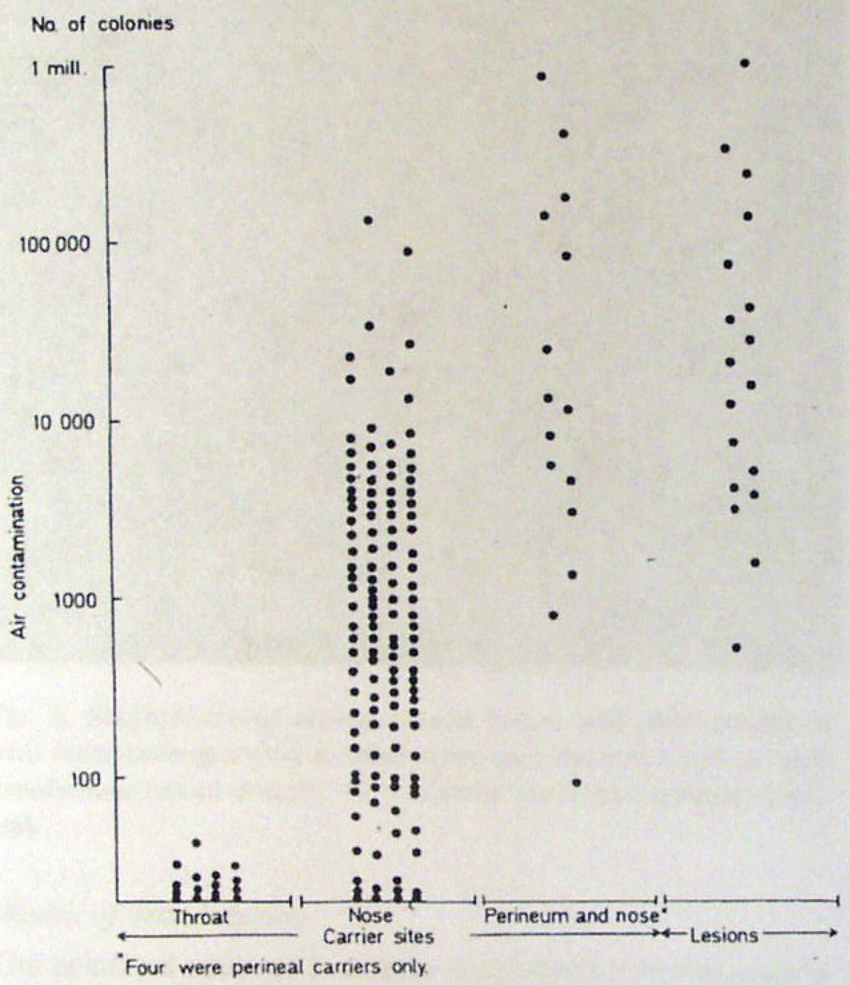

Fig. 1. Staphylococcus aureus air counts from 157 persistent carriers and 18 patients with staphylococcal lesions (mean of 2 examinations).

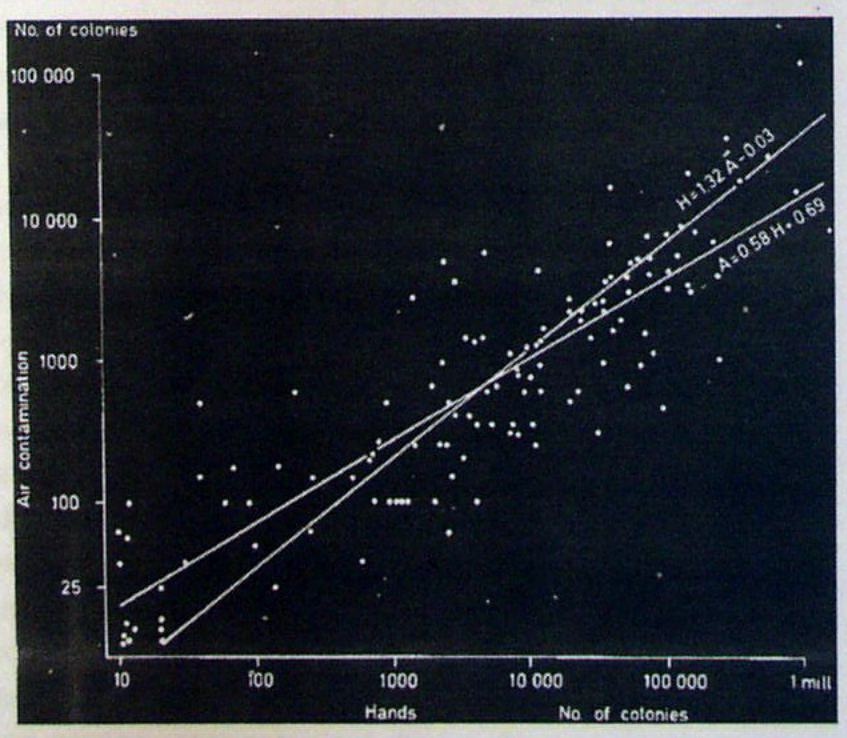

Fig. 2. Correlation between Staphylococcus aureus counts from hands and air (mean of 2 examinations, 126 persistent nasal carriers).

Patients who were carriers of S. aureus in the throat had very few or no staphylococci on the skin, and they dispersed nearly no S. aureus into the air. Patients who were nasal carriers also had small amounts of S. aureus on the skin, except for 1 area: the hands. Here the numbers varied from less than 10 colony-forming units to more than 2,000,000 units in the standardized test, and a fair correlation was observed between the numbers of S. aureus liberated into the air and the numbers isolated from the hands (Fig. 2). For the patients who were combined nasal and perineal carriers or had S. aureus skin lesions, the staphylococcal air contamination also increased within wide limits with the amount of bacteria on the various skin areas, i.e. hands, perineum or skin lesions.

More than 90% of the S. aureus particles were liberated into the air when the bed was made, and by sampling the airborne particles onto slides for microscopy, it was demonstrated that the staphylococci were attached to skin scales. These findings support the view that it is the amount of S. aureus on the skin that determines not only the spread of the microorganisms by direct or indirect contact, but also the airborne transmission. Most likely, staphylococcal nasal carriers contaminate their fingers and hands by direct contact with the anterior nares, as suggested by Hare and co-workers (13, 23). Other skin areas are contaminated via the fingers and hands, and by desquamation, personal clothes or bedclothes become contaminated with skin scales containing S. aureus. Perineal carriers and patients with skin lesions contaminate their clothes and bedclothes directly by S. aureus from the perineum or lesion. When the patients dress or undress or the bed is made, the staphylococci are liberated into the air.

Increased skin carriage and dispersal of S. aureus seem more prevalent in debilitated patients, including patients with chronic renal failure, advanced diabetes mellitus and haematologic malignancy (1, 15). Antibiotic treatment of carriers with resistant S. aureus seems to enhance the spread of the microorganisms, possibly due to increased numbers of resistant S. aureus on the carriage sites resulting from fewer competitors, i.e. susceptible microorganisms (15, 43). Viral upper respiratory tract infection in nasal carriers also markedly increases the spread of their S. aureus strains, sometimes causing outbreaks (44, 45). It is most likely that males are heavier dispersers than females (1, 15, 46).

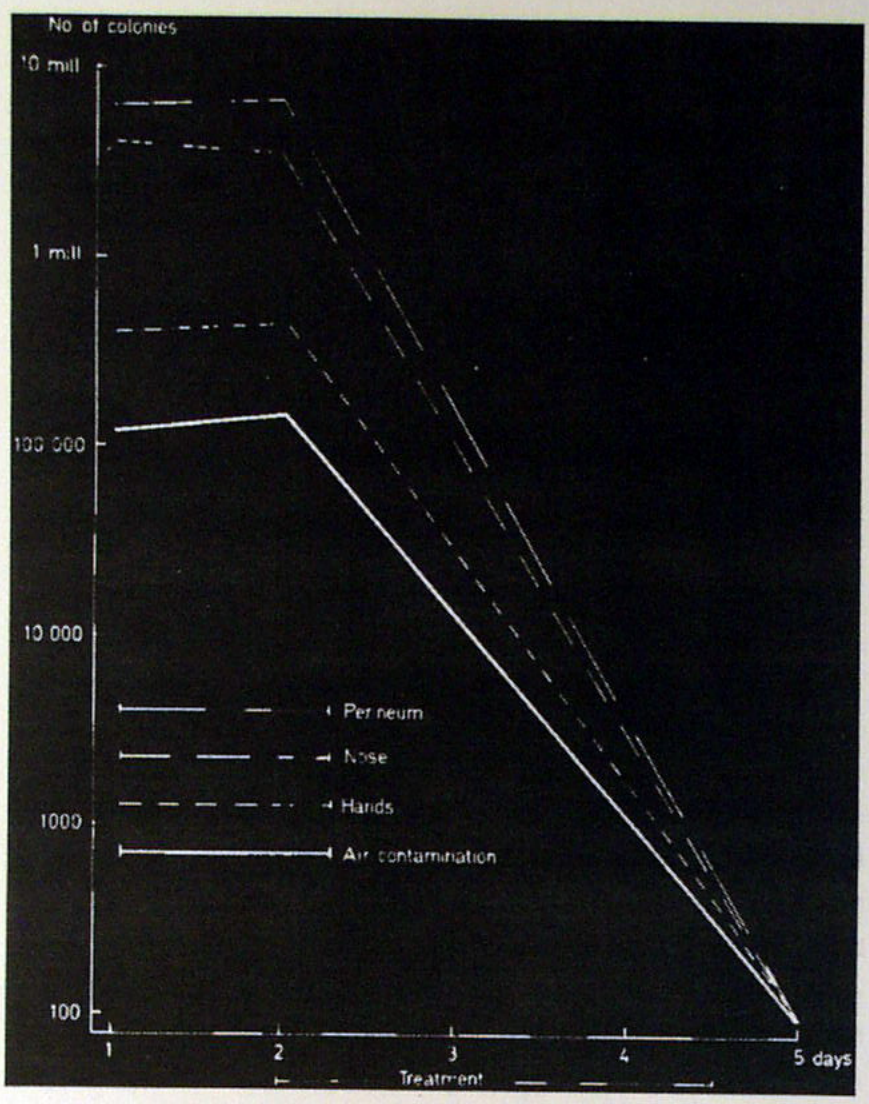

Fig. 3. Staphylococcus aureus counts before and after treatment with framycetin-gramicidin nasal spray and hexachlorophane skin disinfection (mean counts, 10 persistent nasal and perineal carriers).

Modes of transmission

The principal route of S. aureus transmission in hospitals is most likely from patient to patient via transiently contaminated hands of hospital personnel who have acquired the microorganism by direct patient contact or by handling contaminated materials (47, 48). Persistent carriers among hospital personnel have also been implicated in nosocomial transmission (45, 49). However, such events seem uncommon.

The role of airborne transmission of S. aureus in hospital infection is difficult to evaluate. The main reason for this is that whenever there is the possibility of airborne transfer, there is almost always the possibility of transfer by other routes (1). In newborns, the umbilicus and the skin of the abdomen are often colonized before the anterior nares, indicating that transmission by contact is of major importance (2, 50). Mortimer et al. (47) studied the transmission of S. aureus to newborns using a room with 8 bassinets, 2 bassinets occupied by babies who were S. aureus carriers and the remaining 6 by non-carriers. When the carriers and non-carriers were handled by separate teams of nurses to facilitate study of airborne transmission, only 10% of the non-carriers were colonized during the stay in the nursery (average 4 d). When carriers and non-carriers were handled by the same nurses, 43% became colonized, indicating that physical contact is of major importance for the transmission of S. aureus. This figure dropped to 14% when the nurses washed their hands with a hexachlorophane disinfectant between handling of the babies. Transmission by contact is most likely more important in newborns than airborne transfer.

The importance of contact transmission in newborns is not surprising considering infants' low respiratory minute volume (0.5 l) and the frequent handling by nurses who often handle many other infants. When analogous experiments to that of Mortimer and co-workers were carried out in adults, i.e. 3 non-carriers and 1 S. aureus carrier sharing a room and cared for by different teams of nurses, 20–30% of the non-carriers became colonized with the strain of the carrier within a week, provided that he was a combined nasal and perineal carrier, i.e. a heavy disperser (51, 52). Airborne transmission of S. aureus from weak dispersers was uncommon (51, 52). This compares well with the very low nasal acquisition rates in patients nursed in single or isolation rooms (52–54), presumably with low S. aureus air counts, and the high acquisition rates in open wards with high S. aureus air counts (1, 52, 55).

Further evidence for the importance of airborne transmission has been provided by examining the order in which different parts of the body are colonized. In a study of surgical patients, daily cultures were obtained from the anterior nares, various skin areas, wounds and bedclothes in addition to cultures from the environment (56). 34% of the 81 patients who became nasal carriers had S. aureus of the relevant phage type isolated from the skin or wound before the appearance in the nose. In the remaining 66% of acquisitions, however, the microorganism was first isolated from the anterior nares, indicating that the airborne route is important in the acquisition of the nasal carrier state in adults.

Treatment of carriers

The amount of S. aureus on various skin areas and the dissemination into the air by carriers can be most effectively reduced by local treatment with antibiotic nasal ointment or spray and a skin disinfectant (15, 25, 26, 28). Solberg (15, 26) treated 10 S. aureus nasal and perineal carriers with antibiotic nasal spray and hexachlorphane disinfection of the hands and perineum (Fig. 3). During treatment a marked reduction was observed in the number of S. aureus isolated from the various skin areas and the amount liberated into the air. As long as treatment was maintained, the counts remained very low, almost negligible.

Treatment of S. aureus carriers with topical nasal antibiotics and sometimes a skin disinfectant has also significantly reduced the infection rate with these microorganisms in various patient groups, including patients undergoing surgery (10, 28, 57), hemodialysis (33) and CAPD (10). This is most likely due to the marked reduction in S. aureus load

during treatment. However, if treatment is discontinued after 2–3 d in persistent carriers, staphylococcal skin and air counts commonly begin to rise and reach pretreatment levels in about a week (15). Prolonged treatment is often necessary to eliminate persistent carriage. This holds particularly true for nasal carriage where eradication rates have been low and relapse rates high (48, 58–60). Mupirocin seems to be the most promising agent (61–63). However, resistance development has become a problem with most antibiotics, including mupirocin (59, 60, 64, 65).

INFECTION CONTROL

The prevalence of antibiotic-resistant S. aureus in a health care institution depends largely on 3 elements: (i) the constant introduction of resistant microorganisms into the institution from outside, mainly from patient admissions; (ii) the reservoir of resistant S. aureus in the facility due to colonization and transmission of strains between patients and staff; and (iii) the proportion of strains that has become resistant as a result of antibiotic pressure within the institution. Control strategies should, therefore, include screening and isolation of newly admitted patients suspected of carrying MRSA or S. aureus with intermediate resistance to vancomycin, implementation of an infection control program to prevent transmission of resistant microorganisms and institution of a proper antibiotic policy to minimize resistance development. There is no reason to believe that the epidemiology of MRSA and S. aureus with intermediate resistance to vancomycin is different from that of MSSA.

Screening and isolation

Prompt isolation of patients with S. aureus infection is a key element in infection control. Patients who are MRSA carriers may also transmit large numbers of resistant strains to their fellow patients and hospital personnel, and as far as possible, they should also be isolated and treated to eliminate carriage (58). However, the approach to MRSA carriers seems to differ between hospitals where MRSA is non-endemic or endemic.

Approach in hospitals where MRSA is non-endemic

Strict isolation and treatment of patients who are MRSA carriers have been practised for several years in Dutch and Scandinavian hospitals, and despite frequent admissions of patients from abroad with resistant strains, the prevalence of MRSA has remained low ($< 1\%$) (5, 66, 67). Common practice in these countries is to isolate all patients transferred from hospitals outside the country in a single room with toilet and handwashing facilities for at least 48 h (68). The patients are allowed to be treated in open wards only when 3 sets of cultures from carriage sites, lesions, manipulated sites and wounds are MRSA-negative (68).

If a hospitalized patient is found to carry MRSA, cultures are obtained from carriage sites, lesions and manipulated sites of all other patients in the same room, and the roommates are nursed in cohort isolation until cultures are MRSA-negative (68). Only nasal cultures are obtained from the personnel. According to Dutch guidelines, the ward is closed to new admissions if the same MRSA strain is isolated from 2 or more patients or 1 health care worker (68, 69). Intensive care units (ICUs) are closed to new admissions on the first recognition of MRSA in the unit (68, 69). In Scandinavian hospitals, screening and isolation of patients have been preferred to closing of wards or ICUs. However, this so-called 'Search and Destroy' strategy (70) has proved effective so far in The Netherlands as well as in Scandinavia.

Approach in hospitals where MRSA is endemic

In countries where MRSA is endemic, a risk assessment is usually performed and resources utilized in areas where the impact of MRSA transmission is most pronounced, i.e. high-risk areas such as the ICU (48, 58, 71). In the UK, admission screening of patients entering a low-risk hospital area, i.e. a medical or non-neonatal paediatric ward, should include those who are known to have been previously infected or colonized with MRSA or who are admitted from MRSA-affected hospitals, nursing homes or hospitals abroad (58). These patients should, if possible, be admitted to an isolation room or ward until deemed to be free of MRSA.

In high-risk areas such as intensive care and burns units, action also includes admission screening of all patients entering regional, national or international referral centres and all patients transferred from an MRSA-affected ward (58). Screening of all patients (nose, perineum, skin lesions and manipulated sites) and staff (skin lesions) in a unit is carried out when a single case of MRSA is encountered, and MRSA carriers are then isolated. Discharge screening for preventive and surveillance purposes is recommended in MRSA-affected high-risk areas (58). Closure of wards or ICUs is carried out only after a careful risk assessment, including various factors, such as the number of MRSA cases, availability of alternative facilities locally, virulence and transmissibility of the MRSA strain, staffing levels and whether the risk of transmission outweighs the benefit of admission. These guidelines are less restrictive than those introduced in The Netherlands (68, 69).

Screening sites

Detection of MRSA carriage depends primarily upon the patient site and number sampled. In several studies, routine screening has included the anterior nares, lesions, manipulated sites, perineum or groin, tracheostomies, intravenous and stoma sites, urine from catheterized patients and sputum, if available (72). If clinically indicated, other specimens have been obtained, including samples from the throat, axilla, vagina, faeces and umbilicus in newborns. In some studies, samples have been obtained from the gro-

instead of the perineal area. However, the perineum is a more common carriage site than the groin (12), and perineal carriers should not be overlooked, because they are often heavy dispersers of S. aureus (13–15). In a study of 403 MRSA carriers, cultures from the anterior nares identified 78.5% of the carriers, while cultures from the anterior nares, throat and perineum identified as many as 98.3% (12). Positive groin (15.6%) and axillary (10.1%) samples were less frequent than perineal (38.1%) and throat (30.8%) samples (12). It is, therefore, important that the perineal area is included in the screening for MRSA and not substituted by the less sensitive groin area.

The role of nasal carriers among hospital staff as a significant factor in the spread of MRSA is much debated (68, 73). However, studies in the 1960s showed that nasal carriage among staff provided a source of microorganisms for new nasal acquisition of S. aureus by patients (49). Furthermore, during outbreaks, hospital staff tends to become colonized with the outbreak strain and to become part of the transmission chain (68). Screening of the anterior nares of hospital staff for MRSA should, therefore, be carried out when a patient with MRSA infection is diagnosed, and staff members who are MRSA carriers should be taken out of service and treated to eradicate carriage. This holds particularly true for staff in critical care areas such as the ICU, orthopaedic and cardiothoracic wards and also in other wards when spread is continuing despite the introduction of control measures (58). However, when resources for screening are scarce, priority should be given to the patients (73). It should be stressed that even more important than screening of staff for nasal carriage is to inspect them carefully for skin lesions, even minor ones, and to culture these.

Basic infection control measures

Most basic infection control measures are widely agreed upon, including identification and isolation of patients infected with MRSA in a single room with toilet and handwashing facilities, careful handwashing between patients, wearing of gloves and gowns when handling MRSA-infected patients, high standards of aseptic techniques and ward cleaning and avoidance of overcrowding of patients. When it comes to wearing of face masks, however, recommendations vary. Some feel that masks are rarely necessary, except perhaps for procedures that may generate staphylococcal aerosols, such as sputum suction and chest physiotherapy, or procedures on patients with exfoliative skin conditions (48, 58). Others have experienced that staff may become colonized with MRSA merely by standing next to an MRSA-positive patient; they recommend use of masks for strict isolation of MRSA-positive patients to prevent colonization of staff by airborne transmission (68). The importance of airborne transmission has also been demonstrated in studies where S. aureus carriers and non-carriers among bedridden patients in the same room have been treated by separate teams of nurses to eliminate transmission by contact (47, 51, 52). Wearing of face masks should, therefore, be considered when handling MRSA-positive patients.

Carriage by patients and hospital personnel provides an important source of MRSA in hospitals, and elimination of carriage should be attempted. Several antibiotics have been used for eradication of nasal carriage (48, 58, 59), but mupirocin seems to be the most effective topical agent (61, 62). However, strains with low- and high-level resistance to mupirocin are now increasingly encountered (59, 60, 64, 65) and prolonged (> 7 d) or repeated courses (> 2 courses per hospital admission) of mupirocin are not recommended (58). The emergence of mupirocin resistance and the potential loss of an important tool in MRSA control emphasize the importance of using the agent judiciously. A risk assessment should be made in each case to evaluate whether the benefits of treatment outweigh the risks.

The amount of S. aureus on the skin, particularly the hands and perineum, may be most effectively reduced by washing the skin with an antiseptic, e.g. chlorhexidine, hexachlorophane (not marketed in many countries due to toxicity) or povidone-iodine detergents (74, 75). Treatment of carriers with intranasal application of antibiotics and skin disinfectant markedly reduces the amount of S. aureus on the skin and the dissemination into the air (15, 26) and has proved most effective in reducing S. aureus wound infection and colonization in surgical patients (28, 57). Whether this reduction can be achieved with skin disinfection alone is not known, but should be investigated.

Control of MRSA in hospitals demands strict adherence to infection control policies, and education of hospital personnel is an essential part of any infection control program. The education must include all hospital staff associated with patient care, including physicians, nurses, technicians, housekeeping and medical administration. Effective infection control can only be achieved when all personnel are motivated to follow the rules given by the infection control committee. Improved knowledge about the best ways to ensure favourable infection control practices is highly appreciated. This holds particularly true for compliance with such an important but simple measure as handwashing (76). Undoubtedly, an effective infection control team is essential for compliance with prescribed hospital infection control practices.

Antibiotic policy

The introduction of new antimicrobial agents has been followed repeatedly by the emergence of resistant microorganisms. This is also characteristic for S. aureus. When penicillin was introduced in 1944, more than 95% of S. aureus isolates were susceptible, but this proportion has since decreased to 10–15%. By the end of the 1950s, S. aureus had acquired resistance to virtually all available systemic antibiotics, including benzylpenicillin, ery-

thromycin, streptomycin and tetracyclines. Thus, infections with the nosocomial S. aureus of phage type 80/81 became virtually untreatable. The introduction of the β-lactamase-stable penicillins in the early 1960s overcame this problem, but was soon followed by the emergence of the first MRSA. These strains occurred sporadically, were resistant only to β-lactam antibiotics and caused no major problems, perhaps because another effective antimicrobial agent – gentamicin – entered into use (77). However, by the late 1970s, gentamicin-resistant MRSA had emerged, and subsequently a series of epidemic strains have evolved and spread (77, 78). These were consistently susceptible only to the glycopeptides, vancomycin and teicoplanin. More recently, however, MRSA with intermediate resistance to vancomycin and teicoplanin has appeared (7, 8, 79). This series of events of resistance development has demonstrated that the adaptive potential of S. aureus is such that for each new antibiotic that is introduced, new escape mechanisms are soon devised. Accordingly, proper use of antibiotics is important.

In general, development of resistance is most prevalent where use of antimicrobial agents is heaviest. This applies at both national and clinical unit levels. One of the best examples is the excess of resistance in ICUs as compared with general hospital wards or outpatient clinics (5, 63, 80). In countries where MRSA rates are low, such as Denmark (67) and The Netherlands (68, 81), control of resistance development has been attributed to strict antibiotic prescription policies and effective hospital infection control practices supervised by infection control practitioners (doctors and nurses), clinical microbiologists and infectious disease specialists. It is, therefore, important that hospitals adhere to a stringent antibiotic policy.

COST EFFECTIVENESS

The cost of MRSA control includes cost of isolation procedures, identification and eradication of MRSA colonization, temporary closure of wards and redeployment of personnel. Whether these costs are lower than the costs of not enforcing an infection control program has been much debated (58, 68, 82). In the latter situation, it is most likely that the endemic level of MRSA will increase substantially, resulting in an increased incidence of MRSA infection and increased use of vancomycin and teicoplanin, agents which are more expensive than those used for treatment of MSSA infections. Furthermore, there is good evidence that the morbidity and mortality due to S. aureus infections will increase. Studies from Spain (83) and the USA (84) have shown that the mortality rate is higher in patients with MRSA than MSSA infections; in the study from the USA, patients with MRSA infections had an average attributable death rate of 21% vs. 8% for those with MSSA infections. Some of the difference in mortality seemed to be related to the underlying condition of patients who became infected with MRSA (e.g. older patients, drug users, sicker patients, patients previously exposed to other antibiotics), and to the lack of effectiveness of vancomycin itself (84). Patients with MRSA infections are also hospitalized longer than patients with MSSA infections (58, 83, 84). Furthermore, the increased use of vancomycin and teicoplanin may hasten the emergence of vancomycin-resistant enterococci and staphylococci, which will be most difficult to eradicate. Consequently, active intervention against the spread of MRSA is of benefit and is recommended.

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